hearing to determine whether Veterans Administration benefits to all eligible persons enrolled in Hillcrest College of Health Careers, 3300 Sixth Avenue, San Diego, California 92103 should be discontinued, as provided in 38 CFR 21.4134, because a requirement of law is not being met or a provision of the law has been violated. All interested persons shall be permitted to attend, appear before, or file statements with the committee at that time and place.

Dated: March 16, 1982.

Herbert R. Rainwater,

Director, VA Regional Office, 2022 Camino Del Rio North, San Diego, California 92108.

[FR Doc. 82-7699 Filed 3-22-82; 8:45 am]

BILLING CODE 8320-01-M

Sunshine Act Meetings

Federal Register
Vol. 47, No. 56
Tuesday, March 23, 1982

This section of the FEDERAL REGISTER contains notices of meetings published under the "Government in the Sunshine Act" (Pub. L. 94-409) 5 U.S.C. 552b(e)(3).

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1

[M-345, March 18, 1982]

CIVIL AERONAUTICS BOARD.

TIME AND DATE: 3:00 p.m., March 31, 1982.

PLACE: Room 1027, 1825 Connecticut Avenue, N.W., Washington, D.C. 20428.

SUBJECT: Update of Piedmont Airlines' progress under deregulation and its plans for the future.

STATUS: Open.

PERSON TO CONTACT: Phyllis T. Kaylor, the Secretary, (202) 673-5068.

[S-422-82 Filed 3-19-82; 3:14 pm]

BILLING CODE 6320-01-M

2

FEDERAL ENERGY REGULATORY COMMISSION

TIME AND DATE: March 25, 1982, 9:00 a.m.

PLACE: 825 North Capitol Street, N.E., Washington, D.C. 20426, Room 9306.

STATUS: Closed.

MATTERS TO BE CONSIDERED:

(1) Docket No. CI81-14-000, Inexco Oil Company.
(2) Docket No. RI75-112-000, Certain Pipeline and Producer Respondents.
(3) Docket No. CP75-93-001 (Remand), Black Marlin Pipeline Company.
(4) Docket No. IN80-1, Ship Shoal Pipeline System.

CONTACT PERSON FOR MORE INFORMATION:
Kenneth F. Plumb, Secretary, Telephone (202) 357-8400.

Kenneth F. Plumb,
Secretary.

[S-419-82 Filed 3-19-82; 9:31 am]

BILLING CODE 6717-02-M

3

FEDERAL MINE SAFETY AND HEALTH REVIEW COMMISSION

March 17, 1982.

TIME AND DATE: 10:00 a.m., Wednesday, March 24, 1982.

PLACE: Room 600, 1730 K Street, N.W., Washington, D.C.

STATUS: Open.

MATTERS TO BE CONSIDERED: The Commission will consider and act upon the following:

1. Texas Industries, Inc., Docket No. CENT 79-60-M; Petition for Discretionary Review (Issues include whether the judge erred in finding a violation of 30 CFR 56.9-5).
2. Capitol Aggregates, Inc., Docket No. CENT 79-300-M; (Issues include whether violation of 30 CFR 56.9-22 occurred due to failure to provide berms on a loading ramp).

CONTACT PERSON FOR MORE INFO:
Jean Ellen, (202) 653-5632.

[S-419-82 Filed 3-19-82; 1:58 pm]

BILLING CODE 6820-12-M

4

FEDERAL RESERVE SYSTEM
Board of Governors.

TIME AND DATE: 10:00 a.m., Friday, March 26, 1982.

PLACE: 20th Street and Constitution Avenue, N.W., Washington, D.C. 20551.

STATUS: Closed.

MATTERS TO BE CONSIDERED:

1. Personnel actions (appointments, promotions, assignments, reassignments, and salary actions) involving individual Federal Reserve System employees.
2. Any items carried forward from a previously announced meeting.

CONTACT PERSON FOR MORE INFORMATION: Mr. Joseph R. Coyne, Assistant to the Board; (202) 452-3204.

Dated: March 18, 1982.

James McAfee,
Assistant Secretary of the Board.

[S-417-82 Filed 3-18-82; 4:15 pm]

BILLING CODE 6210-01-M

5

FEDERAL RESERVE SYSTEM
Board of Governors.

TIME AND DATE: 10:00 a.m., Monday, March 29, 1982.

PLACE: 20th Street and Constitution Avenue, N.W., Washington, D.C. 20551.

STATUS: Closed.

MATTERS TO BE CONSIDERED:

1. Proposed acquisition of computer equipment within the Federal Reserve System.
2. Personnel actions (appointments, promotions, assignments, reassignments, and salary actions) involving individual Federal Reserve System employees.
3. Any items carried forward from a previously announced meeting.

CONTACT PERSON FOR MORE INFORMATION:
Mr. Joseph R. Coyne, Assistant to the Board; (202) 452-3204.

Date: March 19, 1982.

James McAfee,
Assistant Secretary of the Board.

[S-423-82 Filed 3-19-82; 4:07 pm]

BILLING CODE 6210-01-M

6

FEDERAL RESERVE SYSTEM
Board of Governors.

"FEDERAL REGISTER" CITATION OF PREVIOUS ANNOUNCEMENT: Notice forwarded to Federal Register on March 16, 1982.

PREVIOUSLY ANNOUNCED TIME AND DATE OF THE MEETING: 10:00 a.m., Wednesday, March 24, 1982.

CHANGES IN THE MEETING:

(1) One of the items announced for inclusion at this meeting was consideration of any agenda items carried forward from a previous meeting; the following such open item is added:

Proposal to adopt 1982 fee schedule for wire transfer and net settlement services. (This matter was originally announced for a meeting on Wednesday, March 17, 1982.)

(2) The following open item is deleted from the agenda:

Proposed revisions to the Federal Reserve policy on borrowing by System examiners.

CONTACT PERSON FOR MORE INFORMATON:
Mr. Joseph R. Coyne, Assistant to the Board; (202) 452-3204.

Date: March 19, 1982.

James McAfee,
Assistant Secretary of the Board.

[S-420-82 Filed 3-19-82; 2:15 pm]

BILLING CODE 6210-01-M

7

NUCLEAR REGULATORY COMMISSION

DATE: Week of March 22, 1982 (Revised) and Week of March 29, 1982.

PLACE: Commissioners' Conference Room, 1717 H Street, NW., Washington, D.C.

STATUS: Open/Closed.

MATTERS TO BE CONSIDERED:

Tuesday, March 23
1:30 p.m.: Meeting with the Advisory Panel for the Decontamination of TMI-2 (public meeting) (as announced)
3:00 p.m.: Discussion of Pending Investigation (closed meeting) (continued from 3/19)
Thursday, March 25
10:00 a.m.: Briefing on Steam Generator Problems (public meeting) (as announced)
3:00 p.m.: Affirmation/Discussion Session (public meeting). Items to be affirmed and/or discussed:
a. Proposed Addition on 10 CFR 50.73 Establishing the Licensee Event Report (LER) System (Postponed from 3/18)
b. Psychological Health Under the Atomic Energy Act—Draft Order
c. Amendment to 10 CFR 35 to Require Installation of Radiation Monitors in Teletherapy Rooms and Periodic Inspection and Servicing of Teletherapy Machines
Thursday, April 1
10:00 a.m.: Discussion of Waste Confidence Proceeding (public meeting)
2:00 p.m.: Discussion of Frequency of Emergency Preparedness Exercises (public meeting)
4:00 p.m.: Affirmation/Discussion Session (public meeting). Items to be affirmed and/or discussed:
a. 10 CFR Part 50—Proposed Rule to Clarify Applicability of License Conditions and Technical Specifications in an Emergency
b. Final Rule—Amendment to 10 CFR 50.54(r)—Modification of Requirements for Submittal of Emergency Plans by Research and Test Reactor Licensees
c. Advance Notice of Proposed Rulemaking on Certification of Industrial Radiographers (NDTMA Petition for Rulemaking PRM-34-2)
d. Request for Hearing Following Denial of Renewal of Part 30 Byproducts Materials License
Friday, April 2
10:00 a.m.: Discussion of Management-Organization and Internal Personnel Matters (closed meeting)

ADDITIONAL INFORMATION: By a vote of 3-0, Commissioners Gilinsky and Bradford not present, on March 18, the Commission determined pursuant to 5 U.S.C. 552b(e) and 9.107a of the Commission's Rules that Commission business required that affirmation of Final rule on Intransit Physical Protection of Special Nuclear Material of Moderate Strategic Significance (10 CFR Part 73), held that day, and Briefing on Pending Investigation (Closed Meeting), scheduled for March 19, be held on less than one week's notice to the public.

Discussion of Waste Confidence Proceeding, scheduled for March 23, has been cancelled.

AUTOMATIC TELEPHONE ANSWERING SERVICE FOR SCHEDULE UPDATE: (202) 634-1498. Those planning to attend a meeting should reverify the status on the day of the meeting.

CONTACT PERSON FOR MORE INFORMATION: Walter Magee (202) 634-1410.

Dated: March 18, 1982.

Walter Magee,

Office of the Secretary.

[S-421-82 Filed 3-19-82; 2:57 pm]

BILLING CODE 7590-01-M

federal register

Tuesday
March 23, 1982

Part II

Department of Health and Human Services

Food and Drug Administration

Topical Acne Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 333

[Docket No. 81N-0114]

Topical Acne 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) acne drug products are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Antimicrobial (II) Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by June 21, 1982 and reply comments by July 21, 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. Gilbertson, 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 November 15, 1980 a report on OTC acne drug products from the Advisory Review Panel on OTC Antimicrobial (II) 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 acne 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 judgement 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 acne 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's position on OTC acne drug products will be stated initially when the tentative final monograph is published in the **Federal Register** as a notice of proposed rulemaking. In that notice of proposed rulemaking, the agency also will announce its initial determination whether the proposed rule 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 notice of proposed rulemaking is published. At that time FDA also will consider whether the proposed rule 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 acne 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 acne 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 acne 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 April 22, 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 authorized 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 results 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 products 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 monograph 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 introduced 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 monograph regardless of the date the product was initially introduced 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 antimicrobial active ingredients for the treatment and prevention of specific disorders such as seborrhea, dandruff, acne, athlete's foot, vaginitis, and otitis externa (swimmer's ear) was issued in the **Federal Register** of December 16, 1972 (37 FR 26842). (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 or 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 durg 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 than an 'active ingredient.'")

A subsequent request for data and information on topical antibiotic active ingredients used in OTC products for treatment and prevention of infections in minor skin wounds was published in the **Federal Register** of September 7, 1973 (38 FR 24391). The Panel's conclusions and recommendations for topical antibiotic drug products were published in the **Federal Register** of April 1, 1977 (42 FR 17642).

Products for the treatment of swimmer's ear were referred for review to the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Products. Products for the intravaginal treatment of vaginitis were referred for review to the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products. Products for the treatment of dandruff and seborrhea were referred for review to the Advisory Review Panel on OTC Miscellaneous External Drug Products.

In this document the Panel presents its conclusions and recommendations for acne drug products. The Panel's conclusions and recommendations for topical antifungal drug products are published elsewhere in this issue of the **Federal Register.**

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 the active ingredients contained in antimicrobial products:

Wallace Guess, Ph. D., Chairman
Frank B. Engley, Jr., Ph. D.
Paul D. Stolley, M.D., M.P.H. (resigned June 1977)
William F. Schorr, M.D. (resigned July 1977)
W. Kenneth Blaylock, M.D.
E. Dorinda Shelley, M.D.
Margaret Hitchcock, Ph. D. (resigned September 1974)
David R. Brown Sc. D. (appointed March 1975, resigned March 1976)
Eula Bingham, Ph. D. (appointed July 1976, resigned June 1977)
James E. Rasmussen, M.D. (appointed October 1976)
George B. Youngstrom, M.D. (appointed June 1977, resigned October 1979)
Anne Tucker, Ph. D. (Panel consultant from July 1978 to March 1979; appointed as a Panel member March 1979)
Zenona W. Mally, M.D. (appointed October 1979)

The Panel first convened on July 26 and 27, 1974 in an organizational meeting. Working meetings which dealt with the topic in this document were held on June 9 and 10, 1978; March 23 and 24, April 27 and 28, July 20, August 17 and 18, October 12 and 13, November 16 and 17, 1979; February 22 and 23, March 21 and 22, April 25 and 26, June 6 and 7, July 18 and 19, September 21 and 22, and November 14 and 15, 1980.

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 nonvoting liaison representatives served on the Panel: Sarah Newman, nominated by an ad hoc group of consumer organizations, served as the consumer liaison. Gavin Hildick-Smith, M.D., nominated by the Cosmetic, Toiletry and Fragrance Association, served as an industry liaison until April 1978. Michael Winrow, Ph. D., nominated by the Proprietary Association, also served as an industry liaison until April 1979, followed by Kenneth R. Johannes until January 1980, followed by C. Elizabeth McKinivan, M.D.

The following FDA employees served: Mary K. Bruch served as Executive Secretary; Michael Kennedy served as Panel Administrator in July 1974, followed by Armond M. Welch, R.Ph., until August 1978, followed by Lee Geismar. Melvin Lessing, R.Ph., M.S., served as Drug Information Analyst until October 1974, followed by Joseph Hussion, R.Ph., until July 1976, followed by Anne W. Eggers, R.Ph., M.S., until June 1978, followed by Elaine G. Euchner, R.Ph.

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

Eugene A. Conrad, Ph. D.
Richard Dobson, M.D.
Charles A. Evans, M.D., Ph. D.
Carol Farhi
Samuel B. Frank, M.D.
Arnold Friede
David Fulgham, M.D.
Eugene Gans, Ph. D.
George Hoffnagle, Sc. D.
Albert M. Kligman, M.D., Ph. D.
William H. Lederer, Ph. D., J.D.
James J. Leyden, M.D.
Zenona W. Mally, M.D. (before becoming a Panel member)
Philip Merker, Ph. D.
Sergio Nacht, Ph. D.
Albert Packman, D. Sc.
Peter Pochi, M.D.
Sirje M. Puhvel, Ph. D.
Alan Shalita, M.D.
Vithal Shetty, Ph. D.
John Strauss, M.D.
Harold Upjohn, M.D.

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

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent information submitted through November 15, 1980 in arriving at its conclusions and recommendations.

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

Category I. Conditions under which OTC acne drug products are generally

recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC acne 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 27 active ingredients in topically applied acne products and classified 2 ingredients in Catefory I, 23 ingredients in Category II, and 2 ingredients in Category III.

I. Submission of Data and Information

A. Submissions by Firms

Firms and Marketed Products

AHC Pharmacal, Miami, FL 33125.
bp Gel Medication, bp Gel Medication Strong.
Barnes-Hind Pharmaceuticals, Inc., Sunnyvale, CA 94086.
Komed Acne Lotion, Komed Mild Acne Lotion, Komex Acne Scrub.
Bowman Pharmaceuticals, Inc., Canton, OH 44702.
Bowman Drawing Paste.
Campana Corp., Batavia, IL 60510.
Cuticura Acne Cream (Cutitone).
Carter Products, Inc., Cranbury, NJ 08512.
Persol.
Chattem Drug and Chemical Co., Chattanooga, TN 37409.
Mudd.
Dermik Laboratories, Inc., Fort Washington, PA 19034.
Vlemasque.
Dome Laboratories, West Haven, CT 06516.
Acne-Dome Creme, Acne-Dome Lotion, Acne-Dome Medicated Cleanser, Vlem-Dome Wet Dressing.
Flow Pharmaceuticals, Inc., Palo Alto, CA 94303.
d-SEB.
Fox Pharmacal, Inc., North Miami, FL 33161.
Aktex.
H. B. Distributing Co., West Newton, MA 02165.
Hospital Brand Acne Cream.
Helena Rubinstein, Inc., New York, NY 10022.
Bio-Clear Medicated Cream.
Ketchum Laboratories, Inc., Amityville , NY 11701.
Propoa pH Super Cleanser.
Laboratory Robaina, Inc., Hialeah, FL 33010.
Acetolia Robaina.
Norcliff Thayer, Inc., Tuckahoe, NY 10707.
Oxy-5 Lotion, Oxy-10 Lotion.
Pennwalt Corp., Rochester, NY 14603.
Bare Face Acne Skin Medicine, Ting Antiseptic Medicated Cream.
Poythress, Willian P., & Co., Inc., Richmond, VA 23261.
Bensulfoid Lotion.
Press Chemical & Pharmaceutical Laboratories, Inc., Columbus, OH 43206.
Epsal Ointment.
Preston Pharmaceutics, Inc., Butler, NJ 07405.
Dermakon Dandruff Shampoo, Dermakon Medicated Cream.
Purdue Frederick Co., Norwalk, CT 06856.
Betadine Skin Cleanser, Betadine Skin Cleanser Foam.
Rorer, William H., Inc., Fort Washington, PA 19034.
Loroxide Lotion, Vanoxide Lotion.
Schattner, R., Co., Washington, DC 20016.
Chloraderm.
Smith, Kline, & French Laboratories, Philadelphia, PA 19101.
Acnomel Acne Cake, Acnomel Acne Cream.
Squibb, E. R., & Sons, Inc., New Brunswick, NJ 08903.
Epi*Clear Acne Lotion, Epi*Clear Acne Scrub Cleanser, Epi*Clear Acne Soap, Epi*Clear Antiseptic Lotion 5%, Epi*Clear Antiseptic Lotion 10%, Epi*Clear Squibb Acne Kit.
Sterling Drug, Inc., New York, NY 10016.
Campho-Phenique Liquid, pHisoAc, Stridex Medicated Pads.
Stiefel Laboratories, Inc., Oak Hill, NY 12460.
SAStid Soap, Sulfoxyl Cream Strong, Sulfoxyl Lotion Regular, Sulfoxyl Lotion Strong.
Syntex Laboratories, Inc., Palo Alto, CA 94304.
Microsym Acne Lotion.
Texas Pharmacal Co., San Antonio, TX 78296.
Contrablem, Liquimat, Persadox Cream, Persadox Lotion, Sulforcin Base 4%, Sulforcin Lotion.
Upjohn Co., Kalamazoo, MI 49001.
Plexion, Zinc Sulfide Compound Lotion, Improved.
Vick Divisions Research and Development, Division of Richardson-Merrell, Inc., Wilton, CT 06897.
Clearasil Regular Tinted, Clearasil Stick Medication, Clearasil Vanishing Formula.
Warner-Lambert Co., Morris Plains, NJ 07950.
Listerex Antibacterial Scrub Gel, Listerex Antibacterial Scrub Lotion, Listerex Herbal Scrub.
Westwood Pharmaceuticals, Inc., Buffalo, NY 14213.
Fostex Cake, Fostex Cream, Fostril, Pernox, Transact.

In addition, the following firms or groups provided related information:

Avon Products, Inc., Suffern, NY 10901.
Sulfur-resorcinol combinations.
Herbert Laboratories, Irvine, CA 92715.
Benzoyl peroxide 2.5 percent.
Koppers Co., Inc., Pittsburgh, PA 15219.
Resorcinol.
Miranol Chemical Co. Inc., Irvington, NJ 07111.
Miranol C2M.
Procter & Gamble Co., Cincinnati, OH 45247.
Tetracycline hydrochloride.
Proprietary Association, Washington, DC 20006.
Benzoyl peroxide safety, labeling recommendations.
Schuylkill Chemical Co., Philadelphia, PA 19132.
Alcloxa, allantoin.
Sterling Drug, Inc., New York, NY 10016.
Salicylic acid.
Stiefel Laboratories, Inc., Oak Hill, NY 12460.
Antibacterial data on benzoyl peroxide-sulfur combinations.
Vick Divisions Research and Development, Division of Richardson-Merrell, Inc., Wilton, CT 06897.
Benzoyl peroxide absorpotion, in vitro protocol for determining antibacterial activity, in vivo protocol for testing antibacterial activity, prevention of new acne lesions by topical therapeutic ingredients, resorcinol safety.
Westwood Pharmaceuticals Inc., Buffalo, NY 14213.
Laureth-4 safety, polyethylene safety.

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

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

Alcloxa
Alcohol
Alkyl isoquinolinium bromide
Allantoin
Alpha tocopheryl acetate
Aluminum chlorhydroxide complex
Aluminum chlorhydroxy allantoinate
Aluminum hydroxide
Aluminum magnesium silicate
Aluminum oxide
Bentonite
Benzalkonium chloride
Benzethonium chloride
Benzocaine
Benzoic acid
Benzoyl peroxide
Boric acid
Calcium phosphate
Calcium polysulfide
Calcium thiosulfate
Camphor
Carbomer 940
Carboxyvinyl polymer
Cetyl alcohol
Chlorhydroxyquinoline
Cholesterol
Citric acid
Coal tar
Colloidal alumina
Colloidal sulfur
Cosmetic colors
Dibenzothiophene
Dioctyl sodium sulfosuccinate
Edetate disodium
Epsom salts
Estrone
Glycerin
Glycerol monostearate
Glyceryl monostearate
Hexachlorophene
Hydrocarbon hydrotropes
Isopropyl
Isopropyl alcohol
Isopropyl palmitate
Magnesium sulfate
Menthol
Methylbenzethonium chloride
Methylparaben
Methyl parasept
Methyl salicylate
Micropulverized sulfur
Parachlorometaxylenol
Phenol
Phenyl salicylate
Polyethylene
Polyethylene glycol monostearate
Polyethylene glycol 1000 monostearate
Polyoxyethylene lauryl ether

Povidone-iodine
Precipitated sulfur
Propylene glycol
Propyl parasept
Purified water
Pyrilamine maleate
Rescorcijol
Resorcinol
Resorcinol monoacetate
Salicylic acid
Soapless cleansers
Sodium borate
Sodium hydroxide
Sodium lauryl sulfate
Sodium phenolate
Sodium tetraborate decahydrate
Sodium thiosulfate
Stearic acid
Sulfated surfactants
Sulfonated alkyl benzenes
Sulfur
Sulfur precipitated
Tetracaine hydrochloride
Thymol
Water
Wetting agents
Zinc oxide
Zinc stearate
Zinc sulfide

C. Classification of Ingredients

1. *Ingredients identified by the Panel as active ingredients.* The Panel has adopted the following nomenclature for the active ingredients reviewed in this document. Other nomenclature, where needed for clarification, has been included in parentheses.

Alkyl isoquinolinium bromide
Aluminum salts
  Alcloxa (aluminum chlorhydroxy allantoinate)
  Aluminum chlorohydrex (aluminum chlorhyaroxide complex)
  Aluminum hydroxide
  Magnesium aluminum silicate (aluminum magnesium silicate)
Benzocaine
Benzoic acid
Benzoyl peroxide
Borates
  Boric acid
  Sodium borate (sodium tetraborate decahydrate)
Calcium polysulfide
Calcium thiosulfate
Camphor
Chlorhydroxyquinoline
Chloroxylenol (parachlorometaxylenol)
Coal tar
Dibenzothiophene
Estrone
Magnesium sulfate (epsom salts)
Phenolates
  Phenol
  Phenolate sodium (sodium phenolate)
Phenyl salicylate
Povidone-iodine
Pyrilamine maleate
Resorcinol (rescorcijol)
Resorcinol monoacetate
Salicylic acid
Sodium thiosulfate
Sulfur (colloidal sulfur, micropulverized sulfur, precipitated sulfur, sulfur precipitated)
Tetracaine nydrochloride
Thymol
Vitamin E (alpha tocopheryl acetate)
Zinc salts
  Zinc oxide
  Zinc stearate
  Zinc sulfide

2. *Ingredients identified by the Panel as inactive or pharmaceutically necessary ingredients.* Based on the available literature and in some cases based on concentrations reported in a submission, the Panel considers the following to be inactive ingredients when used for the treatment of acne. In general, most are used as pharmaceutical aids (solvent, vehicle, dispersant, or preservative,) or as product identification materials.

Alcohol
Allantoin
Aluminum oxide
Bentonite
Benzalkonium chloride
Benzethonium chloride
Calcium phosphate
Carbomer 940
Carboxyvinyl polymer
Cetyl alcohol
Cholesterol
Citric acid
Colloidal alumina
Cosmetic colors
Dioctyl sodium sulfosuccinate
Edetate disodium
Glycerin
Glycerol monostearate
Glyceryl monostearate
Hexachlorophene
Hydrocarbon hydrotropes
Isopropyl alcohol (isopropyl)
Isopropyl palmitate
Laureth-4 (polyoxyethylene lauryl ether)
Menthol
Methylbenzethonium chloride
Methylparaben (methyl parasept)
Methyl salicylate
Polyethylene
Polyethylene glycol monostearate
Polyethylene glycol 1000 monostearate
Propylene glycol
Propylparaben (propyl parasept)
Purified water
Soapless cleansers
Sodium hydroxide
Sodium lauryl sulfate
Stearic acid
Sulfated surfactants
Sulfonated alkyl benzenes
Water
Wetting agents

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document includes submissions made by interested persons in response to the call-for-data notice published in the **Federal Register** of December 16, 1972 (37 FR 26842). 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 April 22, 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. Background

Acne affects about 80 percent of the population to some extent during adolescence (Ref. 1). Because this skin condition is common and readily recognizable by consumers, the Panel believes that safe and effective OTC acne medications should be available to the consumer.

Although much has been learned about acne in the past 30 years, much still remains unknown. Even the exact origin of the word "acne" is unknown. Some scholars believe it is a corruption of the Greek word "akne," meaning the highest point or stage (including the peak of growth in humans) (Ref. 2). Another theory is that "acne" comes from another Greek word, "aknesis," which means a rash that does not itch (Ref. 2). In fact, according to Plewig and Kligman (Ref. 3), the only undisputed fact about acne is that it does exist.

The Panel believes that the myths or misconceptions about acne need to be dispelled, including those concerning diet, sexual habits, and the belief that acne can be washed away with soap and water (Ref. 4). For years, people suffering from acne believed that eating chocolates, fatty foods, and "junk foods" either caused acne or made it worse and that abstaining from these foods would cure their acne. Unfortunately, they were often disappointed.

The role of diet is still being studied. For example, a double-blind study tested the effects of large amounts of chocolate on 65 acne patients (Ref. 5). Two kinds of candy bars that looked identical were used. One contained no chocolate; the other was an enriched chocolate bar containing 10 times the amount of chocolate as an average candy bar. The subjects ate one kind of chocolate bar daily for 4 weeks, and for the next 3 weeks they ate no candy. Then they ate the other kind of bar once daily for 4 weeks. Chocolate was found to have no effect on the clinical course of acne.

Another study was conducted with acne patients who believed that certain foods (chocolate, peanuts, milk, or cola) were causing their acne to flare (Ref. 6). These patients were fed large amounts of the suspected food for several days, but no significant change was noted in

the number or character of their acne lesions during the next several days.

According to Cunliffe and Cotterill (Ref. 2), "Iodides have also been blamed for aggravating acne but the evidence for this is rather poor * * *."

Myths about the relationship between sexual habits and the development of acne go far back in history. MacKenna cited Jonston who wrote in 1648 that acne, called "vari," infected young people who were sexually mature but who remained chaste (Ref. 7). More than a century later, according to Cunliffe and Cotterill (Ref. 2), Plenck wrote that marriage could cure acne, but Hebra disagreed. Although some sexual myths may still persist today, there is no evidence to show that they are any more than myths (Ref. 4).

Another misconception is that acne will go away if it is ignored. Although many people no longer have significant acne by the time they are in their early twenties, a number of people still suffer from acne in their forties. The Panel believes it is particularly important that consumers realize that the treatment of acne may have to be continued for several years.

The following discussion summarizes the findings of several surveys on skin conditions.

The most recent report was published by the National Center for Health Statistics and covers the period from 1971 to 1974 (Ref. 8). The data were collected by direct physical examinations, tests, and measurements performed on samples of the population aged 1 to 74 years. Participants were chosen from the civilian noninstitutionalized population.

This report shows that significant skin disease increases rapidly with age. In children aged 1 to 5 years the rate was 142.3 per 1,000. In youths aged 12 to 17 years the rate was 362.0 per 1,000. In young adults aged 18 to 24 years the rate was 365.1 per 1,000. The rapid increase was attributed to acne vulgaris, which, as noted earlier, is common during adolescence and young adulthood. Among the individual types of skin disease that were diagnosed, acne was the most prevalent (68.1 per 1,000 population). The survey also showed that youths aged 12 to 17 years with skin problems are more likely to consult someone who is a "nonprofessional" rather than a dermatologist or other physician.

The Health Examination Survey of 1966 to 1970 (Ref. 9) presented national estimates on the prevalence of facial acne and other skin conditions among noninstitutionalized youngsters aged 12 to 17 by age, sex, geographic region, population, size of place of residence, family income, education of parents, overall health, indication of stress, selected health habits, and physiological development. It was estimated that 28.3 per 100 youths had moderate to severe facial acne. Major findings included the following:

Facial acne (all grades combined) is about as prevalent among girls as boys in the 12–17 year age range. However, such conditions start somewhat earlier and tend to be less severe in girls than boys.

Among youths reporting they had acne, more than half (51 percent) were bothered some or a lot by the condition and (58 percent) were using some treatment for it but only 11 percent had seen a doctor about it.

White youths are slightly more likely than Negro youth to have moderate to severe facial acne but less likely to have mild conditions limited to comedones with little or no inflammatory reaction.

Facial acne is somewhat more prevalent among youths living in the South and West than those in the Northeast or Midwest. However, no consistent urban-rural differences in prevalence rates were found.

Some direct or indirect association is evident between acne prevalence in youths and the education of their parents but not their family income level. The acne prevalence rates decrease consistently with increasing education level of parents.

Facial acne is slightly more prevalent among youths whose health was rated fair-poor than among those considered in good-excellent health by either themselves or their parents.

Facial acne prevalence increases with the degree of nervousness of the youth, the association being stronger and more consistent when based on the youth's own rating of nervousness than that given by his or her parent.

The amount of food eaten particularly among boys appears to be related, directly or indirectly, to the prevalence of facial acne. Acne rates are higher among those who are said, by their parents, to eat too much than those who eat too little.

The prevalence and severity of facial acne increases with the degree of development of secondary sex characteristics among boys 12–16 years and girls 12–15 years of age.

Among girls acne tends to start after the onset of menarche for girls who reach this stage of physiological development before 13 years of age but to precede this point of development for those whose menarche onset is 14 years or later.

A report on a questionnaire survey published in 1972 stated that out of 1,023 high school students whose questionnaires were evaluated, 85.1 percent reported that they had acne (Ref. 10). Of this group, 87.7 percent had not consulted a doctor. The most frequently given reason was that the acne was not severe enough. A few students felt the treatment was too costly; the rest did not specify a reason.

About half of the students surveyed reported a seasonal change in their acne. Among those students reporting a seasonal change, statistically significant improvement was shown during summer.

Most of the students with acne were using some kind of treatment, with girls starting treatment a little sooner than boys. However, the authors reported that only 33.4 percent of the students reported that they never missed their treatment. Statistically, the girls were significantly better than the boys in following a regular treatment schedule.

A total of 117 products was used, with 93.6 percent of the students using one or more products and only 6.4 percent using none. The products included soaps, astringents (which did not claim anti-acne properties), anti-acne preparations, complexion products, and miscellaneous products. Soaps were the most widely used (49.7 percent); anti-acne preparations were the next most widely used (28.8 percent).

People suffering from acne spend millions of dollars yearly for OTC acne preparations as well as prescription drugs (Ref. 11). "Cosmetically" accepted medications are important. In fact, dermatologists say that patient acceptance is as important as effectiveness in acne treatment. They also say that consumers want therapeutic products that work but are not too harsh or unpleasant smelling. Consumers like a product that can be easily applied, feels good, and perhaps may even have a lathering property which enhances the sense of feeling clean and leaves the skin feeling soft.

Dermatologists are often asked questions about the causes of acne, including what foods are responsible. Patients are also concerned about the possibility of scarring. They also ask what they are doing wrong, if makeup can harm the skin, and, in some cases, why they are getting acne at age 30 after having had flawless skin in adolescence. Probably the most difficult question of all to answer is: "When will the acne disappear?"

There are certain aspects of acne therapy that patients most dislike. These include the odor and the stinging and itching of acne products; the staining effect; and dryness and peeling, which to many patients means premature wrinkling. This dryness also makes it difficult to apply a water-base makeup. Patients also dislike the ashy grayness, which is produced by benzoyl peroxide products and cryotherapy and is seen mainly in black skin. Other adverse effects of acne therapy may include vaginal yeast infections as a result of taking systemic antibiotics. A less serious complaint is that having to

remember to apply or take the medication a certain number of times a day is a nuisance. Finally, patients dislike acne surgery, i.e., the comedone extraction and opening up of pustular lesions which many dermatologists routinely do at each office visit.

It has been known since the early 1970's that certain cosmetics and hair pomades can cause blackheads and whiteheads (comedogenic). It has been estimated that up to 50 percent of the popular cosmetic creams will produce comedones when tested on the inner surface of the rabbit ear once daily for 2 weeks (Ref. 3).

The term "acne cosmetica" was coined in 1972 by Kligman (Ref. 12) and refers to acneform eruptions of a low-grade, persistent nature occurring in adult women. These eruptions are caused mainly by prolonged use of cosmetics containing the offending ingredients.

The Panel agrees with the following statement by Sulzberger (Ref. 13): "There is probably no single disease which causes more psychic trauma, more maladjustments between parents and children, more general insecurity and feelings of inferiority, and greater sums of psychic suffering than does acne vulgaris."

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B. Definitions

The Panel adopted the following definitions related to the use of acne drug products:

1. *Comedones (whiteheads and blackheads).* Comedones are the primary lesions of acne and consist of dead cell (keratinous) debris, bacteria, sebum, and hair fragments which plug up the opening of the pilosebaceous unit. The development of the comedo is associated with an increased turnover rate of the epithelial cells lining the sebaceous follicle. The follicle becomes distended with horny material and at this early stage is known as a microcomedo, a microscopic comedo. Further distention of the sebaceous follicle results in the closed comedo.

a. *Whiteheads.* Whiteheads or closed comedones are small, whitish, firm nodules which may be difficult to see. The opening to the comedo is not visible to the naked eye. Closed comedones either rupture and become inflammatory lesions, such as papules, pustules, and nodules, or develop into open comedones. When horny material accumulates in the closed comedo, it causes the opening in the comedo to dilate, pushing horny material to the skin surface. This marks the beginning of the open comedo or blackhead.

b. *Blackheads.* Blackheads are long-lasting lesions that do not usually develop into inflammatory lesions. The tip of the blackhead appears black because of melanin, a pigment.

2. *Lesion.* In this document a lesion is considered as a characteristic area of a skin condition. Acne lesions include open and closed comedones, papules, pustules, and nodules.

3. *Nodule.* A large, red, often painful inflammatory acne lesion that contains pus and leads to scarring. Nodules are deep-seated lesions which affect the dermis. They develop from the rupture of closed comedones and are characteristic of acne conglobata. Nodules may fuse to form odd-shaped lesions. The term "cystic acne" refers to nodular inflammatory lesions and not to true cysts, which are large, round, flesh-colored, noninflammatory lesions with smooth surfaces.

4. *Papule.* A small, inflammatory lesion that appears red and raised. Papules develop from closed comedones. They may develop into pustules and nodules, or they may resolve spontaneously after 2 to 3 weeks.

5. *Pilosebaceous unit.* Consists of a hair follicle and the associated sebaceous gland. These are connected to the surface of the skin by a duct through which the hair passes.

6. *Pustule.* A small, raised, inflammatory lesion that is filled with pus and arises from a papule. Superficial pustules resolve after a few days and rarely cause visible scarring. A deep-seated pustule takes 2 to 6 weeks to resolve, and scarring may result.

7. *Sebum.* A secretion of the sebaceous glands consisting of a mixture of fats and waxes. The severity of acne parallels the degree of sebum secretion.

C. Types of Acne

Kligman (Ref. 1) uses two major classificatioins of acne—true acne and drug-induced acne. The Panel has adapted these classifications to this document, citing other references when appropriate.

1. *True acne*—a. *Acne vulgaris.* A common skin disorder, acne vulgaris is characterized by comedones, papules, pustules, and nodules. Typically, a person with acne will have a variety of acne lesions, although in some individuals one lesion type may predominate. Acne vulgaris primarily occurs on the face, shoulders, back, and chest, but occasionally may be more widespread.

Open and closed comedones are usually the first acne lesions to occur. In the early stages, comedones are generally found on the forehead and chin. Later, papules and pustules appear on the cheeks as well. Although usually a disease of adolescence, acne does not always clear spontaneously when maturity is reached. It may persist into the third or fourth decades of the patient's life (Refs. 2 and 3). In fact, acne may even begin after the teenage years or at any age.

b. *Acne conglobata.* Acne conglobata is a severe and chronic form of acne vulgaris. The lesions tend to be particularly severe on the face, chest, and back. Lesions may also occur on the buttocks, thighs, upper arms, and neck. Most of the lesions are large, painful, and cystic and may be characterized by abscesses and scarring. Males are affected more frequently than females. The disease, which usually begins between the ages of 18 and 30 years, often continues for many years, resulting in severe disfigurement (Ref. 4).

c. *Acne fulminans.* Also termed "acute febrile ulcerative conglobate acne with polyarthralgia," acne fulminans is a

rare, severe form of acne. The main lesions are nodules that become ulcerated. Systemic effects include fever, anemia, and painful, swollen joints (Ref. 5).

d. *Acne tropicalis.* This type of acne occurs when a susceptible person is exposed to excessive heat and humidity. It resembles severe acne conglobata and is unchanged as long as the patient remains in a tropical climate, but clears completely when the patient returns to a cool, dry climate (Ref. 1). Military personnel that are stationed in tropical climates are particularly at risk for developing this type of acne.

e. *Infantile acne.* This is an acne-like rash of unknown cause. Comedones and papules usually occur on the cheeks of male infants under 1 year of age, but the disease generally subsides completely in 2 to 3 years (Ref. 4).

f. *Premenstrual flares of acne.* Many women suffer from premenstrual flares of acne characterized by the rapid appearance of papulo-pustules. The precise cause is still unknown, but is presumed to be related to cyclical hormone fluctuation (Ref. 1).

g. *Gram-negative acne or folliculitis.* This type of acne usually occurs during long-term treatment of acne with antibiotics which specifically act on gram-positive bacteria, thereby permitting gram-negative bacteria to flourish. The invading organisms are usually *Enterobacter, Klebsiella,* or *Proteus.* A change in the characteristics of the facial acne of a previously well-controlled case of acne may be a sign of gram-negative acne (Ref. 1).

h. *Acne venenata or acne caused by external contactants.* Topical agents or exposure to certain chemicals can cause this type of acne (Ref. 5). "Acne cosmetica" is a mild eruption mainly consisting of closed comedones. It is usually caused by facial creams and is seen in women beyond the age of adolescence (Ref. 1). "Pomade acne" is caused by greases and oils applied to the scalp or face. The lesions are usually small, closed comedones concentrated on the forehead and temples (Ref. 5). "Acne detergicans" is a mild form of acne consisting of closed comedones, apparently induced by excessive scrubbing and washing with certain soaps (Ref. 1).

The most extensive cases of acne venenata are caused by industrially used compounds such as chlorinated hydrocarbons, cutting oils, petroleum oil, coal tars, and pitches. This condition is often referred to as "chloracne." The initial treatment in all forms of acne venenata is to stop the exposure to the causative agent (Ref. 5).

i. *Acne caused by radiation.* Both untraviolet light and ionizing radiation may be associated with the development of special types of acne. Excessive exposure to the sun may induce comedones, usually large blackheads, around the eyes and cheeks of elderly people. Ionizing radiation, such as cobalt and X-rays, can cause a comedonal acne. Acne aestivalis (mallorca acne) is a rare seasonal acne which flares up in the summer months and regresses in winter. It usually affects women beyond adolescence, with papules developing on the lower back. These forms of acne generally subsides when the causative agent is eliminated (Ref. 5).

j. *Acne mechanica.* Aggravation of existing acne can develop from localized pressure or friction. For example, resting the chin on the hand can aggravate acne on the chin (Ref. 1).

2. *Drug-induced acne.* Drug-induced acne is not a true acne, but an acne-like eruption caused by drugs. The eruption subsides when the drug is discontinued. The lesions are generally papules and pustules. The condition is usually characterized by a sudden onset after adolescence and an unusual localization (forearm, buttock). Systemic signs of drug toxicity may also be present (Ref. 1). The drugs that are often involved in these kinds of eruptions include steroids, certain anticonvulsants (phenobarbital, phenytoin, and trimethadione), and certain halogenated drugs. Isoniazid, a drug used in long-term therapy of tuberculosis, may also be involved in some acne-like conditions (Refs. 4 and 5).

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D. Development of Acne

Acne generally begins at puberty when substantial androgen secretion takes place. Androgen is the male sex hormone and comes mainly from the testes in the male and from the ovaries and adrenal glands in the female. Although male adrenals also produce androgens, they play only a small role in acne. The most potent androgen is testosterone, the circulating androgen. Testosterone is converted in the skin by the enzyme 5-*alpha*-reductase to dihydrotestosterone, the tissue-active androgen (Ref. 1).

Dihydrotestosterone stimulates the cells of the sebaceous glands to increase protein synthesis and accelerate cell division and cell turnover. Thus the sebaceous glands become larger until they surround and completely dominate the hair follicles. Sebaceous follicles (pilosebaceous units) like these produce large amounts of sebum which cause the characteristic oily skin of acne (Ref. 1). Acne usually occurs on the face, upper chest, and back because there are more pilosebaceous units there than on other areas of the body (Ref. 2).

The size of the sebaceous gland usually varies inversely with the size of the hair follicle associated with it (Ref. 3). The kind of hair in the follicle can also affect the development of acne. A thin, small hair may be unable to keep the duct open and the hair is trapped in the plug. However, heavier facial or scalp hair may push the plug to the surface of the skin and prevent a comedo from forming (Ref. 2).

People with acne have larger sebaceous follicles than those without acne (Ref. 3). Studies have shown a correlation between the severity of acne (as measured by the degree of inflammation) and the rate of sebum excretion (Refs. 4, 5, and 6). In general, from the studies one can conclude that people with acne produce more sebum than those without acne.

Kligman and Katz (Ref. 7) conducted tests on the ears of albino rabbits and demonstrated that sebum can induce comedones. The components of sebum that have been shown to be most comedogenic are squalene and free fatty acids (Ref. 8). Because subjects with acne produce more sebum than subjects with no acne (controls), it is possible that excessive sebum production is the initiating event in comedogenesis. Research has been done on changes that apparently involve increased turnover of the cells that are shed into the canal of the follicle (Ref. 9). The resulting increased cohesiveness of the cells could explain the formation of a comedo. Although the factors involved in the initiation of this abnormality are not entirely known, one factor appears to be sebum.

Because the sebaceous gland is clearly an androgen-sensitive organ, several investigators have searched for differences in circulating levels of testosterone in acne patients. These

studies showed no significant differences in testosterone in males with or without acne and suggest that females with acne may have somewhat elevated levels (Refs. 10, 11, and 12). However, these studies were conducted when there were no techniques for assessing free versus bound testosterone, and little attention was paid to the possibility of excessive production of adrenal androgens.

Lee's studies (Ref. 13) offer another possibility. In a small group of patients, those who developed acne demonstrated an early onset of testosterone production, suggesting that a "hormone abnormality" may exist. The current evidence favors the conclusion that acne patients do not suffer from exessive production of androgens, but have a hypersensitivity of the end-organ sebaceous gland to normal circulating levels of androgens (Ref. 14).

Certain species of microorganisms including *Staphylococcus, Propionibacterium acnes (P. acnes),* and *Pityrosporum* produce lipases (fat-splitting enzymes). These microorganisms live on the surface of the skin and in the horny layer. They also accumulate in the sebum within the opening and the neck of the sebaceous follicles. *P. acnes* appears to be the most important of these microorganisms in the development of acne (Refs.15 and 16).

P. acnes produces cellular products other than lipases which may play some part in the pathogenesis of acne. These products include esterases, proteases, and hyaluronidase. However, the action of lipases is best known. The bacteria produce lipases. The lipases break down triglycerides contained in the sebum into free fatty acids and glycerol, which the bacteria may then use as nutrients. Some researchers believe that the free fatty acids are the irritating, inflammatory, and comedogenic components of sebum (Refs. 8 and 16).

The evidence implicating *P. acnes* in the pathogenesis of inflammation includes the following:

(1) Increasing numbers of *P. acnes* are seen at the light and electron microscopic level with the onset of abnormal keratinization characteristics of acne (Refs. 17 and 18).

(2) Significantly higher densities of *P. acnes* are recoverable from the skin of teenage acne patients than from age-matched controls (Ref. 19).

(3) Successful suppression of *P. acnes* by systemic or topical antibiotics or antimicrobials is accompanied by clinical improvement (Refs. 16 and 20).

(4) *P. acnes* antibody titers tend to parallel the clinical severity of acne (Ref. 21).

(5) Intradermal injection of *P. acnes* produces intense inflammation in subjects with acne and minimal reactions in control subjects who do not have acne (Ref. 22).

(6) Injection of *P. acnes* attracts polymorphonuclear leukocytes to the follicle and results in the release of hydrolase (Ref. 23).

The significance of free fatty acids has been questioned because of the minimal inflammation which develops after a single intradermal injection of amounts of fatty acid comparable to those found in single sebaceous follicles. However, repeated intradermal injections through ruptured follicles can reasonably be expected to contribute to the inflammatory response (Ref. 9).

Some studies suggest that free fatty acids are not the only inflammatory agents in acne. According to Puhvel and Sakamoto (Ref. 22), "the effect of antibiotics in acne is more likely to depend on direct suppression of *P. acnes* as inflammatory agents rather than on indirect reduction of intrafollicular lipase, as the free fatty acid theory of acne therapy had previously supposed."

It is thought that *P. acnes* produces substances that are chemotactic for polymorphonuclear leukocytes (Ref. 24). Chemotactic refers to inducing movement of cells or organisms.

These authors also found that accumulations of polymorphonuclear leukocytes along the periphery of the walls of closed comedones may be the first change marking the transition from noninflamed lesions into inflammatory ones. Furthermore, lipids within comedones have demonstrated chemotactic activity for polymorphonuclear leukocytes (Ref. 24).

More recent studies by the same authors have demonstrated differences in the cytotactic activity of the same microbial strain grown in different media. This varied movement and arrangement, called cytotaxis, may explain why comedones may differ in inflammatory potential (Ref. 25).

Another possible triggering or aggravating factor in acne that should be mentioned is stress. Shalita (Ref. 8) reported that acne becomes worse in many people during times of emotional stress. However, controlled studies to support this view are lacking because of the difficulty in designing studies that can accurately measure these effects.

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E. Classifying the Severity of Acne

The lack of an internationally accepted method of classifying or grading the severity of acne has long been a source of confusion and controversy. For many years, morphologists had classified skin disorders according to the predominant lesion. With acne the lesions included comedones, papules, pustules, and nodules. But simply using these words served little purpose except to indicate the extent of the disease process. Consequently, dermatologists have established many different systems in an attempt to classify acne (Ref. 1). The biggest problem with so many different systems is that data originating in different places cannot be easily compared because the criteria may differ widely (Ref. 2).

One classification system has evolved that grades acne according to the number of lesions. For example, Grade I comedonal acne would be defined as less than 10 comedones on one side of the face (Ref. 2). Acne is often classified by using the terms "mild," "moderate," or "severe." Acne that is primarily comedonal is considered mild; papular and pustular, moderate; and nodular, severe (Ref. 2).

Frank (Ref. 3) classified acne into seven types but using no grading scale. Examples of these types are noninflammatory comedonal acne, inflammatory comedonal acne, and mild papular acne of early adolescence.

Recently a clinical system was devised that uses photographic standards to grade acne on a scale of 0 to 8 (Ref. 4).

Another system, the Pillsbury grading scale, is described here in some detail because it has been widely used by dermatologists. Many studies described later in this document have used this system of classification. Pillsbury (Ref. 5) developed a method of classifying acne by using Roman numerals to grade the severity of the condition. The scale begins with Grade I acne, the mildest type, and ends with Grade IV acne, which is most severe and requires the most aggressive treatment plan. This grading scale is used primarily for acne vulgaris. Other types of acne are generally not graded.

In Grade I acne, comedones are the main lesions with only an occasional small, inflamed pustule. In Grade II acne the inflammatory state becomes more evident. Papules and pustules are more numerous than in Grade I, but the lesions generally remain confined to the face. Grade III acne is a moderately servere acne manifested by numerous small pustules and an occasional larger lesion and usually affects the upper shoulders, back, and chest as well as the face. Grade IV acne is the most severe and is usually called acne conglobata (Ref. 5). (For more details on acne conglobata, see part II. paragraph C.1.b. above—Acne conglobata.)

One problem with Pillsbury's classification is that it does not take into account the number of acne lesions. Most dermatologists would consider a person with hundreds on comedones as having a more severe case of acne compared to an individual with only three or four pustules. Using Pillsbury's classification, the person with the comedones would be considered as having a less severe case of acne. For this reason, other systems of classification have been developed.

Because of the numerous classification systems that have evolved and the various types of lesions present in acne, the Panel believes it is essential that the system used for grading acne in clinical trials be clearly defined.

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F. Treatment of Acne

Acne cannot be cured, but it can be treated successfully. The Panel believes that more than three-fourths of the people suffering from acne can be effectively treated, with visible improvement even in the most severe case. However, treatment may be long and costly in severe cases because many effective medications are available only by prescription and require a physician's supervision. Treatment must be adapted to the individual because no single ideal treatment exists for all types of acne.

Dermatologists generally believe that early treatment can reduce the severity of the disease and, to some degree, also reduce scarring. Nevertheless, many people with severe acne do not see a doctor because they believe there is no satisfactory treatment available or because they cannot afford prescription treatment. Conversely, dermatologists sometimes see patients who are convinced they have acne even though it is barely visible or almost nonexistent.

There is no evidence that any treatment program prevents the onset of acne. However, the Panel believes that the aim of acne therapy is not only to clear up existing acne lesions but also to prevent the formation of new acne lesions. Clinical studies show that individual papules and pustules will resolve without treatment within 14 days (Refs. 1 and 2). Studies reviewed by the Panel have used a conservative estimate of 4 weeks as the natural resolution time of acne pimples (Ref. 3). Using this estimate, any acne therapy that significantly reduces lesion counts over the first 4 weeks of treatment is effective in treating existing lesions. Any treatment that continues to reduce lesion counts beyond 4 weeks is actually preventing the development of new acne lesions. A person who has not been treated for acne will have a natural cyclical rise and fall in the number of acne lesions over this time period.

The Panel has reviewed several studies showing that both benzoyl peroxide and sulfur reduce lesion counts over 8 to 12 weeks. (See part III. paragraph A.1.a. below—Benzoyl peroxide and part III. paragraph A.1.b. below—Sulfur.) The Panel concludes that any ingredient that is shown to be effective in treating acne, by reducing lesion counts over at least 8 weeks, will

also be effective in preventing the development of new acne lesions.

The effect of both mild and severe acne can be significant. The active lesions and resulting scarring may produce emotional distress and social withdrawal. Adolescents suffering from acne may have a particularly difficult time because they are trying to cope with other physical and emotional changes along with the added problem of acne. Cohen and Nadelson (Ref. 4) wrote the following on this subject.

> Physicians are often perplexed by the adolescent's paradoxical behavior. The child who appears most preoccupied with his skin may manipulate his lesions, disregard sensible personal hygiene, or apply harmful medication, in spite of his physician's instructions. At other times, he may impose on himself ascetic, and equally self-destructive, programs of abstinence from foods, overzealous washing, or overuse of prescribed medication. These extremes are at times related to the normal drives in adolescence, painfully magnified by the skin disease. Also, just as eczema may deflect parental attention from other family problems, the child with acne may use his blemishes as an excuse for avoiding social situations which arouse anxiety.

Some of the various available treatments (OTC and prescription) are as follows:

1. *Topical OTC products.*

a. Benzoyl peroxide 2.5 to 10 percent.

b. Salicylic acid 0.5 to 5 percent.

c. Abrasives—soaps, granules; epidermabrasion—polyester fiber sponges.

d. Sulfur-resorcinol combinations.

e. Sulfurated lime topical solution (Vleminckx' solution).

f. Sulfur 3 to 10 percent.

g. Povidone-iodine 7.5 percent.

2. *Topical prescription products.*

a. Benzoyl peroxide 2.5 to 10 percent.

b. Tretinoin (vitamin A acid) 0.05 to 0.1 percent

c. Antibiotics—clindamycin, erythromycin, tetracycline.

d. Aluminum chloride 6.25 percent.

e. Benzoyl peroxide and sulfur combinations.

3. *Systemic prescription products.*

a. Antibiotics by mouth (tetracycline, erythromycin, minocycline).

b. Corticosteroids.

c. Estrogens.

d. Investigational drugs, including 13-cis-retinoic acid and cimetidine.

4. *Local therapies.*

a. Cryotherapy, carbon dioxide solid or slush, liquid nitrogen.

b. Acne surgery, especially for comedones.

c. Intralesional steroids for cysts.

d. Dermabrasion.

e. Fibrin injections for scars.

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G. Use of Oral Zinc in the Treatment of Acne

Although oral zinc was not submitted to the Panel for review, the Panel chose to include a discussion of this ingredient because of its increasing popularity and current availability as an OTC medication in pharmacies and health food stores. The Panel did not include oral zinc under the ingredient statements in this document because the Panel's review was officially limited to topical products. However, the Panel considered it appropriate to bring this use of oral zinc to the agency's attention.

Zinc is a trace element with an atomic weight of 65.38; thus zinc sulfate 220 milligrams (mg) corresponds to 50 mg elemental zinc (Zn^{++}). It is an essential nutrient required by animals and humans. The recommended dietary allowance is set at 15 mg and can be supplied by dietary solids containing 25 parts per million (ppm) (Ref. 1).

The rate at which zinc is absorbed from the small intestine is influenced by the level of zinc in the blood. There is a wide margin of safety between the required intake and the toxic dose. Laboratory animals can tolerate up to 2,000 ppm in the diet. Above this level, growth depression and anemia result. The anemia appears to result from an induced copper deficiency, but the growth depression results from reduced food intake (Ref. 2). Toxic levels must be defined cautiously because the levels of other metals greatly influence zinc toxicity. For instance, if copper is present in a limited concentration, zinc is toxic at lower levels. The effects of zinc on copper and iron metabolism can be found in a review of metal toxicities (Ref. 3). Zinc does not appear to accumulate when administered orally (Ref. 2).

The maximum recommended dose for zinc deficiency is 220 mg zinc sulfate three times daily. Nausea may be a problem, but it may be avoided by taking zinc sulfate in capsules after meals (Ref. 4). The emetic dose of zinc sulfate is 1 to 2 grams (g) or 225 to 450 mg zinc. The usual symptoms of toxicity are fever, nausea, vomiting, stomach cramps, and diarrhea (Ref. 2). An adult died from an oral dose of 28 g zinc sulfate (Ref. 5).

Zinc sulfate has been administered therapeutically for leg ulcers and acne in oral doses of 200 mg taken three times daily. This regimen generally caused the serum zinc level to increase by about 25 to 30 percent above the normal range of 70 to 125 micrograms per 100 milliliters (μg/100 mL). The serum level reached a plateau within 10 weeks (Refs. 6 and 7).

A 4-month study of 27 patients (ref. 8) and a 3-month study of 21 patients (Ref. 9) showed no adverse effects from the use of oral zinc. Greaves and Skillen (Ref. 10), however, reported nausea in 3 out of 18 patients in a 4-month study, but hematology studies were normal.

Weimer et al. (Ref. 11) conducted a 12-week study on 28 patients and noted that half of the patients receiving 220 mg zinc sulfate had nausea, vomiting, or diarrhea. Six of these patients could not tolerate the nausea and had to withdraw from the study. In another 12-week study, 5 out of 20 patients reported side effects after treatment with 200 mg zinc sulfate (Ref. 12).

There are reports of gastric bleeding after the ingestion of zinc sulfate monohydrate capsules (Refs. 13 and 14). These studies suggest that the salt form may be an important factor. The studies described earlier, in which no ill effects were reported, used the heptahydrate (citrate) salt dissloved in water (effervescent dosage form) before ingestion.

Zinc oxide ointment has been used extensively without adverse effects (Ref. 2). Considering the poor absorption of metals from the skin, topical use of zinc salts can be considered safe. However, ingesting amounts higher than the recommended dietary allowance may cause adverse effects and should not be encouraged unless supervised by a physician. Furthermore, the consequences of long-term administration of zinc salts are unknown.

Metabolically, zinc is important in many essential enzyme systems, in protein synthesis, and in the stabliization of membranes and macromolecules. Zinc depletion has been observed in malnutrition and malabsorption states. It may also be induced by diets that depend on food grown in soil that is poor in minerals (Ref. 4). In the skin, zinc deficiency has been associated with poor wound healing (Ref. 15), inflammation of the skin of the hands or feet (Ref. 16), and acrodermatitis enteropathica, a severe

gastrointestinal and skin disease of early childhood (Ref. 17). The relationship between acne and zinc deficiency remains uncertain (Ref. 18).

A possible connection between zinc deficiency and acne vulgaris was observed in a patient with acne and acrodermatitis enteropathica. When this patient was treated with oral zinc, the acne cleared "almost completely" (Ref. 19).

Baer et al. (Ref. 20) reported that a zinc depletion diet (0.2 mg elemental zinc daily) in six young men resulted in the development of acne in four of the men. An acute exacerbation of cystic acne developed in one man after 22 days of zinc depletion, when his serum zinc level had decreased from 78 to 28 μg per 100 mL. Most of the acne lesions disappeared within 4 days of restarting 44 mg elemental zinc (as zinc sulfate) in the diet. Milder acne appeared in other subjects who were on the zinc-depletion diet, but whose serum zinc levels remained normal. The researchers believed that serum zinc levels probably did not reflect the tissue zinc levels of these patients in the early stages of zinc depletion.

This echoed the feeling of Fitzherbert (Ref. 21), who postulated that acne might be associated with deficiencies of zinc not detectable in serum, and that plasma zinc levels were "of little use in assessing whether anyone with acne vulgaris can benefit from zinc replacement therapy." Fitzherbert suggested that zinc levels in hair would be a more accurate method of investigating zinc levels in the skin. He also pointed out that zinc deficiency in rats produces abnormal keratinization of skin and hypertrophy of sebaceous gland cells, causing the sebaceous glands to become more prominent. He further postulated that reversal of these histopathological changes might require administration of daily zinc over periods of 3 to 4 months or longer (Ref. 22). Fitzherbert suggested a dosage of zinc sulfate of 100 mg/day to be taken by teenagers at night, to meet their daily requirement of zinc (Ref. 23).

Several double-blind, controlled studies comparing oral zinc to other medications in the treatment of acne have had conflicting results. Michaelsson, Juhlin, and Ljunghall (Ref. 24) compared oral zinc sulfate 200 mg with oral tetracycline, a well-accepted drug in the treatment of acne, in a 12-week study. No difference was seen between the two drugs in 37 patients with moderate and severe acne. The acne score of each group of patients decreased an average of 70 percent. Serum zinc levels were measured before treatment and after 12 weeks of treatment. There was no correlation between serum zinc levels and clinical response. Although the investigators felt that zinc was more effective than oral tetracycline in treating papular and pustular acne and less effective on comedones, this was not confirmed statistically.

In 64 patients, the same group of investigators also compared the effects of effervescent tablets of zinc sulfate 200 mg three times daily, with placebo, vitamin A 300,000 to 400,000 Internationl Units per day (I.U./day), or a combination of the same doses of zinc and vitamin A (Ref. 19).

After 12 weeks of treatment the total "acne score" in patients treated with zinc was reduced from 100 percent to 13 percent. The pustules and papules had disappeared in most patients after 8 to 12 weeks, and comedones had decreased to 44 percent. The improvement was about the same in patients given zinc and vitamin A. After only 4 weeks of treatment, the two groups receiving zinc showed a mean decrease of 100 percent to 35 percent, but the placebo and vitamin A groups only decreased from 100 percent to 75 percent and 70 percent, respectively. Then zinc was added to the treatment of all but two patients in both the placebo and vitamin A groups. The researchers switched the medication for "ethical" reasons, based on their belief that most patients' acne improved within 4 weeks and that they could not justify placebo treatment for longer than 4 weeks. Their study was later criticized for this position (Ref. 25). The authors concluded that the effect of zinc plus vitamin A was no better than treatment with zinc alone (Ref. 19).

Goransson, Liden, and Odsell (Ref. 26) conducted a randomized, double-blind investigation of 200 mg oral zinc sulfate three times daily versus effervescent placebo tablets in 54 patients with acne. The trial was performed between October and the end of April to minimize natural ultraviolet radiation and included a 6-week active treatment period. Patients were examined and photographed before treatment, after 3 weeks of treatment, and again 6 weeks after treatment. Each type of lesion was counted and multiplied by a "severity index," so that the sums of all lesion types yielded a score of overall "acne load." After both zinc and placebo treatment, a statistically significant reduction in numbers of lesions was evident. Lesion reduction continued during both the first and second 3-week treatment periods in the zinc treatment group, but no statistically significant reduction occurred in the placebo group after the first 3 weeks of treatment. Zinc sulfate therapy was statistically significantly better than placebo, when patients showing 25 percent improvement were compared ($p<0.01$). No statistically significant difference was found when the patients in each group who showed 50 percent improvement were compared.

Overall, the authors concluded that the acne improved "about one-third" after 6 weeks of treatment with zinc. They speculated that the treatment period was probably not long enough to see the full effect of zinc therapy, and that a trial period of 3 months would have been more desirable. According to Fitzherbert (Ref. 23), even 12 weeks is too short a time to see maximal biological changes induced by zinc, as structural changes in the swollen hypertrophic cells of sebaceous glands are only slowly reversed.

A randomized, double-blind trial of 39 patients showed that zinc was not superior to placebo in the treatment of acne (Ref. 12). Patients with papular and pustular acne were given either oral zinc sulfate effervescent tablets 200 mg three times daily or placebo effervescent tablets. Only 25 patients were treated for 12 weeks; the remaining 14 were treated for either 4 or 8 weeks. There was a significant reduction in papules and pustules in both groups, but no statistically significant difference between the groups. Serum zinc levels, which were originally normal in both groups, rose considerably in both groups, although the increase in the zinc group was significantly higher than the placebo group. The researchers thought that the increased zinc levels were possibly caused by seasonal variations in zinc metabolism. They concluded that the negative therapeutic results might have been attributed to the small number of patients or to natural seasonal improvement in acne, as the study was conducted in the spring.

Another double-blind study compared zinc sulfate monohydrate capusles (137 mg three times daily) to placebo (Ref. 7). The use of the monohydrate salt was unique to this study and accounts for the lower dosage. Twelve patients were included in the active treatment group and 10 patients in the placebo group. Patients were evaluated by lesion counts. After 8 weeks of treatment, both groups had decreases in the mean values of papules, pustules, and closed comedones; open comedones remained about the same in the zinc group. No statistically significant differences were seen between the groups in any type of acne lesion. Positive zinc absorption was well documented by rises in zinc levels in serum and urine. The

investigators speculated that the divergent results in their study might have reflected differences in characteristics of their patient population.

In a randomized, double-blind trial involving 40 patients, zinc sulfate capsules (220 mg three times daily) were compared with placebo (Ref. 11). During the 12-week treatment period, patients were seen at 0, 2, 4, 6, 8, and 12 weeks and evaluated with lesion counts. After 12 weeks there was a 37-percent decrease in the pustule counts of the group receiving zinc compared to no change in the placebo group. Comedones and papules decreased 47 percent in the zinc group compared to 37 to 38 percent in the placebo group. This difference was not significant. The researchers concluded that zinc "Appeared to have a slightly beneficial effect on pustules after at least 6 weeks of treatment" but was not helpful for comedones or papules.

From these studies zinc appears to be valuable in the treatment of papular and pustular acne. However, the Panel is concerned that there seems to be unexplained wide variation in the results of double-blind studies with zinc conducted in different geographical areas. Investigators in Sweden believe that zinc is valuable in the treatment of acne (Refs. 19, 24, and 26), but investigators in Denmark (Ref. 12) and the United States (Refs. 7 and 11) remain unconvinced of its efficacy. In general, the Swedish studies, done by three different groups of investigators, involved larger numbers of patients than the other studies and the use of an effervescent dosage form. These patients, because they had fewer gastrointestinal side effects, also appeared to tolerate the zinc better than other groups of patients. The contrasting results between studies from various countries suggest to the Panel that environmental factors such as seasonal variation in ultraviolet light exposure, the amount of zinc in the natural diet, and the dosage form may have influenced the studies.

The Panel concludes that more double-blind, controlled trials could be useful in establishing the effectiveness of zinc sulfate in treating acne. As stated earlier, the Panel is not recommending the OTC use of oral zinc in the treatment of acne, but has included it in this document only for discussion.

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H. Abrasive Scrubs

The Panel realizes that some consumers may prefer acne products that are formulated as abrasive scrubs. For this reason, even though the Panel believes it unlikely that superficial epidermabrasion will remove the tightly adherent comedo, the Panel has included the following discussion on physical abradents.

Saperstein (Ref. 1) reported on a 10-year study of 1,000 acne patients who were treated with abrasives along with other forms of topical and systemic treatment for acne. Saperstein found that fused synthetic aluminum oxide in a soap paste was the most effective abradent of all that were tested. However, no lesion counts were included in this report. According to this researcher, the purpose of epidermabrasion is to keep the sebum washed off the skin and to keep the pores open. Saperstein noted that during this treatment the patients stopped picking and squeezing their acne lesions, "for the abrasion routine apparently replaces the emotional need to scrutinize and express each lesion."

Mills and Kligman (Ref. 2) also studied abrasives for the treatment of acne. They wrote that abrasives "are popular with patients, possibly because the patient is lead (sic) to believe that conscientious scrubbing will clean out 'clogged pores' and that his deliverance is therefore in his own hands." These researchers studied five abradents including one containing aluminum oxide and one containing polyethylene granules to see whether they were effective in helping to remove comedones. Each test group consisted of 10 patients with "moderate acne and conspicuous comedones." Treatment was twice daily for 8 weeks; no other medication was used during this time. Global clinical assessments were done biweekly. Lesion counts were taken before the study and at the end of the study. Mills and Kligman found that "none of the test materials had a clinically significant effect in eliminating comedones." Open comedones were reduced no more than 20 percent; closed comedones were not reduced at all.

Early in the study, all of the treatments reduced the number of papules and pustules to some extent, but in some patients the reduction was followed by an increase in the number of papules and pustules.

Mills and Kligman (Ref. 2) concluded that there was no evidence showing that abradents could effectively remove comedones. They stated that, because skin affected by acne is vulnerable to chemical and physical trauma, they "do not advise the use of abradents as adjuncts in acne treatment."

An unpublished report discussed a half-face study in which 53 subjects were treated either with a combination of polyethylene, 2 percent sulfur, and 1.5 percent salicylic acid or a combination of sulfur and salicylic acid without polyethylene (Ref. 3). Both treatments significantly decreased open comedones, closed comedones, and papules. However, neither formulation decreased pustules significantly over baseline. There was no difference in the results between the combination with polyethylene and the one without polyethylene.

The Panel concludes that aluminum oxide and polyethylene do not have an effect on acne lesions and therefore considers them inactive ingredients.

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I. Evaluation of Safety and Effectiveness

1. *Criteria for evaluating safety.* The Panel has developed flexible criteria for assessing the safety of the many chemical agents used in acne treatment products. This flexibility was needed to accommodate the differences between chemical agents. It should be noted that although some data did not meet all of these criteria, the Panel considered other assessments adequate to allow a safety evaluation for a particular ingredient. Some products had been marketed long before this review began. The Panel's evaluation in those instances was based on limited historical data, new data obtained from various sources, and the Panel's own knowledge and judgment.

Influencing factors in the data assessment were the surface area and the site of application, the frequency and length of application, and the vehicle. The degree of occlusion from clothing was also considered because acne may affect the upper torso as well as the face. The Panel also recognizes that because of acne the stratum corneum may not be intact and inflammation may be severe. These conditions could greatly influence the degree of absorption through the skin.

To avoid needless repetition, these safety evaluation criteria are detailed later in this document. (See part III. paragraph E.1. below—Safety guidelines.)

After the Panel evaluated the safety of an ingredient, it placed that ingredient in Category I, II, or III. When an ingredient was classified Category III for safety, the Panel concluded that the data base was inadequate to fully assess safety. In these cases the safety guidelines discussed below could be used by a manufacturer to move an ingredient from Category III to Category I by generating data where there are none or where existing data are inadequate.

The actual criteria for the movement to Category I are obviously judgmental and have to be examined in their totality. Although in such cases a benefit-to-risk concept may seem desirable, the Panel attempted to assess safety per se rather than by benefit-to-risk.

The Panel is concerned about the safety of certain ingredients or combinations of ingredients when the single ingredient or combination product has a keratolytic or "peeling" effect on the skin. It has long been known that the stratum corneum protects underlying skin areas against irritants and damage from ultraviolet radiation. Research on the effect of reducing the thickness of the stratum corneum by the use of keratolytic agents has not resolved the Panel's concerns, particularly on absorption, irritation, sensitization, or the possibility of carcinoma from exposure to ultraviolet light.

2. *Criteria for evaluating effectiveness.* The Panel required each ingredient to have at least one well-designed clinical trial demonstrating its effectiveness in the treatment of acne in order to be classified as Category I. In evaluating data, the Panel also considered the study design and how it conformed to the following description of a well-designed trial.

The trial should be a multi-center study involving more than one investigator using the same protocol in different geographic locations, thus helping to eliminate geographic influence and investigator bias. The trial should be double-blind, i.e., the investigators and patients should not know the identity of the drugs. The drugs should be randomly assigned. The trial should also be controlled, with the control being the vehicle minus the active ingredient or ingredients. The vehicle may be modified or altered if needed to ensure blinding. No additional treatment other than soap and water should be allowed. The investigators should state which calendar months were included in the study because acne lesions generally clear up somewhat in the summer. A well-designed study should last at least 8 to 12 weeks. Patients should be evaluated once before treatment and at least twice during the study, including the final examination.

The Panel preferred lesion counts, grouped by type of lesion, as a method of evaluating acne ingredients. A lesion count is usually taken before treatment, during treatment, and after treatment. The final results show the percentage of reduction in the number of each type of lesion after treatment, compared to before treatment. Global assessments were also considered acceptable as long as they were on a numbered scale (such as 1 to 6) with a rigidly defined numerical system that could be reliably reproduced.

Active ingredients should be significantly more effective in reducing lesion count than the vehicle. Results should be statistically analyzed.

Studies that showed a statistically significant decrease in free fatty acid content or sebum excretion rate as proof of effectiveness were not acceptable as sole evidence of effectiveness. Studies in induced or experimental acne were similarly not considered as proof of effectiveness. The Panel did not evaluate adjunctive therapies. An ingredient was not considered unless it actually treated acne, i.e., actually reduced lesion count. The Panel did not consider ingredients that reduce inflammation but do not act on the comedone, such as, topical steroids.

If a clinical trial did not meet all of the Panel's criteria, some other supporting evidence was necessary to place an ingredient in Category I. However, the Panel did not intend to be too rigid in setting up criteria for proof of effectiveness. The Panel recognized that not all studies would meet each criterion for a single "best study." Each submission and ingredient was analyzed according to the above criteria, but the final categorization depended upon the total information available at the time.

Ingredients were placed in Category II if there was no rational explanation of their mode of action, no substantial scientific evidence to suggest effectiveness, no general acceptance by the consultant "acne experts," and no supportive evidence of effectiveness in

the medical literature on acne. All of these factors were considered in the Panel's decision on final categorization. The ultimate decision did not rest on any single one of them but on the Panel's general recognition of effectiveness of the ingredient.

3. *Vehicles.* The Panel believes that a proper vehicle is one that will deliver the drug to the site of action at a rate that will allow maximum benefit without causing or allowing toxic effects. However, the Panel recognizes that choosing an appropriate vehicle for adquate drug delivery without contributing to the whole acne problem can be quite difficult. Many drug delivery systems are used today in OTC preparations, ranging from solutions, gels, lotions, and creams, to solid sticks, mascara-like creams, and cosmetic touch-up type formulations. The Panel was unable to accurately assess the influence of such a variety of vehicles on the effectiveness of the therapeutic ingredient.

III. Acne Drug Products

A. Category I Conditions

These are conditions under which OTC acne drug products 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.**

1. *Category I active ingredients.*

Benzoyl peroxide
Sulfur

a. *Benzoyl peroxide.* The Panel concludes that benzoyl peroxide is safe and effective for OTC topical use in the treatment of acne.

(1) *Safety.* The stability of a given preparation of benzoyl peroxide is especially dependent upon the vehicle (Ref. 1). The potential for irritation or other toxic manifestations are undoubtedly affected by stability.

The intraperitoneal LD_{50} of benzoyl peroxide in mice has been reported to be from 75 to 210 milligrams per kilogram (mg/kg) (Refs. 2 through 5). Because most deaths following intraperitoneal administration occur after 24 hours, it is important to note that the 75-mg/kg value was calculated after a 7-day observation (Ref. 2). Several factors may account for differences in the LD_{50} values reported, including vehicle, the length of observation, and the strain of mouse. One study reported the intraperitoneal LD_{50} in mice as 17.1 plus or minus 2.1 micromoles (μmol) or 180 mg/kg per mouse. According to this study, 26 μmol per mouse will result in 100 percent mortality (Ref. 4).

Although benzoyl peroxide is much less toxic orally than intraperitoneally, death occurs faster by the oral route following a lethal dose. To illustrate, the oral LD_{50} in mice in one study was reported as 2,127 mg/kg, but a lethal oral dose caused central nervous system depression and death within hours (Ref. 5). Following oral administration to Swiss mice (7-day observation), an LD_{50} or 1.4 g/kg was calculated (Ref. 6). The animals were lethargic and prostrate, and exhibited labored respiration prior to death.

In another study a lotion containing 10 percent benzoyl peroxide was administered orally to male rats at a dose of 3 g/kg. During the following 2-week observation period there were no deaths. No effects on appearance, behavior, or weight gain were noted (Ref. 6). In rats the LD_{50} is reported as 373 mg/kg intraperitoneally and 6,400 mg/kg orally (Ref. 5).

The difference in intraperitoneal versus oral LD_{50} values suggests that orally administered benzoyl peroxide is not readily absorbed. In fact, the cause of death could be due to the metabolite benzoic acid because the oral LD_{50}'s of the two compounds are nearly identical in the mouse. There is, however, indirect evidence to suggest that benzoyl peroxide can be absorbed by the gut. Oral administration in mice produces central nervous system depression (Ref. 5), which is not characteristic of benzoic acid.

There is some evidence that benzoyl peroxide can be absorbed following dermal application to guinea pigs. When benzoyl peroxide was applied to the shaved backs of guinea pigs at doses up to 1 g/kg and occluded for 24 hours, a dose-related weight loss was observed (Ref. 7). This was probably an effect of the metabolite rather than the parent compound.

Holzmann, Morsches, and Benes (Ref. 8) reported the plasma levels at benzoic acid in 20 patients on benzoyl peroxide therapy. The level peaked 3 days after application of 20 percent benzoyl peroxide lotion and was never higher than 610 micrograms per liter (μg/L). These investigators measured benzoic acid on the assumption that benzoyl peroxide itself does not penetrate the skin.

Two other studies also suggest that benzoyl peroxide does not penetrate the skin. One study consisted of applying benzoyl peroxide to human forearms, waiting 4 hours, then washing the arm with chloroform. Both benzoyl peroxide and benzoic acid were recovered in the chloroform wash in a ratio of 1.5 to 1, indicating conversion to benzoic acid(Ref. 9).

Nacht et al. (Refs. 10 and 11) reported on an in vitro study in which excised human skin was used to measure penetration of C^{14}-benzoyl peroxide. After 8 hours, 1.9 percent of the labeled drug was recovered as benzoic acid on the dermal side. Extraction from the skin itself yielded 2.6 percent of the labeled drug, half benzoyl peroxide and half benzoic acid.

These investigators also applied C^{14}-benzoyl peroxide to the forearms of monkeys and measured radioactivity in the urine. The output peaked between 6 and 30 hours. Forty-five percent of the administered dose was recovered, 98 percent of which was benzoate. Nacht et al. (Ref. 11) concluded that benzoyl peroxide penetrates the skin layers where it is converted to benzoic acid and then absorbed into the systemic circulation. They also concluded that benzoic acid was quickly eliminated through the kidneys without passing through the liver. In the liver, benzoic acid would have conjugated with glycine and formed hippuric acid, but no hippuric acid was recovered in the urine.

In a subchronic study in rats, benzoyl peroxide was administered intragastrically five times weekly for 3 months (Ref. 2). Two control groups of 10 animals, male and female, were used. One group was given the vehicle, 0.1 percent polysorbate 80; the other group was given 2 g/kg benzoic acid. Two other groups were treated with benzoyl peroxide. These groups consisted of 40 animals each, male and female, dosed with either 0.5 or 2 g/kg benzoyl peroxide. The benzoic acid-treated group was removed from the study after 1 week because most of the group developed aspiration pneumonia. During the experiment a hematologic evaluation was done monthly. Gross and histological examination of tissues was done at the end of 3 months.

The following signs were observed near the end of the experiment in the group that was given 2 g/kg benzoyl peroxide: poor appetite, weakness, weight loss (prominent in males), urinary incontinence, intermittent irritability, and transient twisting of the muscles. One striking patholgical change was bladder distension due to blockage of the urinary passage by cartilaginous material. Localized lymphangitis (inflammation of the lymph vessels) of the salivary gland was also noted. The urinary effect was most frequent in the high dose group, whereas the lymphagitis occurred in the control group as well. In the high dose group,

tubular destruction was noted in the kidneys.

Feeding studies were conducted in mice, rats, and dogs (Ref. 12 and 13). These studies used flour treated with benzoyl peroxide and are of little value, because benzoyl peroxide is converted to benzoic acid in flour (Ref. 12).

Benzoyl peroxide is not considered to be carcinogen (a cancer-producing substance). In one study in rats and mice, benzoyl peroxide was given orally, painted on the skin, or injected subcutaneously without evidence of carcinogenicity (Ref. 12). In another study, Swiss mice painted three times weekly with 100 mg benzoyl peroxide did not have a tumor index greater than the controls which had been painted with a solvent (Ref. 14). A report by Heuper (Ref. 15) further supports benzoyl peroxide's lack of carcinogencity.

Benzoyl peroxide was found to be negative in the dominant lethal assay in the mouse when tested at 62 mg/kg intraperitoneally (Ref. 16). The dominant lethal assay is a frequently used method of testing the effect of a chemical substance on spermatogenesis (the maturation of sperm). In another study, benzoyl peroxide was extensively screened for mutagenicity (Ref. 17). The screen consisted of three *Salmonella* mutants and one strain of yeast and was carried out with and without metabolic activation systems. A 0.37-percent concentration of benzoyl peroxide, the highest dose used in the mutagenicity tests, gave 50 percent survival of the test organisms. Results were clearly negative in all tested strains.

A number of subchronic studies have been conducted in rabbits using dermal application of benzoyl peroxide. In one of these, a 10-percent benzoyl peroxide gel was applied to the ears of four rabbits five times weekly for 2 weeks (Ref. 1). The observed irritation in the animals consisted of desquamation and erythema. None of the animals was visibly sick.

A 30-day controlled study was conducted on 16 rabbits, divided into two groups of 8 rabbits each (Ref. 18). The skin was abraded in four rabbits in each group. A lotion containing 5 percent benzoyl peroxide was applied to one group of rabbits five times weekly. The area of application was about 10 percent of the total body surface. Based on the information that 4 to 5 g of lotion was applied, the calculated dose averaged 98 mg/kg. No effects could be detected on body weight, hematology, organ weight, gross pathology, or histopathology. One treated rabbit died from respiratory infection before the end of the study.

A similar study was conducted for 43 days with both 5 and 10 percent benzoyl peroxide lotion (Ref. 6). A group consisted of five rabbits with half of the shaved area abraded on each animal. Based on estimated application, the two test doses were 120 and 240 mg/kg. No effects of benzoyl peroxide were detected other than some reddening of the skin, particularly following application of the 10-percent lotion.

A 12-week study using an ointment containing 10 percent benzoyl peroxide was conducted on rabbits of both sexes (Ref. 2). No adverse effects were noted. Another report contains results of a 3-month study in which 1.9 g of ointment was applied to rabbits five times a week (83 mg/kg estimated dose). The only adverse effect was a slight reddening of the skin during the first few weeks which lessened as the study progressed.

Primary skin irritation was assessed by patch tests on intact and abraded rabbit skin (Ref. 6). The exposure period was 4 hours, after which the reaction was graded immediately and at 24 and 48 hours. Slight erythema was noted only at 4 hours on 5 of 12 sites with 10 percent benzoyl peroxide and 3 of 12 sites with 5 percent benzoyl peroxide. Application of 5 or 10 percent benzoyl peroxide to rabbit eyes produced only a mild, transient erythema (Refs. 6 and 18).

Some irritation occurs when benzoyl peroxide is applied to human skin. This consists of mild burning and itching in most subjects and moderate drying and peeling in all subjects (Refs. 1, 2, and 18).

Complete hematological studies and urinalysis were conducted on 20 out of 147 patients following topical therapy with 5.5 percent benzoyl peroxide (Ref. 19). Results showed no evidence of systemic effects. Also, no sign of sensitivity was noted in any of the 147 patients treated with benzoyl peroxide.

The Panel is particularly interested in the cutaneous toxicity (irrigation and contact sensitization) of benzoyl peroxide on human skin. This is important because the effectiveness of benzoyl peroxide is partly due to its mild peeling action on the skin during the early phase of treatment, and peeling may enhance irritation and sensitization.

The sensitization of the skin to this ingredient is well known among physicians (Ref. 20). Sensitization may be related to the genetic makeup of the individual. Certain types of complexion are highly sensitive to environmental factors as well as topical drugs. People who have an atopic background (an inherited tendencey to develop allergy) and who have allergies will be more easily irritated by certain topical preparations. In general, the concentration of the medicine, the vehicle, and the degree of occlusion should be considered in determining sensitization rates. The skin type, individual immunologic background, and other variables should also be considered.

Repeated patch tests with benzoyl peroxide may produce an experimental contact dermatitis (Ref. 21). However, in clinical use sensitization is low, usually between 1 and 2 percent of users (Ref. 22).

Benzoyl peroxide will produce a primary irritant dermatitis in a person with sensitive skin. Light-complexioned individuals may be easily irritated by a benzoyl peroxide preparation as well as other medications. Skin dryness also makes skin vulnerable to irritations. It is well known to the Panel that skin type (ruddy compared with olive) relates to the ease with which the skin is irritated.

There is evidence that the higher the concentration of benzoyl peroxide, the greater the irritation. For that reason, ideally the lowest effective concentration of benzoyl peroxide should be used in the management of acne.

The Panel appreciates that an increase in concentration and the use of drying vehicles may produce more irritation and desquamation in some people but does not believe this represents a substantial hazard. The Panel concludes that benzoyl peroxide in concentrations of 2.5 to 10 percent is safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Benzoyl peroxide has antimicrobial properties attributed to its capacity to slowly release oxygen. The oxygen acts on certain kinds of bacteria, called anaerobes, which do not live in its presence. *P. acnes* is an anaerobic bacteria.

Another action of benzoyl peroxide is as an exfoliant, i.e., it causes peeling of the outer layers of the skin. Benzoyl peroxide is formed by the reaction of alkaline sodium hydrogen peroxide with benzoyl chloride in water. Benzoyl peroxide has been used since the 1920's for ulcers and burns. Concentrations of benzoyl peroxide in submissions reviewed by the Panel ranged from 2.5 to 10 percent.

The mechanism of action of benzoyl peroxide was studied by using a 5-percent benzoyl peroxide gel applied twice daily. This preparation was associated with a significant depression of the surface bacterial count and a decrease in the concentration of fatty acid formation. The researchers

theorized that the antibacterial activity of benzoyl peroxide reduced the population of *C. acnes (P. acnes)* with a subsequent decrease in free fatty acids. The investigators also believed that benzoyl peroxide is a mild keratolytic, but this was not firmly established (Ref. 23). Although benzoyl peroxide has antibacterial activity, none of the antibacterial studies on this ingredient have met the Panel's in vivo criteria. (See part III. paragraph E.2.c. below—In vivo testing of acne ingredients.)

Vasarinsh (Ref. 24) studied the effects of 5 percent and 10 percent benzoyl peroxide lotions on epidermis and dermis. He was unable to find any microscopic epidermal changes when there was no peeling. Biopsies showed that dermal changes, however, were common in all patients regardless of whether they had clinical signs of erythema and desquamation. These changes mainly consisted of mild dilatation (expansion) of the blood vessels in the upper portions of the dermis and lymphocytes (white blood cells) surrounding the blood vessels, the hair follicles, and the small lobules of the sebaceous glands. Vasarinsh was unable to quantify any keratolytic effect.

Ede (Ref. 19) studied the effectiveness of 5.5 percent benzoyl peroxide in a randomized, controlled, double-blind trial of 196 patients. Patients who entered the study had Grade II or III acne (system of classification unspecified). Four treatment groups were used. One group consisted of 48 patients treated with 5.5 pecent benzoyl peroxide. Another group consisted of 54 patients treated with 5.5 percent benzoyl peroxide-0.25 percent chlorhyaroxyquinoline. In the third group, 45 patients were treated with 5.5 percent benzoyl peroxide-0.25 percent chlorhyaroxyquinoline-0.5 percent hydrocortisone. In the fourth group, 49 patients were treated with the vehicle as a control.

Frequency of application varied from one to four times daily depending upon "therapeutic response and upon the extent of skin peeling and erythema." At least one of the daily applications was made under direct medical supervision. The patients used soap before each application, but no other therapy was allowed. They were evaluated by lesion counts at 0, 14, and 28 days. Statistical analysis showed no statistically significant differences in the number of patients in the groups or in the distribution of patients with regard to sex, age, complexion, skin type (normal, dry, oily), pores, (normal or enlarged), grade of acne, or frequency of application.

After 4 weeks of treatment, the lesion count of patients treated with benzoyl peroxide alone decreased from 10.5 to 6.6. The count increased in the vehicle group from 10.4 to 11.1. Statistical analysis of results showed that all three active treatments were significantly more effective than the vehicle in reducing lesion counts at 2 and 4 weeks ($p<0.001$).

Clinical evaluation showed that 65 percent of the patients treated with benzoyl peroxide improved; 29 percent remained the same; and 6 percent were worse. In the vehicle group, 33 percent improved; 37 percent were the same; and 30 percent became worse. Benzoyl peroxide (along and in combination) was found to be significantly more effective than vehicle when overall clinical response was evaluated.

In another double-blind, controlled, randomized study, 28 patients were treated with 5 percent benzoyl peroxide lotion, and 27 patients were treated with the vehicle used as a control (Ref. 25). Patients entered the study only if they had Grade II or III acne based on Pillsbury's classification (Ref. 26). Patients were treated two or three times daily depending upon the evaluator's initial appraisal of the severity of the acne. Comparison of the makeup of the groups showed no significant differences between age, sex, frequency of therapy, or severity of acne.

Patients were evaluated by lesion counts and global impressions before treatment and after 6 weeks of treatment. The benzoyl peroxide group had a 39.7-percent improvement in lesion counts compared to 7.7 percent improvement for the vehicle group. This difference was statistically significant ($p<0.001$). The investigator rated 68 percent of the patients treated with benzoyl peroxide as excellent or good, 18 percent fair, and 14 percent poor at the conclusion of the study. In the vehicle group, no patients were rated as excellent or good; 30 percent were considered fair; and 70 percent poor. The investigator found treatment with benzoyl peroxide superior to vehicle when evaluated by global impression ($p<0.001$).

Another randomized, controlled, and double-blind study was done on 92 patients to determine the effectiveness of benzoyl peroxide (Ref. 27). Patients were treated twice daily with either 5 percent benzoyl peroxide, 3 percent sulfur, a combination of 10 percent benzoyl peroxide and 3 percent sulfur, or vehicle. Soap and water was the only other treatment allowed. Treatment lasted 12 weeks. Patients were evaluated by lesion counts and clinical impression.

Patients were given a satisfactory rating if continued improvement in lesion counts was noted over 12 weeks or if they were discharged in less than 12 weeks with greater than 50 percent improvement in lesion counts. In the benzoyl peroxide group, 41.7 percent (10 patients) were satisfactory and 58 percent (14 patients) were unsatisfactory at the end of the treatment period. Ten percent of the vehicle group (20 patients total) were rated satisfactory and 90 percent unsatisfactory. For the benzoyl peroxide-treated patients rated as satisfactory, treatment averaged 6.8 weeks with a decrease in lesion count of 71.2 percent.

Good and excellent results in clinical impressions were seen in 58.3 percent of patients treated with the benzoyl peroxide-sulfur combination; 41.7 percent of the benzoyl peroxide group; 29.1 percent of the sulfur group; and 10 percent of the vehicle group.

Although a statistical analysis of results was not presented, the researchers stated that the three active preparations were "demonstrably more effective than the placebo." They also stated that the 5-percent benzoyl peroxide treatment "produced the greatest improvement of acne symptoms in the shortest period of time," but that the benzoyl peroxide-sulfur combination "proved somewhat better than the other formulae."

Two unpublished, randomized, double-blind trials comparing 5 and 10 percent benzoyl peroxide followed nearly identical protocols (Refs. 26 and 28). Each treatment group contained 25 patients with Grade II or III acne (Pillsbury classification). The patients had had no systemic therapy for 1 month before entering the study and no topical therapy for 2 weeks. Each patient was treated one to three times daily, depending upon the severity of acne and tolerance to benzoyl peroxide. No vehicle controls were used. The patients were evaluated by lesion counts and global impression when the study began and at intervals of 2 to 4 weeks for the next 12 weeks. The results were expressed as follows: excellent was 75 to 100 percent improvement; good was 50 to 75 percent improvement; fair was 25 to 50 percent improvement; poor was less than 25 percent improvement.

In one study, good to excellent results were reported in 36 percent of the patients who had used 5 percent benzoyl peroxide and 56 percent of the patients who had used the 10-percent

lotion. The second study showed good to excellent results in 54 percent of the group treated with 5 percent benzoyl peroxide and in 72 percent of the group treated with 10 percent benzoyl peroxide. This report also gave the results of the lesion counts. Overall, 5 percent benzoyl peroxide reduced the count from 17.7 to 11.2, and 10 percent benzoyl peroxide decreased the count from 28.0 to 17.9. Although it appears that 10 percent benzoyl peroxide may be more effective than 5 percent benzoyl peroxide in reducing the number of acne lesions, no statistical analysis of the results was presented.

Belknap (Ref. 29) conducted a parallel comparison of 5 percent benzoyl peroxide gel and 0.05 percent retinoic acid cream. (Retinoic acid, also known as tretinoin or vitamin A acid, is a prescription drug for acne.) Patients with Grade II and Grade III acne (Pillsbury classification) were randomly assigned to treatment with either of the active drugs. They had had no topical or systemic medications for 2 weeks before entering the study. The benzoyl peroxide group (29 patients) was treated twice daily and the retinoic acid group (31 patients) was treated once daily. No topical or systemic therapy was allowed other than soap and water. Length of treatment was 8 weeks. Patients were evaluated with lesion counts grouped by type (papules, open comedones, etc.). Results were considered excellent if improvement was greater than 75 percent.

When overall ratings of the two treatment groups were compared, 16 patients who had used benzoyl peroxide showed excellent results compared to 8 patients who had used retinoic acid. This difference was significant ($p<0.025$).

Both drugs were "extremely effective" for all lesion types, but Belknap (Ref. 29) stated that "it appears that the benzoyl peroxide gel produced a more rapid effect on inflammatory lesions (papules and pustules) than did the vitamin A acid." Both treatments also significantly reduced the number of open and closed comedones after 2 weeks of treatment, although Belknap again reported that "the extent of reduction was greater in the benzoyl peroxide group." The Panel has stated that a Category I acne treatment should be effective against all types of acne lesions and believes this study gives evidence of that effectiveness for benzoyl peroxide.

Several investigators have studied 2.5 percent benzoyl peroxide for effectiveness. One investigator treated 10 males with a 2.5-percent benzoyl peroxide water-based gel twice daily for 28 days (Ref. 30). Ten males were treated with the control. No other significant topical or systemic therapy was allowed. *P. acnes* and free fatty acid/triglyceride ratios were measured. In the group treated with 2.5 percent benzoyl peroxide, the pretreatment level of *P. acnes* (in millions/square centimeter (cm^2)) was 6.0. On the 28th day of treatment the *P. acnes* level was 4.2. In the control group the pretreatment level of *P. acnes* was 5.9; on the 28th day of treatment the level was 5.7. The free fatty acid/triglyceride ratio in the control group was 0.75. On the 28th day the ratio was 0.71. In the group treated with benzoyl peroxide the pretreatment ratio was 0.88. On the 28th day the ratio was 0.36. Reduction of *P. acnes* and the free fatty acid/triglyceride ratio was significantly greater with 2.5 percent benzoyl peroxide than with the control.

In another unpublished study, 50 acne patients were treated with either 2.5 percent or 10 percent benzoyl peroxide twice daily for 8 weeks (Ref. 31). This study was randomized and double-blind, but not controlled. Patients were examined biweekly. Evaluation was made by measuring the reduction in the number of specific lesion types and in the total of these lesion types. Patients were also evaluated by global impression.

At 8 weeks, the percent reduction of total lesions from baseline was 46.7 percent for 2.5 percent benzoyl peroxide and 44.3 percent for 10 percent benzoyl peroxide. Statistical analysis showed that there was no significant difference between the effectiveness of the two concentrations. Also, both treatments significantly decreased the total number of papules and pustules ($p<0.001$). No difference was noted between the two treatments in global evaluation. Good to fair results were noted in 46 percent of patients in each treatment group. In this study, side effects from 2.5 percent benzoyl peroxide were found to be less severe and occurred less frequently than with the 10-percent benzoyl peroxide.

Yong (Ref. 32) conducted an open clinical trial with 2.5 percent and 5 percent benzoyl peroxide gel. He treated 200 patients twice daily. Each concentration was given to 100 patients. No significant other topical or systemic therapy was permitted except soap and water. Treatment lasted 4 to 18 weeks. If the lesion count decreased by greater than 75 percent, improvement was considered excellent. Forty-six patients who had been treated with 5 percent gel compared to 36 patients who had been treated with 2.5 percent gel were rated as excellent. Twenty-eight patients in each group were given a good rating (lesions decreased by 50 to 75 percent). Yong concluded that there was no significant difference in effectiveness between the two different strengths of benzoyl peroxide gel.

Numerous adequately controlled, double-blind, and randomized studies have documented the effectiveness of benzoyl peroxide. The Panel recognizes that acne represents a spectrum of severity ranging from comedones to nodules and pustules. No one concentration of benzoyl peroxide or any other ingredient will be suitable for the wide range of this disease even when the frequency of application is varied. The Panel feels that higher concentrations of benzoyl peroxide may be suitable for severe acne or for mila acne lesions that have not responded to lower concentrations. The Panel concludes that benzoyl peroxide 2.5 to 10 percent is effective for OTC use in the treatment of acne.

(3) *Dosage*—(i) *Concentration.* Benzoyl peroxide 2.5 to 10 percent.

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

(4) *Labeling.* The Panel recommends the Category I labeling for OTC products used in the treatment of acne and in the prevention of new acne lesions. (See part III. paragraph A.2. below—Category I labeling.)

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b. *Sulfur.* The Panel concludes that sulfur is safe and effective for OTC topical use in the treatment of acne.

(1) *Safety.* The Panel reviewed the toxicology of sulfur in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** Although the studies usually conducted to establish a toxicological profile were not done on sulfur, the Panel concluded that sulfur is safe for use in antifungal preparations because of its long history of oral and topical use without serious toxic effects.

Sulfur has been used in acne preparations in concentrations ranging from 2 to 10 percent. Although as much as 50 percent of the body surface area could be exposed to sulfur, there is no indication that absorption occurs, at least not to an extent that could approximate oral doses which have been administered to humans. For this reason, the Panel has focused its attention on the local effects of topically applied sulfur.

Scott (Ref. 1) reported that radioactive sulfur was absorbed by normal skin in 8 hours and disappeared from the dermis within 24 hours. The extent of absorption and the chemical form of the absorbed drug were not discussed. In acne patients, the rate of penetration through the epidermis was the same as for normal skin, but the accumulation of radioactive sulfur in the undischarged contents of the sebaceous glands was 10 times greater than in normal skin and remained in high concentrations for up to 3 weeks.

An unspecified number of rabbits were studied after applications of either a 10-percent sulfur ointment (vehicle not specified) or a combination of 2.5 percent sulfur and 10 percent benzoyl peroxide for a period of 12 weeks (Ref. 2). The only reaction was a redness attributed to mild irritation of the skin. This occurred during the first 3 weeks of the study. No signs of toxicity were noted in the hematological examination, urinalysis, or organ analysis.

Another experiment used a 20-percent sulfur cream or a 20-percent sulfur-20 percent benzoyl peroxide cream on the shaved backs of rabbits for a 2-hour exposure period. No reactions to these materials were noted (Ref. 3).

Sulfur can cause slight skin irritation and irritates the eyes if allowed to remain in them. Neither irritation is serious, however. Also, the Panel is unaware of any systemic toxicity from topically applied sulfur. For these reasons the Panel concludes that sulfur is safe for the treatment of acne. The Panel recommends an upper limit of 10 percent. Although sulfur is safe at higher concentrations, 10 percent is the highest concentration contained in currently marketed acne products. The Panel notes that even though sulfur is a safe, mild, peeling agent for the skin, some data suggested that sulfur may enhance the sensitization potential of benzoyl peroxide. (See part III. paragraph D. below—Combination Products Used in the Treatment of Acne.)

(2) *Effectiveness.* Sulfur has been used medically for centuries and although the rationale for its use in acne is presumed to be its keratolytic and antibacterial effects, the exact mechanism of action remains unknown. There are no studies available on this ingredient that meet the Panel's in vivo criteria for antibacterial claims. (See part III. paragraph E.2.c. below—In vivo testing of acne ingredients.) Strakosch (Ref. 3) indicated that the keratolytic action of sulfur was actually due to its conversion to hydrogen sulfide when in contact with tissue. The degree of tissue conversion of sulfur to hydrogen sulfide is unknown, and there are no additional data available on this subject.

One study showed that sulfur may have a comedogenic effect. Mills and Kligman (Ref. 4) were able to induce comedones in rabbits after applying concentrations of sulfur from 2 to 8 percent to the external ear canal. They also induced comedones in humans by applying from 2.5 to 5 percent concentrations of sulfur in a closed patch test. Strauss et al. (Ref. 5), however, were unable to reproduce these results. They used identical methods in 52 patients who were treated with 5 percent sulfur in either octoxynol 9 or a carbomer 934P base. Either the octoxynol 9 vehicle or a dry patch was used as a control. The researchers used multiple biopsies of the test sites which were sectioned serially to detect the presence of comedones. Only the octoxynol 9 vehicle was associated with the production of comedones.

A single-blind, half-face evaluation of the effectiveness of a 10-percent sulfur lotion was conducted on 29 patients who had Pillsbury Grade II to III acne (Ref. 6). They had had no topical therapy for 2 weeks before the study and no systemic therapy for 4 weeks before the study. Each patient used a soap control on half of the face. The other half of the face was treated with an aluminum oxide scrub and the sulfur lotion at night, and a soap washing followed by the sulfur lotion in the morning. Treatment lasted for 6 weeks with evaluation by lesion counts at 0, 2, 4, and 6 weeks. Both total lesion and specific lesion counts were reduced by treatment with sulfur and aluminum oxide. However, open comedones were the only specific lesion count significantly reduced more by sulfur and aluminum oxide than by the soap treatment.

Sulfur is frequently combined with resorcinol in acne preparations. Numerous studies have established the effectiveness of this combination. (See part III. paragraph D. below—Combination Products Used in the Treatment of Acne.)

In a double-blind, randomized trial (Ref. 7), 92 patients were treated twice daily with one of the following treatments: (1) 3 percent sulfur, (2) 5 percent benzoyl peroxide, (3) 3 percent sulfur-10 percent benzoyl peroxide, or (4) vehicle lotion. Clinical response was evaluated after 2 weeks by lesion counts and clinical evaluation. In order to merit a satisfactory rating, the patients must have had a 50-percent or greater decrease in lesions if treated for less than 12 weeks or have shown continued improvement over a 12-week period.

Of the 24 patients treated with sulfur, 33 percent were rated as satisfactory. This compared to satisfactory ratings of 54 percent for the sulfur-benzoyl peroxide combination, 41.7 percent for benzoyl peroxide, and 10 percent for the vehicle. Clinical assessment of patients treated with sulfur showed 29.2 percent good to excellent, 50 percent fair to no change, and 20.8 percent worse. This compared to vehicle results of 10 percent good to excellent, 45 percent fair to no change, and 45 percent worse. Although the results were not analyzed statistically, it was concluded that the active treatments (sulfur, benzoyl peroxide, and the sulfur-benzoyl peroxide combination) were "demonstrably more effective" than vehicle.

One submission contained a compilation of five half-face studies conducted by different investigators using the same protocol (Ref. 2). The studies were randomized and double-blind. Patients were treated for 8 weeks and evaluated by lesion counts. Treatment consisted of a base cream on one side of the face. On the other side of the face, a cream containing 5 percent sulfur or 10 percent benzoyl peroxide or a combination of the two ingredients was applied.

Treatment results on the 42 patients treated with sulfur showed a 42.8-percent decrease in comedones and a 36.3-percent decrease in other lesions. For the 123 patients using the vehicle the reduction was 28 percent for comedones and 18.3 percent for other lesions. Overall results showed a reduction in lesions of 52 percent for benzoyl peroxide-sulfur combination; 41 percent for sulfur; 40 percent for benzoyl peroxide; and 25 percent for vehicle.

Not all of the studies were statistically analyzed. Some researchers found the combination of benzoyl peroxide and sulfur superior to either ingredient used alone. In other studies, no significant difference was seen between sulfur, benzoyl peroxide, or the combination of sulfur and benzoyl peroxide.

The Panel concludes that sulfur is effective for OTC use in the treatment of acne.

(3) *Dosage*—(i) *Concentration.* Sulfur 3 to 10 percent.

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

(4) *Labeling.* The Panel recommends the Category I labeling for OTC products used in the treatment of acne and in the prevention of new acne lesions. (See part III. paragraph A.2. below—Category I labeling.)

References

(1) Scott, A., "The Behaviour of Radioactive Sulphur After its External Application to the Skin," *British Journal of Dermatology*, 69:39–49, 1957.

(2) OTC Volume 070168.

(3) Strakosch, E. A., "Studies on Ointments. III. Ointments Containing Sulphur," *Archives of Dermatology and Syphilology*, 47:216–225, 1943.

(4) Mills, O. H., and A. M. Kligman, "Is Sulphur Helpful or Harmful in Acne Vulgaris?, *British Journal of Dermatology*, 86:620–627, 1972.

(5) Strauss, J. S., et al., "A Re-examination of the Potential Comedogenicity of Sulfur," *Archives of Dermatology*, 114:1340–1342, 1978.

(6) OTC Volume 070126.

(7) OTC Volume 070099.

2. *Category I labeling.* The Panel reviewed all submitted labels of preparations used for the treatment of acne and recommends the following labeling. The Panel realizes that there may be many similar phrases and terms that can be used in labeling to convey the same information to consumers. However, to ensure conformity to required standards, variations from the labeling recommended below must be obtained through the procedures to amend the monograph in § 330.10(a)(12) (21 CFR 330.10(a)(12)).

a. *Acne treatment labeling.* The Panel recommends that one or a combination of the following phrases be used as labeling for products effective in the treatment of acne.

(1) "For the management of acne."

(2) "For the treatment of acne."

(3) "Anti-acne formula."

(4) "Anti-acne medication."

(5) "Anti-acne formulation."

(6) "Dries and clears acne blemishes."

(7) "Dries and clears acne pimples."

(8) "Dries acne blemishes and allows skin to heal."

(9) "Dries acne pimples and allows skin to heal."

(10) "Dries up acne pimples."

(11) "Helps clear acne pimples."

(12) "Clears up most acne pimples."

(13) "Clears up most acne blemishes."

(14) "Reduces the number of acne lesions."

(15) "Reduces the severity of acne lesions."

(16) "Reduces blackheads."

(17) "Clears up most blackheads."

(18) "Loosens blackheads."

(19) "Helps clear up blackheads."

(20) "Helps clear up acne pimples."

(21) "Helps remove blackheads."

(22) "Helps remove acne pimples."

(23) "Dries up blackheads."

(24) "Dries up acne blemishes."

(25) "Unclogs pores to help clear acne."

(26) "Unplugs pores to help clear acne."

(27) "Penetrates follicles to eliminate most blackheads and acne pimples."

(28) "Penetrates pores to eliminate most blackheads and acne pimples."

(29) "Penetrates follicles to control blackheads and acne pimples."

(30) "Penetrates pores to control blackheads and acne pimples."

(31) "Penetrates follicles to clear most blackheads and acne pimples."

(32) "Penetrates pores to clear most blackheads and acne pimples."

(33) "Penetrates follicles to reduce blackheads or acne pimples."

(34) "Penetrates pores to reduce blackheads or acne pimples."

b. *Acne prevention labeling.* Acne prevention labeling may be used in addition to acne treatment labeling for acne drug products that are effective in preventing the development of new acne lesions. These products should not be used to prevent acne in the person who has never had acne. The Panel believes that ingredients that are effective in treating acne are also effective in preventing new lesions. (See part II. paragraph F. above—Treatment of Acne.) The Panel recommends that one of a combination of the following phrases be used as labeling for products effective in the prevention of new acne lesions.

(1) "Helps keep skin clear of new acne lesions."

(2) "Helps keep skin clear of new acne pimples."

(3) "Helps prevent new blackheads or acne pimples."

(4) "Helps prevent new acne pimples."

(5) "Helps prevent new acne pimples from forming."

(6) "Helps prevent new acne lesions."

(7) "Helps prevent the development of new acne lesions."

(8) "Helps prevent new acne blemishes from forming."

Prevention labeling is to be used only in conjunction with treatment labeling. Examples of acceptable labeling are:

"Clears up most acne pimples and reduces blackheads. Helps prevent new acne blemishes from forming."

"Dries and clears acne blemishes and reduces blackheads. Helps prevent the development of new acne lesions."

c. *Antibacterial claims.* Products containing ingredients which are in Category I for the treatment of acne may also be labeled with one or more of the following antibacterial claims, provided that the product as formulated meets the in vivo effectiveness testing criteria recommended by the Panel. (See part III. paragraph E.2.c. below—In vivo testing of acne ingredients.)

(1) "Antibacterial."

(2) "Kills acne bacteria."

(3) "Kills the bacteria that can cause acne."

(4) "Kills acne bacteria on the skin."

(5) "Kills acne bacteria in the skin."

(6) "Kills acne bacteria and helps clear acne pimples."

(7) "Works to kill bacteria that may cause pimple redness to spread."

(8) "Works to kill bacteria that may cause inflammation to spread."

(9) "Penetrates follicles to kill bacteria associated with acne."

(10) "Penetrates pores to kill bacteria associated with acne."

(11) "Penetrates follicles to reduce bacteria associated with acne."

(12) "Penetrates pores to reduce bacteria associated with acne."

(13) "Reduces *P. acnes,* bacteria associated with acne."

(14) "Reduces the bacterial products associated with the inflammation of acne."

(15) "Reduces the bacterial products associated with the irritation of acne."

d. *Product attributes.* The Panel accepts the use of terms describing certain physical and chemical qualities of OTC topical acne drug products, as long as these terms do not imply any therapeutic effect and are distinctly separated from labeling indications.

These product attributes pertain to the inherent characteristics or the pharmaceutical elegance of the formulation. These properties are usually due to specific inactive, and in some cases active, ingredients included in the final product formulation. Product characteristics appear in the labeling for consumer information or product appeal and involve terms relating to the product's color, odor, and feel. The Panel considers the following list and similar terms acceptable:

(1) "Greaseless."

(2) "Nonstaining."

(3) "Odorless."

(4) "Colorless."

(5) "Nontinted."

(6) "Blends easily with skin."

(7) "Disappearing foam."

(8) "Drying."

(9) "Dries excess skin oils."

(10) "Skin-softening."

(11) "Cools and comforts hot, irritated skin areas."

(12) "Cleans the skin and helps to remove oil."

e. *Warnings*—(1) *For all acne products.* (i) "For external use only."

(ii) "Other topical acne medications should not be used at the same time as this medication."

(2) *For products containing benzoyl peroxide.* "Do not use this medication if you have very sensitive skin or if you are sensitive to benzoyl peroxide. This product may cause irritation, characterized by redness, burning, itching, peeling, or possibly swelling. More frequent use or higher concentrations may aggravate such irritation. Mild irritation may be reduced by using the product less frequently or in a lower concentration. If irritation becomes severe, discontinue use; if irritation still continues, consult a doctor or pharmacist. Keep away from eyes, lips, mouth, and sensitive areas of the neck. This product may bleach hair or dyed fabrics."

(3) *For products containing sulfur.* "Do not get into eyes. If excessive skin irritation developes or increases, discontinue use and consult a doctor or pharmacist."

(4) *For sulfur-resorcinol products.* "Apply to affected areas only. Do not use on broken skin or apply to large areas of the body."

f. *Directions for use.* The Panel suggests the following directions for acne products that are applied and left on the skin:

"Cleanse the skin thoroughly before applying medication. Cover the entire affected area with a thin layer one to three times daily. Because excessive drying of the skin may occur, start with one application daily, then gradually increase to two or three times daily if needed or as directed by a doctor."

Other products, such as soaps or masks, may be applied and removed and should have appropriate directions.

B. Category II Conditions

These are conditions under which OTC acne drug products are not generally recognized as safe and effective or are misbranded. The Panel recommends that the Category II conditions be eliminated from OTC acne drug products effective 6 months after the date of publication of the final monograph in the Federal Register.

1. *Category II active ingredients.*

Alkyl isoquinolinium bromide
Aluminum salts
  Alcloxa
  Aluminum chlorohydrex
  Aluminum hydroxide
  Magnesium aluminum silicate
Benzocaine
Benzoic acid
Borates
  Boric acid
  Sodium borate
Calcium polysulfide
Calcium thiosulfate
Camphor
Chlorhydroxyquinoline
Chloroxylenol
Coal tar
Dibenzothiophene
Estrone
Magnesium sulfate
Phenolates
  Phenol
  Phenolate sodium
Phenyl salicylate
Pyrilamine maleate
Resorcinol and resorcinol monoacetate (as single ingredients)
Sodium thiosulfate
Tetracaine hydrochloride
Thymol
Vitamin E
Zinc salts
  Zinc oxide
  Zinc stearate
  Zinc sulfide

a. *Alkyl isoquinolinium bromide.* The Panel concludes that alkyl isoquinolinium bromide is not effective and that there are insufficient data available to permit final classification of its safety for OTC topical use in the treatment of acne.

(1) *Safety.* Alkyl isoquinolinium bromide is a surface-acting agent and is active against bacteria, molds, and fungi (Ref. 1).

The oral LD_{50} is 230 mg/kg in rats and 200 mg/kg in guinea pigs. Rats that were fed 12.5 mg/kg for 2 years continued to grow normally. Guinea pigs tolerated 1:5,000 alkyl isoquinolinium bromide in drinking water for 6 months (Ref. 2). Normal skin showed no irritation or sensitization from the use of 0.1 percent solutions of this ingredient. Solutions of 0.5 percent can be considered safe for use where accidental contact with the eye may occur (Ref. 1).

The Panel has found the safety data on alkyl isoquinolinium bromide insufficient and therefore considers this ingredient of questionable safety when used topically for the treatment of acne.

(2) *Effectiveness.* Alkyl isoquinolinium bromide is contained in only one product submission reviewed by the Panel (Ref. 1). No data on the effectiveness of this ingredient in the treatment of acne are available in the submission or in the medical literature. For this reason the Panel concludes that alkyl isoquinolinium bromide is not

effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed alkyl isoquinolinium bromide in category II because there are no data available on the effectiveness of this ingredient in the treatment of acne.

References

(1) OTC Volume 070009.

(2) Gloxhuber, C., "Review Articles. Toxicological Properties of Surfactants," *Archives of Toxicology,* 32:245–270, 1974.

b. *Aluminum salts (alcloxa, aluminum chlorohydrex, aluminum hydroxide, and magnesium aluminum silicate).* The panel concludes that the aluminum salts (alcloxa, aluminum chlorohydrex, aluminum hydroxide, and magnesium aluminum silicate) are safe but are not effective for OTC use in the treatment of acne.

(1) *Safety.* The Panel determined alcloxa to be safe for topical use in concentrations of 0.25 to 10 percent as described in its recommendations on topical antifungal drug products published elsewhere in this issue of the Federal Register. The Panel has reviewed additional data (Refs. 1, 2, and 3) which support this finding.

Aluminum chlorohydrex was found safe at concentrations up to 25 percent for topical use in nonaerosol formulations in a report by the Advisory Review Panel on OTC Antiperspirant Drug Products published in the Federal Register on October 10, 1978 (43 FR 46719). Although intradermal injections of aluminum chlorohydrex produced granulomas in guinea pigs (Ref. 4), the Panel believes that this ingredient is safe for topical use, particularly because it is a protein precipitant. With protein precipitants, absorption through the skin is probably minimal.

Aluminum hydroxide and magnesium aluminum silicate are widely used antacids and were found safe for that use by the Advisory Review Panel on OTC Antacid Drug Products in a report published on April 4, 1973 (37 FR 8717). Aluminum hydroxide, like aluminum chlorohydrex, produced granulomas in guinea pigs following intradermal injection (Ref. 4), but again the Panel sees no problem when it is used topically. Patch test and primary skin irritation studies showed tht magnesium aluminum silicate does not irritate or sensitize the skin (Ref. 5). The Panel concludes that the four aluminum salts discussed above are safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Alcloxa apparently works by dissociating into allantoin and aluminum chloride at skin pH. Its mechanism of action in the treatment of acne is presumed to depend upon the astringency of the aluminum chloride as well as the soothing and healing properties of the allantoin. Alcloxa has been used for over 50 years for the treatment of a wide variety of skin problems, such as eczema, sunburn, itching, athlete's foot, impetigo, acne, diaper rash, and psoriasis. Its reputation is based upon "skin softening and tissue-building actions" (Ref. 2).

Submissions reviewed by the Panel (Refs. 1, 2, 3, and 6) contained no clinical trials on alcloxa in the treatment of acne, and there is no information in the gneral medical literature on the effectiveness of this ingredient in treating acne.

Warshaw (Ref. 7) studied an aqueous solution of 20 percent aluminum chlorohydrex on 66 acne patients. She believed the aluminum preparation inhibits sweating and decreases overactivity of the sebaceous gland. All patients in this study were treated with a combination of sulfur and resorcinol. Half of the subjects also used the aluminum chlorohydrex solution. Treatment time varied from 3 weeks to 6 months. The author reported that 32 of the 33 patients treated with aluminum chlorohydrex showed decreased comedones, pustules, and oiliness. The group treated only with sulfur and resorcinol showed "less rapid improvement" and the improvement was not as well maintained.

This study was not randomized, vehicle-controlled, or double-blind. The Panel cannot draw conclusions from this study on the effectiveness of aluminum chlorohydrex as a single ingredient because it was used with the sulfur-resorcinol combination.

Several randomized, blinded, and controlled trials have been conducted on a combination of aluminum chlorohydrex and sulfur (Ref. 8). No statistically significant differences were found between the aluminum chlorohydrex combination, a sulfur-resorcinol combination, and placebo. However, because these studies did not use aluminum chlorohydrex as a single ingredient, they will not be discussed in detail.

The Panel has seen no data in the submissions or in the medical literature to support the use of aluminum hydroxide in acne.

The Panel has received one submission on magnesium aluminum silicate which states that this ingredient is metabolically inert. Magnesium aluminum silicate works by absorbing oils and superficially debriding the skin (Ref. 5).

In an unpublished study of 12 patients, half of the face was treated with magnesium aluminum silicate and the other half of the face served as the control. After 1 month of treatment, "there appeared to be an improvement in the treated area vs. the control in the clearing of comedones" in six subjects. No change was noted in the other six patients (Ref. 5).

In another unpublished study, 55 patients applied magnesium aluminum silicate nightly for 1 week and then twice weekly for the next 3 to 5 weeks. Controls were not used, and criteria for evaluation were not explained. At the end of the study, 45 patients were considered improved, 8 were unchanged, and 2 were worse (Ref. 5).

Neither of the above two studies meets the Panel's criteria for effectiveness and neither study particularly supports the effectiveness of magnesium aluminum silicate. (See part II. paragraph I.2. above—Criteria for evaluating effectiveness.)

The Panel concludes that the aluminum salts are not effective for OTC use in the treatment of acne.

(3) *Evaluation.* The Panel believes that the aluminum salts are not effective ingredients for the treatment of acne. Either no effectiveness data were available on the single active ingredients, or the available studies did not support the effectiveness of aluminum salts.

References

(1) OTC Volume 070030.

(2) OTC Volume 070100.

(3) OTC Volume 070124.

(4) Turk, J. L., and D. Parker, "Granuloma Formation in Normal Guinea Pigs Injected Intradermally with Aluminum and Zirconium Compounds," *Journal of Investigative Dermatology,* 68:336–340, 1977.

(5) OTC Volume 070172.

(6) OTC Volume 070230.

(7) Warshaw, T. G., "A New Approach to the Control of Acne Vulgaris," *New York State Journal of Medicine,* 57:3999–4000, 1957.

(8) OTC Volume 070053.

c. *Benzocaine.* The Panel concludes that benzocaine is not safe and is not effective for OTC use in the treatment of acne.

(1) *Safety.* Benzocaine has been used widely as a local anesthetic , especially in ointments and dusting powders for wounds, burns, and ulcers. The range of concentrations used is from 5 percent to 50 percent. It has been injected subcutaneously once a week in 3 percent solutions and is said to be almost devoid of local irritant action (Ref. 1).

The Canadian government listed the maximum single oral dose limits for an adult at 195 mg and the maximum oral daily intake at 585 mg. It also limits benzocaine to 8 percent concentrations

in pharmaceuticals for external use (Ref. 2). Dreisbach (Ref. 3) lists the maximum amount safe for surface use as 5,000 mg or 25 mL of a 20-percent solution. Gosselin et al. (Ref. 4) report that benzocaine is a local anesthetic of low toxicity. Despite its low water solubility and its reportedly poor absorption from many sites, there are instances of severe methemoglobinemia in infants from the use of either a benzocaine ointment or suppository.

Benzocaine is a common sensitizing agent which can produce allergic contact dermatitis. Approximately one-fourth of the people who are sensitive to benzocaine react when *para*-phenylenedamine, a component of hair dyes, comes in contact with their skin. Cross-reactivity is also noted with the sulfonamides and with sunscreens that contain *para*-aminobenzoic acid or its esters or both. Benzocaine-sensitive patients may also cross-react with injectable local anesthetics, such as procaine and tetracaine (Ref. 5).

Fisher, Pelzig, and Kanof (Ref. 6) studied the ability of *para*-phenylenediamine to act as a sensitizer on the skin to produce an allergic edematous contact type of dermatitis. The authors noted that allergic hypersensitivity to benzocaine and *para*-phenylenediamine may happen repeatedly even years after the initial sensitization. They found that in a group of 50 patients sensitive to *para*-phenylenediamine, 46 were still sensitive when tested 3 to 10 years later. Of these 46 patients, 18 were found to be sensitive to benzocaine. In a separate study, they also found that 10 of 24 patients sensitized to benzocaine were also sensitive to *para*-phenylenediamine.

In a similar study, Gaul (Ref. 7) used a patch test and found that, in a group of 580 dermatologic patients, 50 were sensitive to *para*-phenylenediamine, and 16 were sensitive to benzocaine. Of the benzocaine-sensitive patients, 3 were sensitive only to benzocaine. The rest were sensitive to other drugs such as *para*-phenylenediamine, procaine, and penicillin in addition to benzocaine. The Panel notes that benzocaine is chemically dissimilar from *para*-phenylenediamine,.

In the North American Contact Dermatitis Group's study (Ref. 8), the incidence of allergic sensitivity to benzocaine was 5 percent, equal to some other commonly used drugs, and less than the more frequent sensitizers such as neomycin. This study was on 1,200 patients seeking treatment for skin diseases. These patients were considered high risks for developing alllergy.

The routine topical patch test does not reveal immediate sensitivity, such as an urticarial reaction (hives), to benzocaine. Nasal testing, eye testing, scratch tests, or intradermal testing can be used to screen patients for hypersensitivity (Ref. 9). However, there is concern that scratch testing and intradermal skin testing to detect this type of hypersensitivity may give false-negative results.

Benzocaine is a moderate sensitizer when applied topically over a long period to normal or diseased skin. When used for short periods on noninfected skin, it is only a weak sensitizer. The use of benzocaine should be avoided by people known to be sensitive and by those with skin infections.

(2) *Effectiveness.* Benzocaine is a local anesthetic which may alleviate itching, burning, and pain.

Currently marketed OTC acne products contain benzocaine in a concentration of 0.5 percent. A concentration of 5 to 10 percent is considered useful in relieveing itching (Ref. 1). Ointments containing less than 5 percent benzocaine and acidic preparations of benzocaine are generally ineffective (Ref. 10).

No effectiveness data are available on benzocaine in the treatment of acne. The Panel sees no need for including a local anesthetic in an acne remedy. The Panel concludes that the use of benzocaine is irrational in acne therapy.

(3) *Evaluation.* The Panel has placed benzocaine in Category II for the treatment of acne because this ingredient's sensitizing potential and because there is no acceptable rationale for the use of this ingredient in treating acne.

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(1) Osol, A., and R. Pratt, "United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 186, 1973.

(2) OTC Volume 070138.

(3) Dreisbach, R. H., "Handbook of Poisoning: Diagnosis and Treatment," 8th Ed., Lange Medical Publications, Los Altos, CA, p. 274, 1974.

(4) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., The Williams and Wilkins Co., Baltimore, p. 142, 1976.

(5) Fisher, A. A., "Contact Dermatitis," 2d Ed., Lea and Febiger, Philadelphia, pp. 42 and 312–313, 1973.

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

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

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

(9) Eyre, J., and F. Nally, "Nasal Test for Hypersensitivity, Including a Positive Reaction to Lignocaine," *Lancet*, 1:264–265, 1971.

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

d. *Benzoic acid.* The Panel concludes that benzoic acid is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Free and combined forms of benzoic acid occur in nature. Most berries contain appreciable amounts of this acid.

The acute toxicity of benzoic acid is similar in all species. The oral LD_{50} is 2.53 g/kg in the rat, 2.37 g/kg in the mouse, and 2 g/kg in the cat, dog, and rabbit. Benzoic acid given by other routes yielded these LD_{50}'s: 1.46 g/kg intraperitoneally in mice; 2 g/kg subcutaneously in rabbits; and 1.71 g/kg intravenously in rats (Refs. 1 and 2). After the intravenous injection, rats had tremors and convulsions before death. The surviving rats had excessive salivation, vomiting, and diarrhea (Ref. 2).

Benzoic acid is rapidly absorbed, conjugated with glycine, and excreted in the urine as hippuric acid (Ref. 3). In most species, the liver is the primary site of conjugation. Because there is no accumulation, symptoms of chronic administration are like those seen in acute studies. When rats were fed benzoic acid for 28 days, animals fed 5 percent in the diet died within 2 weeks, showing hyperexcitability, urinary incontinence, and convulsions. Males fed 2 percent benzoic acid exhibited a decrease in body weight (Ref. 4). Dogs can be fed up to 1 g/kg for long periods without effect, but epileptic convulsions and death occur above this amount (Ref. 3).

Benzoic acid was once administered as a 6–g oral dose or a 2–g intravenous dose in humans in a liver function test (Ref. 3). Within 6 hours, 80 percent of the dose is usually eliminated, the remainder being eliminated within 14 hours. Ingestion of 4 to 6 g benzoic acid produces only mild gastric irritation (Ref. 5). "Large oral doses" cause severe gastric pain, nausea, and vomiting (Ref. 6).

Benzoic acid 6 percent is contained in Whitfield's ointment, which has been used as a topical antifungal agent for many years. In view of the use of this ointment for over 50 years without toxic manifestations, the Panel concludes that

benzoic acid is safe for topical use in the treatment of acne.

(2) *Effectiveness.* Benzoic acid is generally considered to be an antifungal agent. It is also widely used as a food preservative. But the Panel has seen only one study (Ref. 7) on the use of benzoic acid in acne treatment and this was not as a single ingredient.

(3) *Evaluation.* The Panel has placed benzoic acid in Category II because it is not generally recognized as an anti-acne agent and because there are no controlled studies on benzoic acid as a single ingredient for the treatment of acne.

References

(1) Fairchild, E. J., "Registry of Toxic Effects of Chemical Substances," Vol. II, U.S. Department of Health, Education, and Welfare, Cincinnati, p. 179, 1977.

(2) Hager, G. P., C. W. Chapman, and E. B. Starkey, "The Toxicity of Benzoic Acid for White Rats," *Journal of the American Pharmaceutical Association (Scientific Edition)*, 31:253–255, 1942.

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(6) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins Co., Baltimore, p. 137, 1976.

(7) Milberg, I. L. "Clinical Evaluation of an Antiseptic Medicated Cream in the Treatment of Acne Vulgaris," *New York State Medical Journal*, 58:2674–2675, 1958.

e. *Borates (boric acid and sodium borates).* The Panel concludes that borates (boric acid and sodium borate) are safe but are not effective for OTC topical use in the treatment of acne.

(1) *Safety.* The toxicology of borates was summarized by this Panel in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** The Panel concluded that borates were safe in concentrations of 5 percent of less. Rather than repeat that data here, the Panel will summarize only the data it has received since completing its recommendations on antifungal drug products.

One preparation used for acne contains boric acid in a concentration of just over 12 percent. For sodium borate, all of the submitted acne preparations contain less than 5 percent except for one which contains 50 percent sodium borate. However, because this preparation is a scrub, which is rinsed off a few minutes after application, exposure time would be relatively short.

In the antifungal recommendations mentioned above, the greatest concern about the use of sodium borate was its irritation potential because so little data had been submitted on this potential. However, two submissions to the acne review added information on irritation potential (Refs. 1 and 2). Both of these submissions suggest that 50 percent sodium borate preparations are irritating to the eye and have recommended warnings to this effect on the label.

Single applications to normal and abraded rabbit skin have shown different results, but most of the evidence shows that 50 percent sodium borate preparations are mildly irritating. Repeated applications over a period of 2 to 3 weeks, however, are severely irritating (Refs. 1 and 2). When used according to labeled directions (i.e., "wet skin with water, apply, and rinse off after 60 seconds,") over a 20-day period, the 50-percent preparation did not irritate either normal or abraded rabbit skin. Blood levels of boron in the treated group were not significantly different from the controls.

In a 30-day study, however, twice-daily application under the same conditions resulted in such severe skin reactions that the study was ended after 8 days. Although the blood boron levels of the treated group were about five times as high at the end of the study, they were still within the normal values for rabbits. Within 4 or 5 days after the study was discontinued, the rabbits' skin returned to normal (Ref. 1).

In a separate study (Ref. 1) a combination product containing 98 percent borax (sodium borate) was used to evaluate percutaneous absorption and irritation potential in rabbits. Doses of 1.0 g/kg and 5.0 g/kg of the product were used after adding enough saline to form a paste. Sodium borate was applied 5 days a week for 3 weeks with daily exposures of 6 hours to both normal and abraded skin. The treated area was covered with polyethylene wrap.

No rabbits died as a result of the treatment. However, weight gain in the test animals was less than in the control animals. Mild to moderate redness, edema, and mild fissuring indicated irritation. The skin also became slightly to noticeably leathery. There were no significant differences from controls in hematologic values, urinalysis findings, organ/body weight ratios, or gross pathological tissue changes.

In a similar experiment using mostly the same conditions, the rabbits treated with 5.0 g/kg sodium borate showed emaciation, depressed righting reflex, and impaired muscular coordination (Ref. 1). Several animals also developed acne-like lesions during the latter part of the application period.

The Panel recognizes that this kind of experiment does not approximate the labeled directions for use of the 50-percent sodium borate product. Such data, however, indicate potentially serious problems when high concentrations of sodium borate preparations remain on the skin for long periods and may be under occlusion.

Contrasted with these results, a 4-hour patch test using a 50-percent sodium borate suspension resulted in no primary irritation (Ref. 1).

A study by Weir and Fisher (Ref. 3) was very helpful in calculating the risk of topical applications of 12 percent boric acid if certain assumptions are made. In this study, definite signs of toxicity were noted when 1,170 ppm boron equivalent was fed to rats or dogs. For example, rats that were fed 1,170 ppm boron equivalent of either boric acid or sodium borate became sterile. Dogs that were fed 1,750 ppm boron equivalent developed atrophy of the testicles. In rats, degeneration of the gonads occurred as well as desquamation of the skin on the paws and tail.

If 1,170 ppm boron equivalent is converted, this would represent 6,685 ppm boric acid in the diet and 10,300 ppm sodium borate in the diet. At the 1,750 ppm boron equivalent level of feeding, this would convert to 10,000 ppm boric acid and 15,400 ppm sodium borate in the diet.

If the average mongrel dog weighs 30 lb or 13.6 kg and consumes 500 g of dry food daily (Ref. 4), it can be calculated that the total daily intake in this experiment would have been 5 g boric acid or 7.5 g sodium borate. The average blood volume of a dog is 35.4 mL per lb body weight (Ref. 4). Therefore, a 30-lb dog would have a blood volume of approximately 1 L. If 5 g boric acid were instantaneously distributed in 1 L of blood, there would be a blood concentration of 5,000 ppm. In a similar calculation, the blood sodium borate concentration would be 7,500 ppm. These concentrations of 1,170 ppm and 1,750 ppm boron equivalent are toxic

levels. About one-fourth of this dose, or 350 ppm, was found to be a "no effect" level by this test. This would amount to 2,500 ppm boric acid or 3,850 ppm sodium borate as the "no effect" level. These calculations were derived from the paper by Weir and Fisher (Ref. 3), but it should be noted that assumptions were made that are probably not the actual case.

If one makes the same assumptions about topical absorption in humans, one can approximate a safety evaluation. Assuming a worst-case type of application of the 12-percent boric acid product to the upper torso of a human and again assuming total rapid absorption into the blood, one arrives at a blood concentration similar to that assumed for the dog above. If 15 g of the 12-percent preparation were applied to the back and chest area twice daily, there would be 3.6 g boric acid available for absorption. If this were distributed into 7 L of blood (the blood volume of a person), the blood concentration would be 0.0005 g/mL or 500 ppm. This blood concentration is below the 2,500 ppm calculated above as the possible "no effect" level in dogs.

Although the Panel believes that high concentrations of borates may be irritating to abraded skin, it concludes that boric acid and sodium borate are safe for OTC topical use in concentrations up to 5 percent.

(2) *Effectiveness.* The Panel has found only one study (Ref. 1) evaluating the effectiveness of borates as single ingredients in the treatment of acne. In this clinical trial, 22 patients (13 females and 9 males) with acne and oily skin were treated with 50 percent sodium borate in a vehicle of soapless cleansers. The sodium borate was present as small abrasive particles that dissolved after 30 to 60 seconds of gentle rubbing on the skin. The rationale for its use was oil removal (the soapless cleansers) and gentle abrasion of the skin (the abrasive particles).

The patients were treated one to four times daily with this gritty scrub. They were also given other topical and systemic agents, including antibiotics and prednisone. At the beginning of the study, 18.2 percent of the patients had mild acne, 72.7 percent had moderate acne, and 9.1 percent had severe acne. After 4 weeks of treatment, half of the patients had mild acne and half had moderate acne.

At the final examination (8 weeks), the results were as follows: no acne in 4.8 percent, very mild acne in 14.3 percent, mild acne in 57.1 percent, and moderate acne in 23.8 percent. The oiliness of the patients' skin was also evaluated. Before treatment, oiliness was mild in 31.8 percent and moderate in 68.2 percent. At the conclusion of the trial, oiliness was absent in 27.8 percent, very mild in 5.6 percent, mild in 50.0 percent, and moderate in 16.7 percent.

The Panel notes that the study was not controlled or double-blind. Lesion counts were not used as a method of evaluation. Concomitant therapy was given. Statistical analysis of results was not presented.

The Panel concludes that borates have not been conclusively shown to be effective in treating acne. Sodium borate may act as a mild physical abrasive to remove superficial pustules, but it probably does not effectively remove the primary lesions of acne (blackheads and whiteheads) because they are deeply rooted in the follicles.

(3) *Evaluation.* Because there is no controlled clinical trial evaluating the effectiveness of boric acid and sodium borate in the treatment of acne, the Panel has placed these ingredients in Category II.

References

(1) OTC Volume 070206.

(2) OTC Volume 070218.

(3) Weir, R. J., Jr., and R. S. Fisher, "Toxicological Studies on Borax and Boric Acid," *Toxicology and Applied Pharmacology*, 23:351–364, 1972.

(4) Siegmund, O. H., "The Merck Veterinary Manual," 4th Ed., Merck and Co., Rahway, NJ, pp 35 and 1270, 1973.

f. *Calcium polysulfide.* The Panel concludes that calcium polysulfide is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Calcium polysulfide releases hydrogen sulfide and elemental sulfur when placed in contact with water (Ref. 1), such as might be present on the skin. The amount of hydrogen sulfide released is unknown but is thought to be below toxic levels when sulfide compounds are used externally. Neither of the submissions to the Panel (Refs. 2 and 3) contained any toxicity data on calcium polysulfide. However, because the Panel considers calcium polysulfide to be essentially elemental sulfur, it does not consider that the external use of this ingredient would present any systemic toxicological hazard. (See part III. paragraph A.1.b. above—Sulfur.) Also, local effects of calcium polysulfide would probably be the same as for elemental sulfur. The Panel concludes that calcium polysulfide is safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Calcium polysulfide is one of the components of a sulfurated lime solution (Vleminckx' solution) which has been used for about 100 years (Ref. 4). In the past, there was no standardized definition of sulfurated lime solution, but it always contained high concentrations of sulfides and sulfates (25 to 35 percent) (Refs. 2 and 3). According to the "United States Pharmacopeia," sulfurated lime solution contains 25 percent sublimed sulfur and 16.5 percent lime (calcium oxide) (Ref. 5).

The product described in the submissions to the Panel (Refs. 2 and 3) contains calcium thiosulfate along with calcium polysulfide. Four mL of this combination added to 1 pint of water produces a sulfurated lime solution for use as a wet dressing. When used as directed, a substantial amount of hydrogen sulfide is liberated, giving off an obnoxious odor. Drying of the skin is also quite pronounced with sulfurated lime solution.

No controlled clinical trials on effectiveness are contained in the submissions and Panel is not aware of such studies in the medical literature. In addition, the Panel does not believe that calcium polysulfide is intended to be used as a single active ingredient.

The Panel concludes that calcium polysulfide is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* Although calcium polysulfide has been used for many years for the treatment of acne, in the absence of controlled clinical trails demonstrating effectiveness, the Panel concludes that it is not effective for this use.

References

(1) Dreisbach, R. H., "Handbook of Poisoning: Diagnosis and Treatment," 9th Ed., Lange Medical Publications, Los Altos, CA, p. 246, 1977.

(2) OTC Volume 070248

(3) OTC Volume 070250.

(4) Schmitt, C. L., "Topical Agents Used in Treatment of Acne," *Clinical Medicine*, 70:1473–1476, 1963.

(5) "United States Pharmacopeia," 20th Revision, United States Pharmacopeial Convention, Inc., Rockville, MD, p. 450, 1980.

g. *Calcium thiosulfate.* The Panel concludes that calcium thiosulfate is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* No safety data on this ingredient were contained in the submissions (Refs. 1 and 2). But calcium thiosulfate or calcium hyposulfite (CaS_2O_3) decomposes to elemental sulfur and therefore presents the same safety considerations as sulfur. (See part III. paragraph A.1.b. above—Sulfur.) The Panel concludes that calcium thiosulfate is safe for OTC topical use.

(2) *Effectiveness.* No controlled clinical trials demonstrating effectiveness in acne are available on

this ingredient. Calcium thiosulfate is a component of sulfurated lime solution, which also contains calcium polysulfide. (See part III. paragraph B.1.f. above—Calcium polysulfide.)

The Panel concludes that calcium thiosulfate is not effective for OTC use in the treatment of acne.

(3) *Evaluation.* The Panel has placed calcium thiosulfate in Category II because there are no clinical studies demonstrating that this ingredient is effective in the treatment of acne.

References

(1) OTC Volume 070248
(2) OTC Volume 070250.

h. *Camphor.* The Panel concludes that camphor is safe but is not effective for OTC topical use in the treatment of acne. The Panel also concludes that at concentrations less than or equal to 0.2 percent, camphor is an inactive ingredient that can be used in formulations for product identification.

(1) *Safety.* The Panel considers camphor to be safe as discussed in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.**

(2) *Effectiveness.* Camphor has been submitted for the treatment of acne in concentrations of 2 to about 11 percent. No effectiveness data were contained in any of the submissions (Refs. 1, 2, and 3), nor is such data available in the medical literature. Depending on the concentration, camphor is considered either a local anesthetic to relieve itching (up to 3 percent) or a counterirritant (3 to 11 percent). The Panel sees no rationale for the use of such an ingredient in treating acne and concludes that this ingredient is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed camphor in Category II because there are no clinical studies available demonstrating effectiveness. Also there is no rationale for the use of this ingredient in treating acne.

References

(1) OTC Volume 070247.
(2) OTC Volume 070249.
(3) OTC Volume 070004.

i. *Chlorhydroxyquinoline.* The Panel concludes that chlorhydroxyquinoline is not safe and is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Chlorhydroxyquinoline (5-chloro-8-hydroxyquinoline) is an antifungal agent structurally similar to oxyquinoline (8-hydroxyquinoline) (Ref. 1). The latter compound was evaluated by this Panel in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register** and further studies were recommended to define the safety of oxyquinoline. There is even less information available on the toxicology of chlorhydroxyquinoline. Available data on the carcinogenicity of quinoline and oxyquinoline (Refs. 2 through 5), coupled with the mutagenicity of quinoline, 8-hydroxyquinoline, and 5-hydroxyquinoline in the Ames test (Refs. 6 and 7) make carcinogenicity tests on chlorhydroxyquinoline imperative. These tests should be carried out in a system using a tumor-promoting agent as well.

The Panel conclude that chlorhydroxyquinoline is not safe because there are no safety data available on this ingredient.

(2) *Effectiveness.* The Panel found only one study that evaluated chlorhydroxyquinoline as a single ingredient in the treatment of acne. Witkowski and Parish (Ref. 8) treated 100 patients with Grade II acne (Pillsbury's classification) with either 5 percent benzoyl peroxide-0.25 percent chlorhydroxyquinoline lotion (50 patients) or 0.25 percent chlorhydroxyquinoline lotion (50 patients). Patients were randomly assigned to either treatment group. They were instructed to wash the affected areas daily with "a commercially available soap used at home." Frequency of application was not explicity defined but apparently varied from patient to patient and with the patient's response to therapy. No other systemic or local therapy was allowed. Patients were examined at 2-week intervals using lesion counts to evaluate responses.

The results shown as percentage of reduction in lesion count after 6 weeks of treatment are as follows: 75 to 100 percent in 4 patients treated with chlorhydroxyquinoline and 10 treated with chlorhydroxyquinoline-benzoyl peroxide; 50 to 74.9 percent in 4 patients treated with chlorhydroxyquinoline and 17 treated with the combination; 25 to 49.9 percent in 5 patients treated with chlorhydroxyquinoline and 3 treated with the combination; 0 to 24.9 percent in 11 patients treated with chlorhydroxyquinoline and 9 treated with the combination. Eleven patients in the chlorhydroxyquinoline-benzoyl peroxide group became worse compared to 26 patients in the chlorhydroxyquinoline group. The combination product was found to be more effective than chlorhydroxyquinoline used alone ($p < 0.0005$). Chlorhydroxyquinoline does not appear to be effective in the treatment of acne, but it is difficult to draw conclusions because the trial was not vehicle controlled.

Chlorhydroxyquinoline is generally combined with benzoyl peroxide in marketed OTC products. The Panel believes that chlorhydroxyquinoline is not intended to be used as the sole active ingredient for the OTC topical treatment of acne. Because there is no vehicle-controlled trial evaluating the effectiveness of chlorhydroxyquinoline, the Panel concludes that this ingredient is not effective in the treatment of acne.

(3) *Evaluation.* The Panel has placed chlorhydroxyquinoline in Category II because there are no safety data available, particularly carcinogenicity studies. Also, there is not vehicle-controlled clinical trial evaluating the effectiveness of chlorhydroxyquinoline as a single ingredient for the treatment of acne.

References

(1) Windholz, M., "The Merck Index," (9th Ed., Merck and Co., Rahway, NJ, p. 276, 1976.
(2) Yamamoto, R. S., et al., "8-Hydroxyquinoline: Chronic Toxicity and Inhibitory Effect on the Carcinogenicity of N-2-Fluorenylacetamide," *Toxicology and Applied Pharmacology*, 19:687–698, 1971.
(3) Hirao, K., et al., "Carcinogenic Activity of Quinoline on Rat Liver," *Cancer Research, 36:329–335, 1976.*
(4) Hueper, E. C., "Experimental Studies on 8-Hydroxyquinoline in Rats and Mice," *Archives of Pathology*, 79:245–250, 1965.
(5) "World Health Organization, International Agency for Research on Cancer Monographs of Evaluation of Carcinogenic Risk of Chemicals to Man," Vol. 13, World Health Organization, Lyons, France, pp. 101–112, 1976.
(6) Talcott, R., M. Hollstein, and E. Wei, "Mutagenicity of 8-Hydroxyquinoline and Related Compounds in the *Salmonella Typhimurium* Bioassay," *Biochemical Pharmacology*, 25:1323–1328, 1976.
(7) Hollstein, M., R. Talcott, and E. Wei, "Quinoline: Conversion to a Mutagen by Human and Rodent Liver," *Journal of the National Cancer Institute*, 60:405–410, 1977.
(8) Witkowski, J. A., and L. C. Parish, "Chlorhydroxyquin-Benzoyl Peroxide Lotion in the Treatment of Acne—An Objective Evaluation," *CUTIS: Cutaneous Medicine for the Practitioner*, 5:1481–1484, 1969.

j. *Chloroxylenol.* The Panel concludes that chlorozylenol is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* The Panel considers chloroxylenol to be safe in concentrations up to 3.75 percent as discussed in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.**

(2) *Effectiveness.* Chloroxylenol is active in vitro against fungi and gram-positive and gram-negative bacteria.

The Panel has received one submission on 2 percent chloroxylenol (Ref. 1) which did not contain any clinical studies on effectiveness. To the Panel's knowledge, this ingredient has not been clinically studied for effectiveness in treating acne. Standard dermatology reference texts do not list chloroxylenol as an active ingredient for the treatment of acne. The Panel concludes that chloroxylenol is not effective for OTC use in the treatment of acne.

(3) *Evaluation.* The Panel has placed chloroxylenol in Categoy II because no controlled clinical trials are available evaluating the effectiveness of this ingredient.

Reference

(1) OTC Volume 070060.

k. *Coal tar.* The Panel concludes that coal tar is not safe and not effective for OTC topical use in the treatment of acne.

(1) *Safety.* The Panel thoroughly reviewed the toxicology of coal tar in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** Coal tar was placed in Category II because of substantial data indicating that it has a carcinogenic potential. Since that time, no other safety data were submitted to the Panel.

The Panel concludes that coal tar is not safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Crude coal tar 0.4 percent in an alcohol base was submitted as an active ingredient in one combination product used to treat acne (Ref. 1). The submission stated that coal tar USP "is a local irritant used topically in lotions and ointments in a range of 1 to 20% concentrations," but no data were included pertaining to the rationale for including the 0.4-percent concentration.

In its earlier review of crude coal tar for use in fungal infections, the Panel found references stating that coal tar 0.1 percent is astringent (Ref. 2); 2 to 4 percent is antipruritic; and 6 to 20 percent is keratoplastic, causing thickening of the upper layers of the skin (epidermis and stratum corneum) (Ref. 3). The Panel is unaware of any studies documenting the effect of 0.4 percent coal tar on skin.

In a letter referring to a presentation before the Panel on coal tar, Cullen (Ref. 4) stated: "There is no evidence in the medical literature that topical tar is of any value in the therapy of pruritus, chafing, tinea pedis, acne vulgaris, or soft corns."

The Panel was able to find only one other mention of the use of coal tar in acne in a book by Plewig and Kligman (Ref. 5). They wrote that "virtual cures (of acne) have been claimed for the combination of ultraviolet light and crude coal tar. The latter is a potent acneigen; moreover, its capacity to induce comedones is enhanced by sunlight."

The ability of coal tar to photosensitize the skin is well known. It is used therapeutically in the Goeckerman treatment of psoriasis and other skin diseases (Ref. 6).

The principal photosensitizing ingredients of coal tar are the acridine compounds in the anthracene oil fraction. Presumably, after absorption by the cells of the epidermis, these compounds become intimately associated with oxidizable substances in the cell. They are then activated by capture of a quantum (a unit of energy) of radiant energy of a specific wave length and react with oxygen, causing damage to the cell structure. The resulting oxygen deficiency then retards the development of keratin in the epidermis (Ref. 6).

Although exposure to sunlight alone is sometimes beneficial in treating acne, and photosensitization caused by coal tar might be theoretically beneficial in increasing the effects of sun exposure, no evidence of this is known to the Panel. On the contrary, Plewig and Kligman (Ref. 5) state that phototoxic reactions induced by coal tar may complicate acne in workers exposed to coal tar.

The Panel is aware of many reports stating that coal tar can induce acne and is a "potent comedogenic agent" (Ref. 5). Occupational "tar acne" is a common skin problem in road builders, roofers, and conduit makers exposed to coal tar, heavy coal tar distillates, or coal tar pitch (Ref. 7). Such workers develop extensive eruptions, comedones, and small yellowish cysts, which are most prominent on skin surfaces touched by soiled clothing. Hyperpigmentation of skin is also marked on the sun-exposed skin areas of these workers. Tar acne is probably caused by hydrocarbons, especially chloronaphthalene, deposited in the skin. The lesions resolve slowly, probably due to high tissue concentrations of the insoluble acnegenic substances (Ref. 5).

Coal tar induces hyperkeratosis in all keratinizing epithella, including the upper part of the pilosebaceous duct, which is usually not involved in comedo formation (Ref. 8). The first comedones which become visible in tar acne are of the open type, as the pilosebaceous canal orifice becomes distended with retained keratin (Ref. 9). The follicular horny papules are often black and surrounded by erythema (Ref. 10), and there is usually uniform involvement of most of the follicles within a certain area of the skin (Ref. 11). The tar comedones usually do not rupture to create papulopustules typical of acne vulgaris. The tar comedones also differ from the comedones of acne vulgaris by the virtual absence of *P. acnes* bacteria, probably due to bacteriostatic substances in the tar. The absence of inflammation in the tar comedones may be due to the lack of bacteria, which are thought to produce follicular irriation (Ref. 9).

A human model of coal tar acne was developed by Kaidbey and Kligman (Ref. 9) using a continuous occlusive application of crude coal tar to the backs of young adult males. A 25-percent concentration of coal tar distillate regularly induced an acneiform eruption after 3 weeks, but a 10-percent concentration produced only a mild follicular thickening in a few subjects.

The Panel concludes that coal tar is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel concludes that coal tar should be placed in Category II for the following reasons: (i) There are no clinical studies supporting the effectiveness of coal tar for the treatment of acne. (ii) Coal tar has been observed to induce acne in human models and in people exposed to it in their occupations. (iii) There are abundant data demonstrating a carcinogenic potential of crude coal tar and preparations derived from crude coal tar containing aromatic hydrocarbons.

References

(1) OTC Volume 070004.

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

(3) Pusey, W. A., "The Principles and Practice of Dermatology Designed for Students and Practitioners," 4th Ed., D. Appleton and Co., New York, pp. 132–135, 1924.

(4) Letter from Cullen, S. I. to A. M. Welch, Summary of proposed presentation to the Panel, included in OTC Volume 07BPA3.

(5) Plewig, G., and A. M. Kligman, "Acne: Morphogenesis and Treatment," Springer-Verlag, New York, pp. 59, 239, and 276, 1975.

(6) Cole, H. N., Jr., "Goeckerman Therapy in the Management of Common Dermatoses," *Archives of Dermatology and Syphilology,* 80:788–791, 1959.

(7) Ormsby, O. S., and H. Montgomery, "Diseases of the Skin," 7th Ed., Lea and Febiger, Philadelphia, p. 1330, 1948.

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(9) Kaidbey, K. H., and A. M. Kligman, "A Human Model of Coal Tar Acne," *Archives of Dermatology*, 109: 21–215, 1974.

(10) Domonkos, A. N., "Andrews' Diseases of the Skin," 6th Ed., W. B. Saunders Co., Philadelphia, p. 88, 1971.

(11) Rook, A., D. S. Wilkinson, and F. J. G. Ebling, "Textbook for Dermatology," Vol. II, F. A. Davis Co., Philadelphia, pp. 1350–1351, 1968.

1. *Dibenzothiophene.* The Panel concludes that dibenzothiophene is not safe and that there are insufficient data available to permit final classification of its effectiveness for OTC topical use in the treatment of acne.

(1) *Safety.* Very little safety data are available on dibenzothiophene. The Panel received only one submisson (Ref. 1) which contained two animal studies.

Acute oral toxicity was tested in rats using dibenzothiophene suspended in olive oil. Twelve dose levels ranging from 0.25 to 4.0 g/kg were included in the study. Although there were 32 animals in the study, many dose groups consisted of only one animal. The "approximate" LD_{50} was 0.5 g/kg. All deaths were delayed, and some animals remained comatose for several days. Other signs of toxicity were a rough coat, weakness, diarrhea, and a red crust above the eyes.

From this study, a level of 0.05 g/kg/day was chosen for administration to dogs in a chronic study. Four male beagles were dosed five times a week for 3 months. None of the dogs exhibited any signs of toxicity, including gross pathology and histopathology.

The Panel notes that derivatives of benzothiophene are highly toxic and many are carcinogenic. Because there are not enough toxicity data available to evaluate this ingredient, the Panel concludes that dibenzothiophene is not safe for OTC topical use in the treatement of acne.

(2) *Effectiveness.* The mechanism of action of debenzothiophene is thought to be the liberation of organic sulfur (Ref. 1), although this has not been well studied. In vitro testing of dibenzothiophene was done using the plate diffusion method (cup plate) with *Staphylococcus aureus (S. aureus)* and "a casual mixed culture or organisms found inhabiting normal skin" (Ref. 1). The site was not specified. Falcon plastic assay spiders were inserted into cups filled with 5.0 percent dibenzothiophene cream or lotion and then placed in wells in sterile agar. After 24 hours' incubation at 37° C, the zone of inhibition was measured. The zone of inhibition against *S. aureus* was 22 millimeters (mm) for the lotion and 21 mm for the cream. With the mixed culture, the zone was 40 mm for the lotion and 32 mm for the cream.

There are several unpublished clinical trials on the effectiveness of dibenzothiophene. One study of 82 patients used 5 percent dibenzothiophene in 10 different creams and lotions (Ref. 1). Some also contained hexachlorophene, sulfur, neomycin, and a cosmetic pigment. Twelve patients has excellent results; 57 had fair results and 13 had results rated as "minimal." However, this study did not meet the Panel's criteria. The specifics of the study were not given. The study was not double-blind or controlled. No definitions of how acne was measured or of treatment results were included. In addition, patients used many other treatments including soaps, systemic antibiotics, "something to relieve premenstrual tension and irregularity," superficial X-ray therapy, ultraviolet light, and staphylococcal vaccine. The length of time necessary to achieve the results was also not specified.

In another study (Ref. 1), 16 patients with Grade I to III acne (based on number of acne lesions) were treated with 5 percent dibenzothiophene cream and lotion. The patients were given no other therapy and used the cream or lotion three or four times daily. Results showed nine patients excellent, three much improved, three improved, and one worse. There was no control in this trial. Also, it was not clear how long it took to achieve the results.

A study on 51 patients treated with 5 percent dibenzothiophene for 3 months showed the following results: 13 excellent, 20 good, 8 fair, and 9 poor. No explanation was given for the one patient who apparently dropped out of the study. Some patients with cystic acne were treated concurrently with superficial X-ray therapy and vaccines. No specific information was given on frequency of application or definition of results (Ref. 1).

Another unpublished study was conducted on over 100 patients treated with 5 percent dibenzothiophene cream or lotion (Ref. 1). No details were given on the frequency of application, other medications used, or the length of the trial. Although no specific results were given, the investigators noted "it is an effective topical agent with good patient acceptance."

Although dibenzothiophene appears useful in the treatment of acne, there are no controlled clinical trials that meet the effectiveness criteria established by the Panel. The Panel concludes that this ingredient is of questionable effectiveness for OTC use in the treatment of acne.

(3) *Evaluation.* Dibenzothiophene has been placed in Category II because the safety data are quite limited. The compound was fairly toxic when given in an acute study. There was no suggestion of a mechanism of action. Also, the Panel considered the only chronic study poorly designed (only four dogs, no controls). The Panel is also concerned about toxicity because many derivatives of benzothiophene are highly toxic.

Reference

(1) OTC Volume 070096.

m. *Estrone.* The Panel concludes that estrone is not safe and is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Estrone is a metabolite of estradiol, an ovarian hormone. Generally the estrogens used in therapy are readily absorbed through the skin and can have systemic effects. During enterohepatic circulation, they are gradually oxidized and conjugated to less active products. Normally, up to 100 μg of estrogens are excreted daily by females at the midcycle ovulating maximum, up to 25 μg per day by males, and 30 mg per day in pregnant females who are near term. The usaul prescription dose of oral estrone given for various uses is 5 mg. Nausea is the most frequent symptom associated with oral estrogen therapy. In addition, it has been suggested that there is an increased risk of thromboembolism and cancer as a result of long-term estrogen therapy (Ref. 1).

The use of creams containing estrone 2.5 mg/g, which results in a daily does of 5 mg, had not caused obvious side effects (Refs. 2, 3, and 4). However, it is generally agreed that, to achieve local efficacy, estrone must be absorbed in sufficient quantity to cause systemic effects (Refs. 5 and 6). The Panel notes that these studies were not looking specifically for side effects. The studies were short term and included small numbers of patients. The panel concludes that estrone is not safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Estrogens were first reported as being used topically in the treatment of acne in the late 1940's. Acne was thought to be primarily caused by an endocrine disturbance affecting the pilosebaceous unit (Refs. 2, 3, and 7). Acne patients were shown to have an increased ratio of androgens to estrogens, the androgens being responsible for pilosebaceous gland activity. It was believed that topical application of estrogens would result in a more normal androgen-estrogen ratio.

resulting in reduction of sebum secretion and subsequent reduction of acne lesions. The substance most commonly used in these studies was a water-soluble, conjugated equine estrogen, sodium estrone sulfate. One mg estrone is equal to 10,000 I.U.

Shapiro (Ref. 7) treated 30 patients with acne that had not responded to the usual treatments with 2.5 to 5 mg estrone applied two to four times daily. Within 6 weeks he noticed improvement shown by a decrease in papules, pustules, and oiliness. The applications were then gradually reduced to once daily or once every other day. After 16 weeks of treatment, Shapiro reported that 20 of the 30 patients showed a satisfactory clinical remission. He stated that treatment with estrone offered "a promising approach to therapy-resistant acne vulgaris." The Panel notes that Shapiro expressed the patients' comedones during the treatment period. (The word "express," as used in dermatology, means to remove contents by squeezing or pressing.) The Panel considers this study not well controlled because expression is also a type of therapy.

In a later study, Shapiro (Ref. 3) tested the effectiveness of estrone in 25 patients. Again he chose patients who had not responded to the methods of treatment usually used then, including X-ray therapy, ultraviolet irradiation, dietary regimens, and various peeling agents. The total daily application of estrone was 5 mg. Treatment was continued for 1 to 7 months (average 4 months). The estimated total amount of estrogenic substances applied in this time ranged from 150 to 700 mg.

As in the previous study by Shapiro (Ref. 7), lesions were not counted. Evaluation was based on clinical judgment, i.e., whether there was an apparent decrease in skin oiliness or a reduction of pustules, papules, comedones, and cysts. Shapiro reported that excellent results were obtained in 15 patients (60 percent). Results were good in four patients and fair in three. Three patients could not tolerate the cream and were dropped from the study.

Shapiro (Ref. 3) also monitored changes in menstrual cycle, breasts, and libido to determine any systemic effects. He found no adverse effects from the use of estrone.

Sawicky, Danto, and Maddin (Ref. 2) evaluated the effectiveness of estrone in a half-face study of 26 patients. Half of the face was treated with 2.5 mg estrone daily. The vehicle control was applied to the other half of the face. The patients were unaware of which side of the face received the active treatment. Patients were treated for 2 to 16 weeks with the total amount of hormone applied ranging from 38 to 204 mg.

The investigators found estrone to be more effective on cystic lesions than on papules and pustules. Three male patients with cystic acne showed great improvement on the side of the face treated with estrone. Patients with papules and pustules were reported to have moderate, slight, or no improvement.

The clinical data from several researchers (Refs. 8, 9, and 10) indicate that perhaps males benefit more from topical estrogen therapy than females. For example, Whitelaw (Ref. 8) used a cream containing 0.625 mg estrone/g and found that 55 percent of his male patients (76 patients) were much improved after treatment for 6 months or more, but that only 21 percent of the female cases (23 patients) responded satisfactorily.

Using diethylstilbestrol dilaurate (a synthetic estrogen) lotion on 84 patients, Philip (Ref. 9) came to a similar conclusion. Patients applied 3.5 to 7 mg diethylstilbestrol daily. The dosage was gradually reduced after 6 weeks of treatment. The length of treatment, however, is unclear. Of the 36 males in the study, 33 (92 percent) showed good or excellent improvement. Ten (21 percent) of the 48 females were reported as good or excellent at the conclusion of the trial. Philip concluded that estrogen therapy "appears to be effective and desirable only in the management of acne vulgaris in the adolescent male."

Peck, Klarmann, and Spoor (Ref. 10) reported good or excellent results in 55 of 69 patients treated with a lotion containing estrone. The lotion also contained numerous other ingredients including zinc oxide, zinc sulfide, sulfur, salicylic acid, aluminum hydroxide, and oxyquinoline. The authors believed the lotion to be somewhat more effective in males than in females. They stated that natural estrone was more satisfactory than synthetic estrogenic hormones such as diethylstilbestrol.

The researchers also stated that the optimal concentration of estrone is 50,000 I.U./ounce (5 mg/ounce). This is considerably lower than the concentrations used in the studies described above (150,000 to 600,000 I.U./ounce). Concentrations above 50,000 I.U. would produce undesirable systemic effects. Peck, Klarmann, and Spoor (Ref. 10) found no effect of topical estrogen on blood estrogen level, menstrual cycle, or vaginal cornification after 1 month of applications to 12 subjects.

Estrone was contained in only one product submission to the Panel (Ref. 11). The concentration of estrone in this product is quite low—0.333/mg ounce (3,333 I.U./ounce).

Damrau (Ref. 12) tested the estrone cream described above (which also contains salicylic acid) on 45 subjects. He reported that the action of the cream is hyperemizing, meaning that it causes an increased blood flow to a part of the body. It is keratolytic and "produces an unusual degree of absorption and effectiveness of estrone."

A control group of 16 subjects used a "leading acne product" (ingredients not specified). Both groups were instructed to apply a thin layer of cream over the affected area of the face twice daily. The total amount was one-half teaspoonful. After 5 minutes the cream was washed off with soap and water.

The total amount of estrogenic hormone applied in 1 month was under 2 mg (20,000 I.U.). Length of treatment was 6 months in the estrone group and 3 months in the control group.

The results showed 80 percent of the estrone-treated patients improved after 1 month, with 2 percent of the patients completely cleared. After 6 months, 73 percent of the patients were completely cleared, and the remaining patients were improved. In the control group after 3 months, 75 percent were improved and the rest showed no change.

Overall acne counts decreased from 6.2 to 0.6 in the treated group and from 6.2 to 4.8 in the controls. The acne count was not specified as to lesion type. Although the results were not analyzed statistically, Damrau (Ref. 12) concluded that the estrone cream was a superior product.

Most of the studies reviewed by the Panel reported favorable results for estrone in the treatement of acne. Several authors in medical journals (Refs. 13, 14, and 15), however, held that local estrogen therapy was of limited value.

It is apparent from the review of the literature that there has been little work done in the last 20 years to indicate that topically applied estrogen is an effective ingredient to treat acne. None of the studies reviewed met the standards the Panel has recommended to determine effectiveness. None of the studies were randomized or double-blind and most did not use a vehicle control. Methods of evaluating patients were not rigidly defined and in some cases were difficult to determine. Results were not statistically analyzed.

The effectiveness of topical estrogens in acne is not attributed to a local effect on the skin (Ref. 16). Theoretically, estrongens may affect the sebaceous glands by inhibiting androgen

production. The Panel believes, however, that very high concentrations of estrone would have to be applied topically for sufficient amounts to be absorbed systemically to produce this effect.

The Panel notes that in the only submission on estrone, this ingredient occurs in such a small concentration (3,333 I.U./ounce) that a systemic effect is unlikely. The panel concludes the estrone is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed estrone in Category II because it is toxic at the high concentrations needed to produce an effect on acne lesions.

References

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n. *Magnesium sulfate.* The Panel concludes that magnesium sulfate is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Magnesium sulfate is also known as epsom salts. One gram is equivalent to 4.06 millimoles or 8.12 milliequivalents (meq) of magnesium (Ref. 1). The primary use of this salt is as a cathartic, where the usual dose is 15 g. Although the mechanism of action may be fluid retention due to an osmotic gradient, absorption of up to 20 percent does occur and can result in symptoms of magnesium intoxication in persons with kidney failure (Ref. 2). A study of five patients with kidney insufficiency who received high doses of magnesium described symptoms of hypermagnesemia (an abnormally large magnesium content in the blood plasma) as nausea, vomiting, malaise, hypotension, and drowsiness (Ref. 3).

In evaluating magnesium sulfate for OTC use as a laxative, one Panel suggested that a warning label for people with kidney disease be included on products in which a daily dose would be more than 50 meq (40 FR 12910). In evaluating this drug as an antacid, the Advisory Review Panel on OTC Antacid Drug Products suggested a similar warning in its recommendations published in the **Federal Register** on April 5, 1973 (38 FR 8719).

Other therapeutic uses of magnesium sulfate include treatment of eclampsia (convulsions and coma occurring in pregnancy or after childbirth) and hypomagnesemia (an abnormally low magnesium content in the blood plasma). For eclampsia magnesium sulfate can be given intramuscularly or intravenously. Magnesium sulfate functions as a sedative and anticonvulsant (Ref. 4). For treatment of hypomagnesemia, magnesium sulfate can be given as intramuscular doses of 2 g four times daily, or as intravenous doses of 2 to 4 g daily (Ref. 1).

Magnesium sulfate has also been extensively used topically to alleviate local inflammatory conditions. No adverse effects were noted (Ref. 5). Because magnesium is poorly absorbed through the skin (Ref. 6), it is unlikely that, even in patients with impaired kidney function, topical use could result in absorption of magnesium in sufficient quantities to cause systemic toxicity. The Panel concludes that magnesium sulfate is safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* The Panel received one product submission containing magnesium sulfate at concentrations of 40 to 43 percent (Ref. 7). The Panel notes that this ingredient is formulated in a hydrophilic ointment base, a known comedolytic agent. According to the submission (Ref. 7), the mechanism of action of magnesium sulfate is "drawing inflammation to the surface of the skin by osmotic pressure." Another submission included a report of a study in which magnesium sulfate was used to treat a dermatological condition (Ref. 8). However, no information on the use of magnesium sulfate in the treatment of acne was included.

There are no studies in the submission or in the medical literature indicating that magnesium sulfate is of value in treating acne. The Panel concludes that magnesium sulfate is not effective for OTC use in the treatment of acne.

(3) *Evaluation.* The Panel has placed magnesium sulfate in Category II because there are no studies that demonstrate that this ingredient is effective in the treatement of acne.

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(7) OTC Volume 070245.

(8) OTC Volume 070276.

o. *Phenolates (phenol and phenolate sodium).* The Panel concludes that the phenolates (phenol and phenolate sodium) are not effective and that there are insufficient data available to permit final classification of their safety in concentrations of 1.5 percent or less for OTC topical use in the treatment of acne.

The Panel considers phenol and phenolate sodium as a single ingredient when both are contained in a product

formulation. The total level of phenol equals the sum of the phenol and phenolate sodium concentrations.

(1) *Safety.* The potential toxicity of phenol in concentrations greater than 1.5 percent was described by the Advisory Review Panel on OTC Antimicrobial I Drug Products elsewhere in the **Federal Register** (39 FR 33121) published September 13, 1974. This Panel agreed with that assessment and further described the toxicity of phenol in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** Phenol was considered of questionable safety for OTC topical use in concentrations less than 1.5 percent. The Panel has received no new data that leads it to change this evaluation.

The Panel concludes that there are insufficient data to adequately determine the safety of phenol in concentrations less than or equal to 1.5 percent. The reason for this decision is the lack of controlled studies evaluating (1) the absorption from small areas of application to either broken or intact skin, (2) the local effects on wound healing, and (3) the potential for hypersensitivity or idiosyncratic reactions.

(2) *Effectiveness.* Phenol has anesthetic, bactericidal, and fungicidal properties (Ref. 1). Apparently, the anesthetic effect of phenol is the reason for its inclusion in acne products.

Phenol has been studied in a variety of inflammatory diseases, athlete's foot, and infected eczema (Refs. 1, 2, and 3). However the Panel could find no clinical trials examining the effectiveness of phenol in treating acne.

Plewig and Kligman (Ref. 4) state that most "traditional exfoliants turned out to be surprisingly weak or ineffective: phenol, resorcinol, beta-naphthol, sulfur, Vleminckx's solution and sodium thiosulfate. Hence, only a few agents which cause peeling are in fact comedolytic. The probable explanation is that most 'peelers' affect only the epidermis and not the follicular infrainfundibulum."

The Panel concludes that there are no data to show that the phenolates are clinically effective in the treatment of acne.

(3) *Evaluation.* In the absence of clinical trials demonstrating effectiveness in the treatment of acne, the Panel has placed phenolates (phenol and phenolate sodium) in Category II.

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p. *Phenyl salicylate.* The Panel concludes that phenyl salicylate is not effective and that there are insufficient data available to permit final classification of its safety for OTC topical use in the treatment of acne.

(1) *Safety.* The Panel reviewed the safety of phenyl salicylate in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** Since the Panel made those recommendations, no additional safety data were submitted. In the absence of data on irritation, sensitization, and effects on broken skin, the Panel concludes that phenyl salicylate is of questionable safety for topical use in the treatment of acne.

(2) *Effectiveness.* The Panel received only one product submission on phenyl salicylate (Ref. 1). This submission contained no data and the Panel could not find mention in the medical literature of phenyl salicylate for the treatment of acne. The Panel concludes that phenyl salicylate is not effective in the OTC topical treatment of acne.

(3) *Evaluation.* The Panel has placed phenyl salicylate in Category II because there are no effectiveness data available. The Panel believes there is no rationale for the use of this ingredient in the treatment of acne.

Reference

(1) OTC Volume 070004.

q. *Pyrilamine maleate.* The Panel concludes that pyrilamine maleate is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Pyrilamine maleate is a widely used antihistamine. The Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products reviewed pyrilamine for that use and considered it safe in its recommendations published in the **Federal Register** of September 9, 1976 (41 FR 38391). The recommended oral dose is 25 to 50 mg three to four times daily.

Submissions to the Panel indicated no toxic effects or irritation from the topical use of pyrilamine maleate (Refs. 1 and 2). Patch tests on a combination product containing 1 percent pyrilamine maleate showed no cutaneous sensitivity (Refs. 1 and 2), although this ingredient is known to be a mild sensitizer when used topically.

In the Panel's view, pyrilamine maleate is safe for topical use.

(2) *Effectiveness.* The Panel is not aware of any clinical trials demonstrating the effectiveness of pyrilamine maleate in treating acne. According to the submissions received by the Panel (Refs. 1 and 2), pyrilamine maleate is used in acne treatment products as an antipruritic and is effective in treating wheals which are flat or raised lesions that may itch or burn and are typical of hives. The Panel believes it is irrational to use an antihistamine or antipruritic to treat acne. The Panel concludes that pyrilamine maleate is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed pyrilamine maleate in Category II because there is no rationale for the inclusion of an antihistamine in acne treatment products.

References

(1) OTC Volume 070046.

(2) OTC Volume 070047.

r. *Resorcinol and resorcinol monoacetate.* The Panel concludes that resorcinol and resorcinol monoacetate are safe but are not effective as single ingredients for OTC topical use in the treatment of acne.

(1) *Safety.* Resorcinol is a phenolic compound which was reviewed by this Panel in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** The Panel considered resorcinol in high concentrations (10 percent) to be unsafe for topical use. As discussed in the publication mentioned above, resorcinol resembles phenol in its systemic actions but causes more prominent central stimulation. Acne preparations contain up to 2 percent resorcinol or 3 percent resorcinol monoacetate.

Patty (Ref. 1) reported that the cutaneous application of solutions or salves containing from 3 to 25 percent resorcinol could result in local toxicity including edema, itching, dermatitis, or peeling. Systemic toxicity could also occur. Some signs of systemic toxicity include restlessness, methemoglobinemia, convulsions, or death. The Panel recognizes that the severity of the signs would be related to the dose.

Patty also noted that ingestion of 4 g resorcinol caused dizziness and sleepiness in a 4-year-old child. In another case after ingestion of 8 g resorcinol the signs and symptoms included fall in blood pressure and low

body temperature. Both patients recovered.

A combination of 8 percent sulfur and 1 percent resorcinol was used in an eye irritation study conducted in rabbits. This study confirmed the potential for irritation if the sulfur-resorcinol combination was allowed to remain in the eye. Washing the eyes after 30 seconds of exposure greatly reduced the irritation (Refs. 2 and 3).

Acute dermal irritation studies in rabbits confirmed the mild irritation potential of this combination (Refs. 2 and 3).

Subacute studies (Refs. 2 and 3) of the above combination were conducted in rabbits on both normal and abraded skin. Some of the studies were done over 20-day periods and others over 30-day periods. Dose levels of 0.1, 0.3, and 1.0 g/kg body weight were applied daily to the shaved backs of rabbits (both males and females). At the end of these studies, hematology studies, urinalysis, gross pathology, and histopathological evaluations were done. In general, all values within normal limits, except that skin changes of an irritant nature were noted for the higher dose levels.

Although these studies appeared to be comprehensive, well-controlled, and well-conducted, the Panel noted several deficiencies. For example, in the dermal exposure of rabbits about 6 to 7 percent of the body surface area was exposed to the sulfur-resorcinol combination. However, in actual human use for acne, the area of application includes the face, shoulders, chest, and back and represents about one-half of the body surface area. In addition, the study indicated the material was applied once daily. But in the treatment of acne in humans the recommended application is three times daily. Also, at the highest dose used, 1 g/kg/day, the total exposure of the rabbit to resorcinol amounted to 20 mg/kg/day with a limited surface area for absorption. This study did not address the Panel's major concern about the absorption potential when large amounts of resorcinol are applied to large surface areas, particularly when it is applied three times daily.

In subchronic studies, resorcinol used alone was administered by various routes to rats and rabbits. The only noteworthy toxicological finding was an increase in the weight of the thyroid. In the rat a no-effect level was reported as 154 mg/kg given twice daily subcutaneously for up to 38 days (Ref. 4).

The results of the micronucleus test in rats and a modified Ames test using *Salmonella typhimurium* showed that resorcinol was not mutagenic (Refs. 5 and 6). Following application to the skin of mice for 368 days or to the skin of the rabbit ear for up to 160 weeks, resorcinol was not found to be carcinogenic (Refs. 7 and 8).

The Panel also received limited data on human exposure to airborne resorcinol in the work place. Workers were exposed for 10 years or longer to an "inhaled threshold limit value" of 10 ppm. This equals a total inhaled dose of about 6.43 mg/kg/day. Workers did not complain of irritations or discomfort, nor did they display abnormal clinical signs referrable to the thyroid gland, central nervous system, or hematological system. Blood determinations for thyroid-stimulating hormone (TSH) and thyroid hormone (T_4) showed that values were within the normal range (Refs. 9 and 10).

In vitro skin penetration studies were done using excised human skin to determine the percutaneous absorption of resorcinol applied as a 2-percent resorcinol-8 percent sulfur cream (Ref. 11). Data indicated a lag time of about 3 hours followed by a maximum rate of skin penetration of 6.1 $\mu g/cm^2/h$. This would yield a pharmacokinetically calculated steady-state blood level of resorcinol of 19 $\mu g/100$ mL in persons with acne. (Pharmacokinetics is the study of the action of a drug over a period of time. Steady state refers to the point at which the amount of drug absorbed is equal to the amount eliminated.) This level is reported to be 1/161 to 1/653 of the blood levels estimated to have been reached in leg-ulcer subjects who had systemic toxicity (ref. 11).

Plasma, tissue distribution, and excretion data indicated that resorcinol (containing trace amounts of ^{14}C-resorcinol) was rapidly eliminated from the rat following a single subcutaneous injection of 10, 50, or 100 mg/kg (Ref. 12). Resorcinol was also rapidly eliminated after repeated dosing with a total daily dose of 100 mg/kg given daily over 14 days. The amount of the resorcinol dose eliminated in the urine was 85.7 percent in about 3 hours and 93.6 percent in 24 hours. Between 1 hour and 24 hours following injection, plasma levels decreased from 0.32 percent to 0.01 percent of the administered dose. One hour after administration, the amount of the administered dose contained in potential target organs was 0.005 percent in the thyroid, 0.02 percent in the brain, and 0.03 percent in the spleen. Plasma half-life was determined using doses of 50 and 100 mg/kg. The half-life was 0.5 hour during the first 2 hours after treatment and about 4 hours thereafter. No significant difference in plasma elimination rates were observed between the single dose and the repeated doses of resorcinol. Organ disposition data showed that vital and potential target organs did not accumulate resorcinol during the time in which plasma levels were declinng (Ref. 12).

Resorcinol excreted in rat urine was about 75 percent glucuronide and 25 percent sulfate ester. No free resorcinol was detected (Ref. 12).

The percutaneous absorption and metabolic disposition of resorcinol were investigated in three human volunteers. Resorcinol 2 percent in a hydroalcoholic vehicle was applied to the face, neck, shoulders, back, and chest (about 30 percent of the available skin area). Blood samples were collected 1 week after this first drug application and weekly for 3 more weeks. No resorcinol was detected at the limit of the assay (0.5 $\mu g/mL$).

After 2 weeks of continuous application (800 mg/subject/day), an average of 1.64 percent of the administered dose was excreted in the urine at 24 hours. The excreted resorcinol was in the form of either the glucuronide or the sulfate ester. Thyroid function was assessed at 2, 3, and 4 weeks and found to be normal. Blood chemistries were also normal in all subjects throughout the study (Ref. 12).

The Panel concludes that 2 percent resorcinol or 3 percent resorcinol monoacetate is safe for OTC topical use in the treatment of acne. However, the Panel is concerned about the potentially large surface area of the body that could be available for absorption if an acne preparation were applied to the entire upper torso (about 1 square meter of absorption area through broken skin). For this reason the Panel recommends the following warning for acne combinations containing resorcinol: "Apply to affected areas only. Do not use on broken skin or apply to large areas of the body." (See part III. paragraph A.2. above—Category I labeling.)

(2) *Effectiveness.* The concentration of resorcinol generally used in acne products is 1 to 2 percent. Resorcinol monoacetate 3 percent is equivalent to 2 percent resorcinol. Resorcinol has antibacterial, antifungal, and mild keratolytic activity. Resorcinol monoacetate slowly liberates resorcinol, producing a milder, but longer-lasting effect (Ref. 13).

As mentioned above, sulfur and resorcinol are often used together in the treatment of acne, but it is difficult to document the historical origin of this combination. The precise mechanism of action of these combinations has never

been proven, but may depend on keratolysis or on the ingredients' ability to produce erythema and desquamation with enhanced resolution of comedones, papules, and pustules. (For a review of sulfur-resorcinol combinations, see part III. paragraph D.1. below—Category I combination product—sulfur-resorcinol.)

No study has examined the effectiveness of resorcinol used as a single ingredient in the treatment of naturally occurring acne. The Panel concludes that resorcinol is not effective for OTC topical use as a single ingredient in the treatment of acne.

(3) *Evaluation.* In the absence of data documenting the effectiveness of resorcinol and resorcinol monoacetate used alone in the treatment of acne, the Panel has placed these ingredients in Category II.

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(1) Patty, F., "Industrial Hygiene and Toxicology," 2d Ed., Vol. 2, Interscience Publishing Co., New York, p. 1379, 1963.

(2) OTC Volume 070234.

(3) OTC Volume 070235.

(4) OTC Volume 070284.

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(8) Stenback, F., "Local and Systemic Effects of Commonly Used Cutaneous Agents: Lifetime Studies of 16 Compounds in Mice and Rabbits," *Acta Pharmacologica et Toxicologica*, 41:417–431, 1977.

(9) OTC Volume 070287.

(10) OTC Volume 070288.

(11) OTC Volume 070271.

(12) OTC Volume 070290.

(13) Harvey, S. C., "Antiseptics and Disinfectants; Fungicides; Ectoparasitides," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, p. 991, 1975.

s. *Sodium thiosulfate.* The Panel concludes that sodium thiosulfate is safe but is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Sodium thiosulfate, $Na_2O_3S_2$, is a water-soluble reducing agent used in veterinary medicine to treat ringworm and mange (Ref. 1). It has also been used extensively as an antidote for cyanide posioning in humans (Ref. 2). In this treatment, the stomach contents are washed out with a solution of 5 percent sodium thiosulfate, leaving 10 g of the solution in the stomach.

The lowest subcutaneous dose known to cause death in the rabbit is reported as 4 g/kg (Ref. 3). The intravenous LD_{50} in the rat is greater than 2.5 g/kg (Ref. 1). One study used oral gavage and determined the minimal lethal dose in the rat to be greater than 5 g/kg (Ref. 4). At this dose, labored breathing and panting were the only symptoms observed. Sodium thiosulfate at concentrations up to 22 percent was found to be nonirritating to intact or abraded rabbit skin occluded for 24 hours and read at 24 and 72 hours (Ref. 4).

The Panel concludes that sodium thiosulfate is safe for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Sodium thiosulfate is contained in marketed acne products in concentrations of 2 to 8 percent. The apparent rationale for the use of this ingredient is a potential keratolytic and antibacterial activity either by sodium thiosulfate itself or by sulfur that is liberated when the compound comes in contact with the skin.

Numerous unpublished studies have evaluated the effectiveness of sodium thiosulfate (Ref. 4). However, none of these studies met the effectiveness criteria set by the Panel. All involved a combination product containing sodium thiosulfate, resorcinol, and salicylic acid. None used a vehicle control. The method of patient evaluation and treatment results were usually not explained. In one study, the combination product mentioned above was tested on 74 patients with acne vulgaris. The results were as follows: 46 percent very good, 39 percent good, 8 percent "medium," and 7 perent poor. No other details were given.

In an uncontrolled clinical trial, Sewell (Ref. 5) evaluated 224 patients who had mild to severe acne. No mention was made of randomization or blinding. A sodium thiosulfate combination product was applied four times daily for 2 to 50 weeks. The patients also washed with a soap containing salicylic acid and sulfur. Of the 28 subjects using a 2-percent sodium thiosulfate-1 percent salicylic acid-1 percent resorcinol lotion, 64.3 percent showed marked improvement and the rest were improved by the end of the study. The other 196 patients applied an 8-percent sodium thiosulfate-2 percent salicylic acid-2 percent resorcinol lotion. Of these patients, 33.7 percent were improved and 65.8 percent were markedly improved. Sewell concluded that the sodium thiosulfate combinations were effective in the treatment of acne, although it is difficult to determine the contribution made by sodium thiosulfate as a single ingredient.

Hall and Lupton (Ref. 6) studied 44 patients with acne in a double-blind, half-face trial. One-half of each patient's face was treated with 8 percent sodium thiosulfate-2 percent salicylic acid-2 percent resorcinol. An alcohol-water vehicle was applied to the other half of the face. Treatment was twice daily for 8 weeks. Patients were allowed to continue medications they were previously using including abrasive cleansers and tetracycline. At the final evaluation, the researchers determined which side of the face showed greater improvement. In 19 patients, the treated side showed more improvement. Five patients were more improved on the placebo side. In the remaining patients, no difference was noted between the combination product and the placebo.

Although the effectiveness of sodium thiosulfate has been studied extensively, none of the studies have evaluated sodium thiosulfate as a single active ingredient. For this reason the Panel concludes that sodium thiosulfate is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* In the absence of data demonstrating effectiveness as a single ingredient in the treatment of acne, the Panel has placed this ingredient in Category II.

References

(1) Windholz, M., et al., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, pp. 1122–1123, 1976.

(2) Thienes, C. H., and T. J. Haley, "Clinical Toxicology," 5th Ed., Lea and Febiger, Philadelphia, p. 205, 1972.

(3) Fairchild, E., "Registry of Toxic Effects of Chemical Substances," Vol. II, United States Department of Health, Education, and Welfare, Cincinnati, p. 907, 1977.

(4) OTC Volume 070088.

(5) Sewell, J. W., Jr., "Therapeutic and Cosmetic Advantages of a Nonpigmented Acne Lotion," *CUTIS; Cutaneous Medicine for the Practitioner*, 1:473–476, 1965.

(6) Hall, J. H., and E. S. Lupton, "Topical Acne Therapy: A Double-Blind Study," *CUTIS; Cutaneous Medicine for the Practitioner*, 9:545–547, 1972.

t. *Tetracaine hydrochloride.* The Panel concludes that tetracaine hydrochloride is not safe and is not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Tetracaine hydrochloride is a derivative of *p*-aminobenzoic acid similar to benzocaine. (For a discussion of benzocaine, see part III. paragraph B.1.c. above—Benzocaine.)

The aminobenzoic acid derivatives are known to cause allergic sensitivity reactions. Also, cross-sensitivity

between members of this group is frequently reported. Sensitivity tests such as skin, conjunctival, and patch tests are not considered reliable for predicting the possibility of allergic reactions (Ref. 1).

Tetracaine hydrochloride is used as a 0.5-percent solution for the topical anesthesia of the eye. On mucous membranes of the nose and throat, a 2-percent solution is used (Ref. 2). However, considering the large surface area of application and the possibility of long-term use in acne, the Panel concludes that tetracaine hydrochloride is not safe for OTC topical use in the treatment of acne because of the potential for sensitization.

(2) *Effectiveness.* According to a submission to the Panel, tetracaine hydrochloride, a local anesthetic, is included in acne preparations to help "relieve the irritation and discomfort usually associated with acne vulgaris" (Ref. 3).

Tetracaine hydrochloride was found to be one of the most effective and longest lasting drugs in a series of topical anesthestics studied by Adriani and Zepernick (Ref. 4). These researchers reported the maximum effective concentration as 1 percent. The concentration of tetracaine hydrochloride currently marketed in acne products is 0.25 percent.

There are no clinical trials establishing the effectiveness of tetracaine hydrochloride in treating acne. The Panel believes the use of a local anesthetic in acne treatment is irrational therapy and concludes that tetracaine hydrochloride is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed tetracaine hydrochloride in Category II because it is a recognized sensitizer and there is no rationale for the use of a local anesthetic in the treatment of acne.

References

(1) Swinyard, E. A., "Local Anesthetics," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by A. Osol and J. E. Hoover, Mack Publishing Co., Easton, PA, pp. 986–987, 1975.

(2) Ritchie, J. M., and P. J. Cohen, "Cocaine; Procaine and Other Synthetic Local Anesthetics," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, pp. 379–400, 1975.

(3) OTC Volume 070046.

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

u. *Thymol.* The Panel concludes that thymol is not effective and that there are insufficent data available to determine its safety for OTC topical use in the treatment of acne.

(1) *Safety.* The toxicology of thymol was discussed in the Panel's recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register**. The Panel determined that this ingredient is of questionable safety because of inadequate data evaluating the absorption of thymol from small areas of application to intact and broken skin. Data on the local effects of thymol on wound healing and thymol's irritation potential were also lacking. Acne submissions on thymol (Refs. 1 and 2) were reviewed and found to contain no new information. The Panel concludes that thymol is of questionable safety for OTC topical use in the treatment of acne.

(2) *Effectiveness.* Thymol, an ingredient with antibacterial and antifungal properties, is used in acne preparations in concentrations of about 0.16 to 0.5 percent. At these low concentrations thymol has questionable antibacterial activity.

Several affectiveness studies (Ref. 3) have been reviewed by the Panel, but none evaluated thymol against a vehicle control. In one study, 60 subjects applied a 0.16-percent thymol scrub once or twice daily for 3 months. The patients were evaluated on a scale of 0 to 4 for comedones, papules, pustules, and oiliness at the pretreatment examination and at the conclusion of the study. Results showed that the subjects had significantly fewer acne lesions and less oiliness after 3 months than at the beginning of the trial ($p < 0.01$).

Thymol was also evaluated in an 8-week trial of 139 patients (Ref. 3). Forty-seven subjects applied a thymol gel; 44 subjects used a thymol lotion. The remaining patients used soap and water. Again, acne lesions were not counted. Evaluation of blackheads, whiteheads, papules, pustules, and oiliness was based on a severity scale (1 to 5). Analysis of results showed that the thymol gel and lotion were significantly more effective than soap and water in the overall evaluation at 8 weeks ($p < 0.05$ and 0.01, respectively). Treatment with soap only, however, also showed a statistically significant improvement over the initial examination ($p < 0.01$).

The Panel doubts that thymol is effective as a single active ingredient for treating acne. This ingredient has little or no antibacterial activity in the concentrations currently used in OTC acne products. To the Panel's knowledge, the effectiveness of this ingredient for treating acne has never been established in a vehicle-controlled clinical trial. Thymol is not listed in standard medical texts as beneficial in acne therapy. The Panel concludes that thymol is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* In the absence of data evaluating the effectiveness of thymol in a vehicle-controlled study for the treatment of acne, the Panel has placed thymol in Category II for effectiveness.

References

(1) OTC Volume 070002.

(2) OTC Volume 070155.

(3) OTC Volume 070156.

v. *Vitamin E.* The Panel concludes that vitamin E is not effective and that there are insufficient data available to determine its safety for OTC topical use in the treatment of acne.

(1) *Safety.* Vitamin E (*alpha*-tocopherol acetate) is a naturally occurring oil found primarily in plant materials (Ref. 1). The highest concentrations are found in wheat germ, sunflower seeds, soybean oils, and other plant sources. Deficiency of this vitamin in animals results in symptoms which closely resemble various conditions in the human that allegedly benefit from vitamin E therapy. These include disorders of the reproductive, muscular, cardiovascular, and hematopoietic systems (Ref. 2). (Hematopoietic refers to the production of blood cells.)

There are no notable pharmacological or toxicological effects of oral vitamin E, nor any explanation of its mode of action. Presumably, it exerts its effect by virtue of its properties as an antioxidant (Ref. 2). This concept is supported by observations on the protective effect of vitamin E against the lethality of carbon tetrachloride, mediated by lipid peroxidation (Ref. 3).

Vitamin E is absorbed like other fat-soluble vitamins, entering the blood stream by way of the lymph, and is distributed to all tissues. It is excreted primarily by the liver. Some metabolic derivatives, though, are found in the urine (Ref. 2). Numerous experiments indicate that high dietary intakes of vitamin E are apparently without toxic side effects (Ref. 4). Up to 800 I.U. (about 600 mg) per day for 3 years has been consumed in these studies.

Topical vitamin E is rated 0 to 1 as an irritant and 3 to 4 as a sensitizer. According to Fisher (Ref. 5), vitamin E was a sensitizer when used in an antiperspirant. Sensitization is more of a problem when the ingredient is occluded but also occurs when vitamin E is applied to the face. The risk of sensitization increases when vitamin E is used with a second preparation which causes peeling.

Because this vitamin accumulates in the body, has an unknown mechanism of action, and has some potential for sensitization, the Panel concludes that vitamin E used topically is of questionable safety.

(2) *Effectiveness.* The effectiveness of vitamin E used as a single ingredient in treating acne has never been established in a well-controlled clinical trial.

Nikolowski (Ref. 6) stated that acne vulgaris responds to combined vitamin E and vitamin A treatment. However, he was referring to systemic and not topical use of these drugs. In a later publication, Nikolowski (Ref. 7) stated that "alone and in combination with vitamin A and nicotinamide it (vitamin E) is helpful in treating kraurosis, purpuras, roentgen therapy, acne vulgaris * * *"

Schuppener (Ref. 8) successfully treated 93 acne patients with a combination of 0.1 percent vitamin E, 1 percent sulfur, 0.003 percent estradiol, 0.3 percent prednisolone, and vitamin A 50,000 I.U./100 mL in an ointment base. It is not clear which of the ingredients in the combination was responsible for the results.

The Panel believes there is no rationale for using vitamin E in topical acne therapy. The Panel concludes that vitamin E is not effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed vitamin E in Category II because the effectiveness of this ingredient in acne has not been demonstrated in a controlled clinical trial.

References

(1) Windholz, M., et al., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 1290, 1976.

(2) Cohn, V. H., "Fat Soluble Vitamins: Vitamin K and Vitamin E," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by L. S. Goodman and A. Gilman, MacMillan Publishing Co., New York, pp. 1595–1598, 1975.

(3) Plaa, G. L., "Toxicology of the Liver," *in* "Toxicology: The Basic Science of Poisons," Edited by L. J. Casarett and J. Doull, MacMillan Publishing Co., New York, p. 181, 1975.

(4) Scott, M. L., "Vitamin E," *in* "The Fat-Soluble Vitamins," Edited by H. DeLuca, Plenum Press, New York, p. 195, 1978.

(5) Fisher, A. A., "Contact Dermatitis," 2d Ed., Lea and Febiger, Philadelphia, p. 419, 1973.

(6) Nikolowski, W., "Vitamin E in Dermatology and Related Fields," *Parfumerie und Kosmetik*, 37:65–68, 1956.

(7) Nikolowski, W., "Vitamin E and its Indication for the Treatment of Skin Disease," *Medizinische Klinik*, 55:415–418, 1960.

(8) Schuppener, H. J., "On the Clinical Aspects and Modern Therapy of Acne. Experience with a New Anti-Acne Agent," *Deutsches Medizinisches Journal*, 17:711–714, 1966.

v. *Zinc salts (zinc oxide, zinc stearate, and zinc sulfide).* The Panel concludes that the zinc salts (zinc oxide, zinc stearate, and zinc sulfide) are safe but are not effective for OTC topical use in the treatment of acne.

(1) *Safety.* Zinc oxide, zinc stearate, and zinc sulfide are insoluble compounds of zinc. It is recognized that a small amount of zinc sulfide may be converted into the soluble zinc sulfate.

Several submissions were reviewed by the Panel, but none contained any toxicity data on the zinc compounds. It has long been recognized that the soluble zinc salts (zinc sulfate and zinc chloride) can cause toxicity when ingested and are somewhat corrosive on the skin. These salts have not been used topically in acne treatment and will not be discussed here. Oral zinc was discussed earlier in this document. (See part II. paragraph G. above—Use of Oral Zinc in the Treatment of Acne.)

Zinc stearate has a relatively long history of use in baby powders. Upon ingestion, it has "a low order of toxicity" (Ref. 1). Topically, salts of zinc have been used as astringents and mild "antiseptics," probably through the precipitation of protein by the zinc ion. Zinc salts have been incorporated into ointments, powders, and pastes and used as absorbents and protectives on epithelial surfaces, ulcers, and wounds (Ref. 2).

Gosselin et al. (Ref. 3) gave the insoluble zinc salts an estimated toxicity rating of 3, meaning that they are "moderately toxic" with a probable oral lethal dose of 0.5 to 5 g/kg. However, this was only an estimate, because, according to Gosselin et al., acute oral toxicity data could not be located. Aspiration of zinc stearate powder has produced fatal pneumonitis in infants. Powdered zinc oxide, however, does not cause a pulmonary reaction. Heat volatilization of zinc produces fine airborne particles of zinc oxide. Inhalation of freshly formed fumes may cause "fume fever," an influenza-like illness (Ref. 3).

McNally (Ref. 4), in a review on zinc toxicity, pointed out that zinc is normally found in the tissues of the human body and plants as well as being a common constituent in many foods. As much as 200 mg zinc was excreted by a human who had been fed a zinc-enriched meal the previous day.

Zinc sulfide lotion, an official topical preparation in Great Britain for many years, has been used in acne treatment (Ref. 5). This lotion is a mixture of various zinc sulfides, including polysulfides, and probably exerts its action on the skin as an astringent zinc salt. Zinc sulfide is reported to liberate hydrogen sulfide and elemental sulfur when placed in contact with water such as might be present on the skin (Ref. 6). The amount of hydrogen sulfide released is unknown but is thought to be below toxic levels. The Panel views this compound as elemental sulfur and considers it safe. (See part III. paragraph A.1.b. above—Sulfur.)

Despite the scarcity of toxicity data on zinc compounds, their long history of topical use without reported ill effect has led the Panel to conclude that these ingredients are safe for the treatment of acne.

(2) *Effectiveness.* The zinc salts have been used as astringents, protectives, and antiseptics.

In the past, white lotion (lotio alba) containing zinc sulfate, sulfurated potash, and water was frequently prescribed for the treatment of mild acne (Ref. 7). This lotion should be freshly compounded because it is unstable. It has an unpleasant odor and may cause excessive drying and redness of the skin.

It appears that any beneficial effect of white lotion in dermatologic conditions results primarily from the sulfur content of the lotion. Guth and Mansour (Ref. 8) stated that when it was freshly prepared, white lotion contained zinc monosulfide, zinc polysulfide, zinc hydroxide, and free sulfur suspended in a solution of sulfate, thiosulfate, and potassium ions. Exposure of the lotion to ultraviolet light or sunlight resulted in the formation of hydrogen peroxide which oxidized sulfides to sulfites and sulfates. When the lotion ages, there is a marked increase in free sulfur in its contents.

No effectiveness data on zinc salts were contained in the submissions to the Panel. To the Panel's knowledge, these ingredients have never been studied in a clinical setting for the treatment of acne.

The Panel concludes that there are no data to show that zinc salts are effective for OTC topical use in the treatment of acne.

(3) *Evaluation.* The Panel has placed the zinc salts (zinc oxide, zinc stearate, and zinc sulfide) in Category II because the effectiveness of these ingredients in treating acne has not been established in a controlled clinical trial.

References

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(2) Goodman, L. S., and A. Gilman, "The Pharmacological Basis of Therapeutics," 5th

Ed., MacMillan Publishing Co., New York, pp. 948 and 1000–1001, 1975.

(3) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., The Williams and Wilkins Co., Baltimore, pp. 69–70 and 99, 1976.

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(5) Blacow, N. W., "Martindale, The Extra Pharmacopeia," 26th Ed., The Pharmaceutical Press, London, p. 455, 1972.

(6) Dreisbach, R. H., "Handbook of Poisoning: Diagnosis and Treatment," 9th Ed., Lange Medical Publications, Los Altos, CA, p. 246, 1977.

(7) Lubowe, I. I., "Modern Drugs in Dermatology," *Clinical Medicine*, 78:31–35, 1971.

(8) Guth, E. P., and Z. Mansour, "Photochemical Formation of Hydrogen Peroxide in White Lotion U.S.P.," *Journal of Pharmaceutical Sciences*, 56:376–379, 1967.

2. *Category II labeling.* The Panel concludes that certain labeling claims related to safety or effectiveness of an ingredient are unsupported by scientific data or, in some instances, by sound theoretical reasoning. The Panel therefore concludes that such labeling should be removed from the market.

Many claims from current labels have been placed in Category II either because they are vague, too broad, incomplete, modified incorrectly, or do not specifically indicate that the product effectively treats acne. Such labels mislead the lay person.

Many claims would appear to be acceptable; however, certain modifying words can make these claims unclear or even imprecise. For this reason, modifiers such as "fast" are not allowed. Examples of labels with vague modifers include the following:

"Clears up more pimples faster."

"Fights blemishes fast."

"Works fast against surface pimples."

"Clinically proven for prompt effective relief of acne."

"Instantly active medicated cream for acne pimples."

"Speeds up gentle, natural peeling of acne pimples."

Because the following labeling claims do not specifically indicate that the product effectively treats acne or imply that the product treats conditions other than acne, the Panel considers them misleading to the lay person:

"Helps prevent skin infections."

"Degerming."

"For temporary relief of minor soreness, irritations, and itching."

"Anesthetic."

"Pain-relieving antiseptic for the skin."

"Designed to protect against infection while it relieves local soreness, irritations, and dryness."

"Temporary relief of surface pain and discomfort."

"Helps clear up complexion problems."

"It not only goes to work drying out your pimples and blackheads, it does much more."

"Promotes healing."

"Aids healing."

"Helps heal acne and other minor skin conditions."

"Helps clear acne and related skin blemishes."

"Makes externally caused skin flare-ups look better while they're getting better."

The Panel believes that the following labeling claims are either inaccurate or not clear or may be meaningless to the consumer:

"Helps pull loosened oils from pores."

"Helps prevent the reinfection of pimples."

"Minimizes redness and itching."

"Aids in removing greasy oils from your skin. This can prevent the pores from becoming clogged again."

"Hypoallergenic."

"Bactericide."

"Hypoacnegenic."

"An effective antimicrobial against a wide variety of both gram positive and gram negative bacteria and fungi."

"Scientific treatment (or formula)."

"Vitaminized."

"Antiseptic."

"Special ingredients help dry the acne pimple."

"Special medicated skin cleanser."

"Erases worn out cells."

"Dermatologist-tested."

"Dries quickly to give long-term medication."

"Helps heal and clear acne by molecular action."

"100% medication, not a cosmetic."

"Continues to work over a longer period of time."

"Fights acne pimples."

"Kills facial germs."

"Kills germs commonly associated with acne."

"Strips away oils and waxy buildup that can lead to pimples and blackheads."

"Drinks up excess oils."

"Benefits oily and acne-blemished skin."

"Aids in the removal of superficial dry skin."

"Produces a soft, light peeling of the skin."

"Allows healthy new skin to grow."

"Helps normalize underlying tissue."

"Minimizes scarring."

"Anti-irritant."

"Helps involute inflamed pustules."

"Promoted involution of acne lesions and stimulates healing of the underlying tissues after effectively debriding any necrotic tissue which may be present."

"Bacteriostatic action, especially against Staph bacteria usually present in cases of infected acne lesions."

"Combines the same type of medications prescribed by many leading skin specialists for external application to pimples and blemishes associated with acne."

"Contains time-proved ingredients."

"For mild acne or maintenance therapy."

"Unique base keeps the medication in close contact to the skin all day long."

C. Category III Conditions

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

The safety and efficacy of the following ingredients were classified on the basis of activity and use as ingredients for the treatment of acne. Ingredients for which no acne claim is made, including ingredients that have been reviewed by the Panel and are ultimately placed in Category II for efficacy, may still be included in formulations for purposes other than the treatment of acne providing these ingredients are safe at the concentrations used.

1. *Category III active ingredients.*

Povidone-iodine
Salicylic acid

a. *Povidone-iodine.* The Panel concludes that povidone-iodine is safe but that there are insufficient data available to determine its effectiveness for OTC topical use in the treatment of acne.

(1) *Safety.* Povidone-iodine is a complex of iodine with a carrier agent, povidone (polyvinylpyrrolidone), which liberates free iodine in solution. The Panel reviewed the safety of povidone-iodine in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** Povidone-iodine is considered safe for topical antifungal use in concentrations up to 10 percent. However, because the Panel concluded that in some instances iodine may be an irritant or sensitizer, particularly with long-term use and under occlusion, a caution label was recommended.

Povidone-iodine was submitted for the treatment of acne at a concentration of 7.5 percent in a detergent vehicle. The Panel concludes that providone-iodine is safe for OTC topical use in the treatment of acne. Again, a caution on irritation is recommended.

(2) *Effectiveness.* Povidone-iodine is an antimicrobial agent that has been

widely used on wounds, burns, and abrasions to treat or prevent surface infection. It has also been used as a scrub before and after surgery. Povidone-iodine contains about 10 percent available iodine.

Millikan (Ref. 1) evaluated the effectiveness of 7.5 percent povidone-iodine in two studies on acne patients. In the first study, providone-iodine was compared to its vehicle control in a double-blind fashion. Patients with mild acne washed two or three times daily with one of the treatments for 3 to 4 months. Evaluation was based on global impression. At the time of the study, 9 of the 10 patients using povidone-iodine were considered improved or much improved. In the control group, three out of seven patients were rated as improved.

Millikan (Ref. 1) also studied 27 patients with Grade II to IV acne (grading system based on type and location of lesions). Povidone-iodine was compared to the vehicle control, but in this study all patients also received systemic tetracycline concomitantly. There was no significant difference in effectiveness between the vehicle and providone-iodine. The author concluded that the oral tetracycline was responsible for this result.

Brown (Ref. 2) used a 7.5-percent povidone-iodine foam to treat 32 patients who had mild to moderate acne. The patients used the preparation twice daily for at least 6 months. Methods of evaluating patients were not defined. Of the 10 subjects using only povidone-iodine, 8 were good or fair at the conclusion of the trail. The remaining 22 patients used concomitant therapy including oral tetracycline, oral contraceptives, topical agents, and ultraviolet light. In this group, 19 patients showed a favorable response, but it is impossible to determine which ingredient produced this result.

In an uncontrolled study, Hudson (Ref. 3) evaluated the effectiveness of 7.5 percent povidone-iodine in 500 patients with moderate to severe acne. Patients washed with povidone-iodine one to three times daily for 3 months to more than 1 year. Tetracycline and sulfur lotions were used in addition to povidone-iodine. Hudson reported that the skin looked and felt less oily and that patient reaction was not defined and specific treatment results were not reported.

In an unpublished study (Ref. 4), 10 patients with Grade III acne (grading system was not defined) were treated twice daily with 7.5 percent povidone-iodine. A vehicle control was not used in this study. Patients were assessed by global impression 2 weeks after treatment and 4 weeks after treatment. All patients showed good or fair improvement. Lesion counts at the final visit compared to baseline showed decreases of 79 percent for pustules, 28 percent for open comedones, 18 percent for closed comedones, and 20 percent for papules.

The studies described above indicate that povidone-iodine may be an effective acne treatment; however, none of the studies met the Panel's effectiveness criteria. Deficiencies in study design included one or more of the following: (1) Lack of vehicle control, (2) concomitant therapy used, and (3) method of evaluating patients and treatment results not well defined. Also, none of the studies included a statistical analysis of results. Other studies were reviewed by the Panel (Ref. 4), but are not detailed here because they were not controlled and included concomitant therapy. The Panel concludes that povidone-iodine is of questionable effectiveness in the treatment of acne.

(3) *Proposed dosage*—(i) *Concentration.* Povidone-iodine 7.5 percent.

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

(4) *Labeling.* The Panel recommends the Category I labeling for products used in the treatment of acne. (See part III. paragraph A.2. above—Category I labeling.)

Cautions should include the following statement: "If redness or itching occurs or persists, discontinue use and consult a doctor or pharmacist."

(5) *Evaluation.* The Panel recommends that studies be conducted to determine the stability of povidone-iodine and availability of elemental iodine from the complex. The Panel also recommends one double-blinded, vehicle-controlled clinical trial to determine the effectiveness of povidone-iodine in the treatment of acne. These studies should be conducted in accordance with the guidelines set forth below for OTC topical acne ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

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(4) OTC Volume 070239.

Salicylic acid. The Panel concludes that salicylic acid is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC topical use in the treatment of acne.

(1) *Safety.* Salicylic acid and its derivatives are a widely used group of compounds. Whether the salicylates are administered orally, rectally, intravenously, or cutaneously, systemic absorption occurs. Whatever the mode of administration, the toxic effects from overdosage are essentially the same, i.e., nausea, decreased ability to hear, tinnitus (ringing in the ears), confusion, metabolic disturbances, hallucinations, and death. The possible toxic reactions are collectively known as salicylism.

The Panel reviewed the toxicity of salicylic acid in its recommendations on topical antifungal drug products published elsewhere in this issue of the **Federal Register.** Those data will not be repeated here. This discussion will include data dealing with salicylic acid in the treatment of acne or data received by the Panel since it completed its recommendations on topical antifungal drug products.

The major difference in the use of salicylic acid in acne as opposed to its use in fungal infections of the foot or groin is the very large surface area over which acne may be involved. In fact, roughly half of the body surface could be afflicted with acne. In adult humans, this would amount to close to 1 square meter of absorptive surface area.

Salicylic acid has been applied to relatively small areas of skin or in concentrations of less than 10 percent without apparent ill effects as a keratolytic agent in the treatment of various skin disorders. Salicylic acid for topical use on acne will be considered in concentrations ranging form 0.5 to 5 percent.

Most of the reports submitted for the use of salicylic acid in acne evaluated combination ingredient products. However, the following new data on salicylic acid as a single ingredient were contained in two submissions (Refs. 1 and 2). The acute oral LD_{50} of salicylic acid in male Sprague-Dawley rats was 800 mg/kg. When concentrations of 0.5 to 2 percent were applied to either normal or abraded skin of rabbits, salicylic acid was judged to be a mild irritant.

A lotion containing salicylic acid 2 percent was applied to normal and abraded rabbit skin at a rate of 2 mL/kg and held under occlusion for 24 hours (Ref. 3). If a rabbit weighed 2 kg, then it received 4 mL of the 2-percent lotion, amounting to a total of 80 mg salicylic

acid. There were no signs of acute toxicity in any of the test animals.

When an undiluted 2-percent salicylic acid lotion was applied to the eyes of rabbits and allowed to remain in the eye, the lotion was found to be an eye irritant. When the lotion was immediately washed out after application, there was no irritation (Ref. 3).

Five mL/kg of the lotion administered by oral gavage to female rats caused no toxic symptoms (total salicylic acid dose, 100 mg per 200 g rat). In mice the acute oral LD_{50} of the lotion was 32 mL/kg, or a total dose of approximately 666 mg/kg (Ref. 3).

In humans, a blood concentration of 30 to 50 mg salicylic acid per 100 mL is considered to be toxic (Ref. 4). If a human applied 15 g of a 5-percent salicylic acid preparation to the entire upper torso, the amount of salicylic acid available for absorption would be 750 mg. If all of this were instantly absorbed and distributed into 7 L of blood, the blood concentration would be approximately 10 mg/100 mL. Blood concentrations of 6.5 mg to 15 mg/100 mL have been reported to be nontoxic (Refs. 4 and 5). Based on this calculation and the data submitted, the Panel concludes that preparations containing up to 5 percent concentrations of salicylic acid would be safe for use in treating acne.

(2) *Effectiveness.* Salicylic acid has been used for over 100 years in the treatment of acne and various keratinizing diseases. It is used alone or often in combination with sulfur or resorcinol. Despite its long history of use, the exact mechanism of action has never been determined and, in fact, no study has documented the efficacy of salicylic acid used as a single ingredient in the therapy of acne.

An extensive review of the medicinal uses and pharmacologic properties of salicylic acid was published in a series of three articles co-authored by Weirich, Longauer, and Kirkwood (Refs. 6, 7, and 8). Weirich and his associates described 10 specific pharmacological properties of salicylic acid and offered many reference sources to document their viewpoints. These properties included action such as germicidal, photoprotector, astringent, antipruritic, and anti-inflammatory. Other properties discussed were a deep keratolytic action at concentrations greater than 5 percent, a superficial surface keratolytic action at 1 to 4 percent, and an acidifying effect at 0.1 percent and above. The ability to produce an increase in penetration of topical drugs was also described. It is not certain which, if any, of these qualities is responsible for the clinical responses noted in acne. It is usually assumed, however, that salicylic acid is working as a keratolytic agent and possibly as a substance which promotes the penetration of other active ingredients. Shalita (Ref. 9), Leyden (Ref. 10), and Plewig and Kligman (Ref. 11) believe that salicylic acid, in addition to its keratolytic and anti-inflammatory action, has a comedolytic effect; that is, it causes an increased turnover of follicular ephithelial cells and an apparent decrease in the cohesiveness of these cells when they are shed into the cavity of the follicle.

A commercial product containing 2 percent sulfur and 2 percent salicylic acid in a cream base has been studied in numerous investigations (Refs. 12, 13, and 14). One study was conducted to show the effectiveness of this preparation in seborrhea associated with acne. Robinson (Ref. 12) treated 120 patients using either a cake or cream containing 2 percent sulfur and 2 percent salicylic acid. Although the specific details of the study were not given, the investigator noted, "* * * (the) cake and cream quickly dried the skin and were particularly helpful in cleansing comedones."

In another study, Riley (Ref. 13) treated 150 acne patients with a salicylic acid-sulfur combination. Depending upon the severity of the acne condition, the treatment also included a restricted diet, ultraviolet light, acne surgery, astringents, colloidal sulfur, oral vitamin A, oral antibiotics, or X-ray therapy. All patients were instructed to wash their faces with ordinary soap for the first 2 weeks. At the end of the 2-week preliminary phase, patients showing little improvement were continued on the same therapeutic routine except for washing with a 2-percent salicylic acid-2 percent sulfur cream or cake instead of soap. The patients used the salicylic acid-sulfur combination one to four times daily for 4 to 12 months. The method of evaluating patients was not explained. Results showed a good response in 147 patients. The salicylic acid-sulfur combination was helpful in one patient, but two others had a poor response. Riley concluded that the cream or cake containing salicylic acid and sulfur did contribute to the improvement of acne vulgaris. However, the study made no mention of blinding or randomization, and the results were not evaluated statistically.

Baird (Ref. 14) treated 371 patients with acne vulgaris, with 133 cases classified as severe and 238 as moderate. All patients followed a simple, restricted diet, washed their faces with the 2-percent salicylic acid-2 percent sulfur cream, and were treated with acne surgery. In addition, the severe cases may have been treated with X-rays, oral antibiotics, staphylococcus vaccines, or estrogenic hormones. In conclusion, the investigator stated that the simplified treatment plan improved all the mild to moderate cases of acne. In the severe cases, the author believed that scrubbing with the cream shortened the course of therapy. However, the study made no mention of vehicle control, blinding, randomization, or statistical analysis.

In another study, using a randomized but not blinded method, 109 patients were treated once or twice daily with a 2-percent salicylic acid lotion or a commercially available soap (Ref. 3). Patients included in the study had mild to moderate acne. They were evaluated by global assessment after 4, 7, and 14 days. After 14 days the lotion proved to be significantly superior to the soap for reducing blackheads ($p = 0.029$). There were no statistically significant differences between the two products in the frequency of "breaking out" in acne blemishes, in improvement in overall condition, or in reduction of blemishes (inflammatory lesions). The researchers considered 14 days inadequate to evaluate the frequency of "breaking out." Consequently, a somewhat similar study of 117 patients with mild to very severe acne was conducted for 3 months. The study was blinded.

In this 3-month study, patients were untreated for 2 weeks before enrollment in the study (Ref. 3). After evaluation, they were randomly assigned to the 2-percent salicylic acid lotion (57 patients) or the commercially available soap (60 patients). Patients were treated once or twice daily depending upon the severity of their acne and the oiliness of their skin. The severity of blackheads, pimples, and oiliness was measured as 0=absent, 1=mild, 2=moderate, 3=severe, and 4=very severe. The overall clinical evaluation showed good to excellent results in 72.2 percent of the patients treated with salicylic acid compared with 10.5 percent of those who had used the soap. The group using the salicylic acid lotion had a statistically significant greater improvement than the group using the soap ($p < 0.001$). More importantly, fewer blackheads and pimples were observed in the lotion-treated group. The average reduction in "severity units" at 3 months compared with baseline for salicylic acid was 1.28 for blackheads and 1.41 for pimples. For soap the average reduction was 0.37 for blackheads and 0.19 for pimples. These results were statistically significant at

the $p < 0.001$ level. This was a well-designed study; however, lesion counts were not used and the control was not the vehicle used in the 2-percent salicylic acid lotion.

Another study was conducted using a lotion containing 2.2 percent salicylic acid and 2.2 percent resorcinol in an ethyl alcohol vehicle (Ref. 15). Sixteen patients were treated for 2 months using a twice-daily regimen. Evaluation was by lesion counts. After 2 months, reduction in lesion counts was 42.9 percent for blackheads, 43.8 percent for whiteheads, 66.2 percent for pustules, and 31.0 percent for cysts. Slight to marked improvement was noted in 81 percent of the patients. However, there were no controls or randomization and the study was not blinded.

In another study (Ref. 16), 44 adolescent males with mild to moderate acne were treated twice daily for 2 weeks with a preparation containing 0.5 percent salicylic acid. There was no mention of other treatments, how the evaluations were done, whether the study was blinded, or whether a vehicle control was used. At the end of the study, 57 percent of the patients showed improvement in overall severity of acne. A decrease in facial oiliness was noted in 77 percent. Seventy-three percent of the patients showed a decrease in the amount of pressure needed to express comedones. The investigator concluded that 0.5 percent salicylic acid was effective in the treatment of mild acne.

The effectiveness of 0.5 percent salicylic acid was also evaluated in an unpublished, single-blind trial of 120 patients. Patients with mild to moderate acne were treated with either 0.5 percent salicylic acid, a commercial product containing 6 percent sulfur and 1.5 percent resorcinol, or soap. Application was made twice daily for 3 weeks. No other topical or systemic treatment was allowed. Patients were evaluated by global impression. At the end of the trial, the two active treatments were found to be significantly more effective than soap in effecting overall improvement, decreasing oiliness, and making it easier to express comedones ($p<0.01$) (Ref. 17).

In a single-blind study, patients with Grade I to III acne (grading system was not specified) were treated with either 0.25 or 0.5 percent salicylic acid. Each treatment group contained 50 patients. Patients applied the solutions once daily for 6 weeks. The method of patient evaluation was not described. At the end of the study, improvement was noted in 70 percent of the group receiving the 0.5-percent concentration. Fifty-four percent of the patients treated with 0.25 percent salicylic acid were reported as improved. Although the results were not statistically analyzed, the investigator concluded that the 0.5-percent solution was superior to the 0.25-percent solution (Ref. 18).

In a study of 95 patients, treatment with 0.5 percent salicylic acid lasted for 1 to 8 months. Patients entered into the study had Grade I to III acne (grading system based on type of lesion). Controls were not used and methods of evaluation were undefined. Results showed good to excellent improvement in 25 percent, satisfactory improvement in 38 percent, and no improvement in 37 percent (Ref. 18).

In a double-blind, randomized trial, 49 patients with Pillsbury Grade I to II acne were studied. A medicated pad containing 0.5 percent salicylic acid in an alcoholic detergent solution was compared with placebo (pads soaked in buffered water). No systemic therapy was used, and soap and water was the only other topical treatment.

Patients were evaluated before treatment and at 4, 8, and 12 weeks by lesion counts and global evaluation. After 12 weeks, inflammatory lesions were reduced by 54 percent in the salicylic acid group and 29 percent in the placebo group. This difference was significant ($p=0.005$). Salicylic acid also reduced open comedones by 39 percent compared with placebo, 28 percent ($p<0.05$). There was no significant difference between treatments on closed comedones (Ref. 19). The Panel notes that this study did not use a vehicle control.

A 0.5-percent salicylic acid solution has been evaluated in five other trials involving 282 patients with mild to moderate acne (Ref. 18). Vehicle controls were not used in any of these studies. Although none of the studies included a statistical analysis of results, all indicated that 0.5 percent salicylic acid reduces the severity of acne and oiliness of the skin. Also, comedones were easier to express.

Various other submissions discussed combinations of salicylic acid but none provided any specific data; however, the general medical literature contains several pertinent articles. Kaidbey and Kligman (Ref. 20) used 50 percent crude coal tar with plastic occlusion to induce the formation of comedones on 12 subjects' backs. Comedones produced this way remain evident on the skin for months. Therefore, any reduction of comedones is considered attributable to the peeling agents and not to time.

After 2 to 4 weeks of applying the crude coal tar followed by 2 weeks of no application, the patients were treated with a wide variety of peeling agents. The comparative comedolytic activity in order of decreasing effectiveness was 0.1 percent tretinoin, 15 percent salicylic acid, 10 percent benzoyl peroxide, and 15 percent trichloroacetic acid. Neither the ethanol control nor a combination of 5 percent sulfur and 2 percent resorcinol showed comedolytic activity. A 15-percent salicylic acid preparation applied topically twice daily for 6 weeks resulted in a greater than 50 percent reduction in the number of comedones. This model is valuable only for comparing agents that are capable of dislodging or reducing the size of the comedones.

Davies and Marks (Ref. 21) studied the effects of varying concentrations of salicylic acid on normal skin of the thigh or the forearm. The strengths applied were between 2 and 12 percent in either a water-washable base or in white paraffin. Vehicle controls were applied to the opposite thigh and forearm. The patients were treated twice a day for 1 week and then biopsied. No changes were apparent except when the electron microscope was used to examine the biopsies. Using this technique, Davies and Marks noted "striking differences" in the outer layer of the skin which had been treated with 6 to 12 percent concentrations of salicylic acid. This study was undertaken in the hope of determining the exact action of salicylic acid on the skin. The authors' theory was that salicylic acid preparations enhance the shedding of the outer layer of skin by dissolving the material which holds the cells together.

The Panel concludes that salicylic acid is of questionable effectiveness as a single ingredient in the treatment of acne. Although considerable clinical experience as well as uncontrolled studies suggest that salicylic acid is an effective ingredient, there has been no vehicle-controlled, double-blind study to confirm salicylic acid's effectiveness in the treatment of acne.

(3) *Proposed dosage*—(i) *Concentration.* Salicylic acid 0.5 to 5 percent.

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

(4) *Labeling.* The Panel recommeds the Category I labeling for products used in the treatment of acne. (See part III. paragraph A.2. above—Category I labeling.)

(5) *Evaluation.* The Panel recommends one double-blind, vehicle-controlled clinical trial to determine the effectiveness of salicylic acid in the treatment of acne. This study should be conducted in accordance with the guidelines set forth below for OTC topical acne ingredients. (See part III.

paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

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(3) OTC Volume 070188.
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(12) Robinson, A. M., "A New Treatment for Seborrhea and Allied Skin Conditions (Fostex)," *Journal of the South Carolina Medical Association*, 52:253–254, 1952.
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(17) OTC Volume 070181.
(18) OTC Volume 070242.
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2. *Category III Labeling.* None.

D. Combination Products Used in the Treatment of Acne

The Panel concurs with the rationale expressed in the OTC drug combination policy regulation (21 CFR 330.10(a)(4)(iv)) as follows:

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

The Panel concludes that combination products for the treatment of acne should contain the minimal number of active ingredients necessary to achieve effectiveness. In general, the fewer the ingredients, the safer and more rational the therapy. Consumer interests are best served by exposure to the fewest ingredients possible at the lowest possible dosage regimen that is consistent with a satisfactory level of effectiveness.

In the past, combinations of ingredients were based largely on personal experience and testimonials. The Panel believes, however, that combinations should be based on clinical trials. In order to achieve the goal of efficacy consistent with exposure to the least number of ingredients, the Panel considered only those studies that demonstrated each ingredient's contribution to the efficacy of the complete conbination. The Panel realizes that such a clinical trial for Category III combinations to move to Category I will require a substantial effort. The study should be designed so that each single active ingredient makes a statictically significant contribution to the efficacy of the combination, and the combination itself should be more effective than the vehicle control.

1. *Category I combination drug product—Sulfur resorcinol.* The Panel concludes that a conbination of 8 percent sulfur with either 2 percent resorcinol or 3 percent resorcinol monoacetate is safe and effective for OTC use in the treatment of acne. Sulfur and resorcinol are often used together in the treatment of acne, but it is difficult to document the historical origin of this combination. The precise mechanism of action of these combinations has never been proven, but it may depend on keratolysis or the ability to produce erythema and desquamation with enhanced resolution of comedones, papules, and pustules.

A half-face study was conducted on 25 males (Ref. 1). After washing the entire face with soap and water, the patients applied a cream containing 8 percent sulfur and 2 percent resorcinol to half of the face three times daily for 3 weeks. No other therapy was allowed. The weekly evaluation was based on clinical impression with acne rated as slight, moderate, or severe. The sulfur-resorcinol combination was found to significantly improve acne at 1 and 2 weeks when compared to no treatment ($p < 0.001$).

In a single-blind, half-face trial, the effectiveness of 8 percent sulfur-2 percent resorcinol cream was studied in 28 subjects (Ref. 1). The patients applied the combination to one side of the face and a placebo lotion to the other side twice daily. The only other therapy allowed during the 8-week treatment period was soap and water. Patients were evaluated by global impression. After 8 weeks, the side of the face treated with the sulfur-resorcinol cream was improved in 75 percent of the cases. Improvement on the placebo side was noted in 46.4 percent of the patients. Sulfur-resorcinol was concluded to be effective in the treatment of acne.

Another single-blind study was conducted on 79 patients with Pillsbury Grade II or III acne (Ref. 1). Patients used no topical therapy for 2 weeks and no systemic therapy for 1 month before entering the study. They were divided into three treatment groups: (1) 8 percent sulfur-2 percent resorcinol cream, (2) "phosphate-stabilized" sulfur-resorcinol cream, and (3) no treatment. The patients applied the active medications twice daily. At regular intervals during the 12-week study they were evaluated by lesion counts and global impressions.

At the end of the treatment period, good to excellent results were reported for 44 percent of the group treated with sulfur-resorcinol, 38.5 percent of the group who had used the stabilized cream, and 17.4 percent of the no-treatment group. The investigators concluded that the sulfur-resorcinol formulations gave significantly better results than no treatment in reducing the overall severity of acne. No difference was noted between the three groups in reduction of comedones. The two active treatments showed significantly better results than no treatment in reducing inflammatory lesions.

In a half-face study of 25 patients with mild to moderate acne, 8 percent sulfur-2 percent resorcinol cream was compared to a placebo cream (Ref. 2). This study was randomized and single-blind. Before treatment there was a 4-week washout period during which no systemic or topical therapy was given. The patients were evaluated weekly with lesion counts and global assessments.

After 8 weeks of treatment, 12 patients were improved on the side of the face treated with sulfur-resorcinol and 1 patient improved on the side treated with the placebo. One patient

was worse on the side of the face treated with the placebo but had no change on the side treated with the combination. Seven patients had no change on either side of the face and four patients were worse on both sides.

Inflammatory lesions decreased 30.5 percent in the group treated with sulfur-resorcinol; in the control group the lesions increased 4 percent. Open comedones decreased 20.7 percent in the combination group and 1.8 percent in the control group. The statistical analysis showed that sulfur-resorcinol significantly decreased open comedones ($p<0.05$), papules ($p<0.001$), and pustules ($p<0.005$) compared to placebo. There was no significant difference between the two groups for closed comedones, which actually increased during the course of the trial.

Another study evaluating the effectiveness of sulfur-resorcinol used four treatment groups of about 60 subjects each. The groups were as follows: (1) 2.66 percent sulfur-1 percent resorcinol, (2) 8 percent sulfur-2 percent resorcinol, (3) 2.66 percent sulfur, and (4) placebo. The patients included in the study had mild to moderate acne and were randomly assigned to a treatment group. No concurrent topical or systemic therapy was allowed. The creams were applied three times daily for 8 weeks. The patients were evaluated at 0, 2, 4, 6, and 8 weeks. Lesion counts were not used, but global assessment was based on the number of blackheads, whiteheads, papules, pustules, and on oiliness and overall complexion.

Results after 8 weeks showed that the two sulfur-resorcinol creams were equivalent and superior to the placebo and to sulfur alone in reducing papules and whiteheads. No differences in blackheads, pustules, oiliness, or overall complexion were noted between the four treatment groups. Also, there was no statistically significant difference between sulfur alone and the placebo in any category (Ref. 3).

Sulfur-resorcinol cream was compared to benzoyl peroxide in a half-face, single-blind study (Ref. 2). The vehicle of the benzoyl peroxide cream served as a control. The study included 50 institutionalized male patients with Pillsbury Grade II to III acne. The patients were allowed no other topical or systmic therapy. All medications were applied by dispensary personnel. Twenty-four patients had half of the face treated with 5 percent benzoyl peroxide and the other half treated with 8 percent sulfur-2 percent resorcinol. In the remaining patients, one side of the face was treated with benzoyl peroxide and the other side with the vehicle. Assignment of treatment and side of application were randomized. Treatment was twice daily for 8 weeks. The patients were evaluated weekly by lesion counts and global assessments.

Final results showed that there was no significant difference between sulfur-resorcinol and benzoyl peroxide. Both sulfur-resorcinol and benzoyl peroxide were more effective than the vehicle in the reduction of pustules, open comedones, the closed comedones ($p<0.01$ to $p<0.001$).

A double-blind, randomized, multiple-center trial was conducted in three European countries (Ref. 2). Patients were admitted to the study with Pillsbury Grade II to III acne. There was a 4-week washout period during which no therapy was allowed. Fifty-four patients were treated with 8 percent sulfur-2 percent resorcinol; 53 patients were treated with a sulfur-resorcinol combination plus 0.1 percent triclosan, an antibacterial agent.

The medications were applied twice daily for 8 weeks. Patients were evaluated by lesion counts every 4 weeks. Both treatments showed a statistically significant decrease in open comedones, closed comedones, total number of comedones, and inflamed lesions when the washout period was compared to the treatment period ($p<0.05$ to $p<0.01$).

Although resorcinol has been placed in Category II as a single ingredient because it is not effective, the Panel believes that resorcinol enhances the activity of sulfur. The Panel concludes that a comination of 8 percent sulfur with either 2 percent resorcinol or 3 percent resorcinol monoacetate is safe and effective in the treatment of acne but recommends that products containing this combination not be used on broken skin or over large areas of the body. The Panel recommends that sulfur-resorcinol combination products contain the following warning: "Apply to affected areas only. Do not use on broken skin or apply to large areas of the body."

The Panel recommends that Category I combinations be labeled according to the Category I labeling for products used in the treatment of acne, as outlined elsewhere in this document. (See part III. paragraph A.2. below—Category I labeling.)

References

(1) OTC Volume 070039.
(2) OTC Volume 070236.
(3) OTC Volume 070256.

2. *Category II combination drug product—Benzoyl peroxide-sulfur.* A combination is classified by the Panel as a Category II drug product, i.e., one that is not generally recognized as safe or effective, if it contains any ingredient that is listed elsewhere in this document as a Category II ingredient for safety reasons. Although benzoyl peroxide and sulfur are Category I as single ingredients for OTC use in the treatment of acne, the Panel recommends that the benzoyl peroxide-sulfur combination be Category II because of the possibility of sensitization.

Combinations of benzoyl peroxide and sulfur are currently available by prescription only and the Panel does not recommend that these combinations be switched to OTC. However, a combination of 7.5 percent benzoyl peroxide and 5 percent sulfur was submitted for review. The Panel concludes that this combination is effective but is not safe for OTC topical use in the treatment of acne. Other concentrations of these two ingredients are used in prescription acne preparations and were submitted, but the effectiveness of these combinations has not been adequately studied in a clinical trial which meets the Panel's criteria.

a. *Safety.* Because benzoyl peroxide and sulfur are safe as single ingredients, in considering the safety of the combination one need be concerned only with the possible effect one chemical might have on the potential toxicity of the other. One such possibility is increased absorption of benzoyl peroxide due to irritation by sulfur. There is evidence, however, that benzoyl peroxide is not absorbed from rabbit skin even in the presence of 5 percent sulfur (Ref. 1). Topical studies on rabbits with a formulation containing 7.5 percent benzoyl peroxide and 5 percent sulfur showed no systemic effects (Ref. 2).

The primary concern regarding the safety of benzoyl peroxide is direct cutaneous toxicity. There is evidence that this enhanced by the presence of sulfur. Poole, Griffith, and MacMillan (Ref. 3) demonstrated a 40-percent rate of hypersensitivity to benzoyl peroxide in guinea pigs and humans who were given a patch test with an ointment containing 10 percent benzoyl peroxide and 1 percent sulfur. In the study on guinea pigs it was clearly demonstrated that sulfur was needed in addition to benzoyl peroxide to produce sensitization. Guinea pigs tested with benzoyl peroxide alone, sulfur alone, or the vehicle showed no reaction (Ref. 3). Histological alterations, particularly dermal changes, produced by benzoyl peroxide are also enhanced by sulfur (Ref. 4). In the rabbit ear assay, greater irritation was observed from the combination than from either

ingredients along (Ref. 5). Using the Draize-Shelanski test (Re. 1), true allegic responses to benzoyl peroxide-sulfur lotion were demonstrated in 19 out of 221 people, which is a higher rate than expected with benzoyl peroxide alone.

It is difficult to understand why sulfur would enhance the sensitization potential of benzoyl peroxide. Perhaps an oxidation product of sulfur is formed and this product is irritating. Because the possibility of sensitization increases when sulfur is combined with benzoyl peroxide, the Panel recommends that this combination remain available by prescription only.

b. *Effectiveness.* A double-blind, controlled, randomized trail was conducted on 80 males with moderate acne (Ref. 2). The patients applied creams containing no benzoyl peroxide or containing benzoyl peroxide in concentrations of 2.5, 5, 7.5, or 10 percent either with or without 5 percent sulfur. Half of the group was treated for 2 weeks; the other half was treated for 8 weeks. The patients were assessed by lesion counts. The statistical analysis of results showed that the most effective formulation contained 7.5 percent benzoyl peroxide and 5 percent sulfur. This combination was effective against all types of acne lesions (comedones, papules, pustules, and all lesions combined). The duration of treatment did not affect the results.

One submission contained a compilation of five half-face and five full-face studies using 10 percent benzoyl peroxide, 5 percent sulfur, a combination of these two ingredients, or a placebo base (Ref. 2). These studies were randomized and blinded. Treatment lasted 8 weeks with evaluation by lesion counts. The results of the half-face studies showed that improvement in comedones was 58.3 percent for the combination, 42.8 percent for sulfur, 49.1 percent for benzoyl peroxide, and 28 percent for the base. For inflammatory lesions the improvement was 40 percent for the combination, 36.3 percent for sulfur, 23.7 percent for benzoyl peroxide, and 18.3 percent for the base.

Most of the studies were not analyzed. However, analysis of one study showed that the benzoyl peroxide-sulfur combination was more effective than benzyol peroxide alone ($p < 0.05$).

In the full-face studies, one investigator found the combination product to be superior to sulfur used alone ($p < 0.05$). Another researcher, however, reported no significant differences between active treatments (Ref. 2).

In a double-blind, randomized study, 48 patients were treated with either a combination containing 7.5 percent benzoyl peroxide and 5 percent sulfur, 7.5 percent benzoyl peroxide, or the placebo (Ref. 2). The patients applied the lotions twice daily for 8 weeks. They were evaluated by lesion counts at 0, 2, and 8 weeks, but the numerical results of these counts were not reported. However, using a "means of slope estimate" (rate of lesion decrease) for the three treatments, the researchers found the combination product to be superior to the placebo in the treatment of comedones and in all lesions combined ($p < 0.05$ and $p < 0.025$). In treating inflammatory lesions, no significant difference was noted between the combination and the placebo. Also, no significant difference was seen between benzoyl peroxide and placebo for any lesion type.

In a double-blind, randomized, half-face study (Ref. 2), 48 patients applied a combination of 7.5 percent benzoyl peroxide and 5 percent sulfur to one side of the face. On the other side of the face, they used benzoyl peroxide alone. Treatment was twice daily for 7 weeks. The patients were examined by global assessment and lesion counts at 0, 2, and 7 weeks. Both treatments reduced lesion counts, but by this method of evaluation no significant difference was noted between treatments. Analysis of global results showed that the combination product was superior to benzoyl peroxide in the treatment of comedones at 2 weeks ($p < 0.05$) and in the treatment of inflammatory lesions at 7 weeks ($p. < 0.05$).

In a multiple-center trial (Ref. 2), three investigators treated 156 patients with acne. The study was double-blind and randomized. The patients applied either a combination of 7.5 percent benzoyl peroxide and 5 percent sulfur, a placebo cream, or a commercially available cream containing sulfur and resorcinol. Treatment was twice daily. No concurrent therapy was allowed. The patients were evaluated at 0, 2, 8, and 12 weeks by lesion count.

The results of each investigator's work were statistically analyzed. One researcher reported greater improvement with the combination than with the other two treatments, but the difference was not significant. Another investigator found no significant difference between the three preparations in reducing comedones. However, benzoyl peroxide-sulfur combination was superior to sulfur-resorcinol and the placebo in reducing inflammatory lesions ($p < 0.001$). The third investigator found benzoyl peroxide-sulfur combination to be superior to the placebo for all lesion types ($p < 0.05$).

c. *Evaluation.* The Panel concludes that 7.5 percent benzoyl peroxide and 5 percent sulfur is an effective combination for topical use in the treatment of acne. However, the Panel does not recommend that this combination be made available OTC because of the potential for sensitization.

References

(1) OTC Volume 070259.

(2) OTC Volume 070168.

(3) Poole, R. L., J. F. Griffith, and F. S. K. Macmillan, "Experimental Contact Sensitization with Benzoyl Peroxide," *Archives of Dermatology*, 102:635–639, 1970.

(4) Vasarinsh, P., "Benzoyl Peroxide-Sulfur Lotions, A Histological Study," *Archives of Dermatology*, 98:183–187, 1968.

(5) OTC Volume 070207.

3. *Category III combination drug products.* A combination is classified as a Category III product if one of the following apply:

(1) The combination contains one or more ingredients listed elsewhere in this document as a Category III ingredient.

(2) The combination contains one or more ingredients listed elsewhere in this document as a Category II ingredient for effectiveness only. (An exception is sulfur-resorcinol combinations where resorcinol enhances the activity of sulfur.)

(3) The effectiveness of the combination has not been shown in a controlled clinical trial.

a. *Calcium polysulfide-calcium thiosulfate.* Calcium polysulfide and calcium thiosulfate the active ingredients in sulfurated lime topical solution (Vlieminckx' solution). This solution is most frequently used as a scabicide (Ref. 1). It has also been used in the treatment of severe pustular or cystic acne. Although sulfurated lime topical solution has been used in dermatology for over 100 years, there are no clinical trials establishing its effectiveness in treating acne.

Sulfurated lime topical solution works as a peeling agent. Plewig and Kligman (Ref. 2) stated that "only a few agents which cause peeling are in fact comedolytic." They listed sulfurated lime topical solution as one of the traditional exfoliants which is "surprisingly weak or ineffective."

Only one submission contained a clinical trial testing the effectiveness of calcium polysulfide-calcium thiosulfate combination (Ref. 3). In this double-blind, randomized study, 59 patients used either the medicated facial mask or a a nonmedicated mask (vehicle). The masks were applied once every other day and rinsed off after 15 minutes. Patients were evaluated by lesion

counts and global assessment at the initial visit and at 2, 4, 7, and 10 weeks. At each visit the patients using the combination showed a significant decrease in comedones compared to baseline ($p<0.001$). In the vehicle group the decrease in comedones was significant only at 2 and 4 weeks ($p<0.05$). The reduction of papules, however, was significant at each visit for both treatments when compared to baseline ($p<0.01$). Both groups also showed a significant decrease in the pustule counts over the 10-week course of treatment ($p<0.025$).

The Panel notes that a calcium polysulfide-calcium thiosulfate combination is generally used by dermatologists to treat severe acne that does not respond to other treatments. In this study, however, the combination was no more effective than the vehicle on papules and pustules. Although the combination was more effective than the vehicle in reducing comedones, effectiveness should be shown against all lesion types. The Panel concludes that a combination of calcium polysulfide and calcium thiosulfate is of questionable effectiveness for OTC use in the treatment of acne.

References

(1) Osol. A., and J. E. Hoover, "Remington's Pharmaceutical Sciences," 15th Ed., Mack Publishing Co., Easton, PA, p. 1180, 1975.

(2) Plewig, G., and A. M. Kligman, "Acne: Morphogenesis and Treatment," Springer-Verlag, New York, p. 278, 1975.

(3) OTC Volume 070291.

b. *Sulfur-aluminum chlorohydrex.* The Panel concludes that a combination of 5 percent sulfur and 10 percent aluminium chlorohydrex is safe but that there are insufficient data available to permit final classification of the effectiveness of this combination.

The Panel reviewed two double-blind, randomized, and controlled studies that compared the combination to the individual active components and to the vehicle (Ref. 1). However, because there was no washout period between the cross-over segments of these trials, the results were difficult to interpret.

Another study on this combination was also double-blind, randomized, and controlled. Forty-five patients with Pillsbury Grade I to III acne completed the 8 weeks of treatment. They were treated twice daily with either 5 percent sulfur-10 percent aluminum chlorohydrex, 5 percent sulfur, or the vehicle. No other treatment was allowed. Patients were evaluated by lesion counts and global assessments.

Results of global assessments showed that the combination was significantly more effective than sulfur or vehicle. Sulfur-aluminum chlorohydrex was also significantly better than sulfur and vehicle in reducing the lesion counts of papules and pustules ($p<0.05$). Reduction in the number of open comedones and cysts was greater for the combination than for the other two preparations but this was not a statistically significant difference. None of the treatments had an appreciable effect on closed comedones, difficult lesions to treat (Ref. 1).

The only side effect noted was excessive dryness. In the first 2 weeks of treatment, there were significantly more reports of this side effect with the combination product than with sulfur. At that time, the amount of drug and the frequency of administration were adjusted.

There was only one report of excessive dryness from the combination in the next 6 weeks of the trial (Ref. 1).

The Panel concludes that 5 percent sulfur-10 percent aluminum chlorohydrex is safe, but that its overall effectiveness is questionable because of its lack of effect on comedones. The Panel has stated previously that acne treatments should be effective against all lesion types to be considered as Category I. Although this combination was significantly more effective on papules and pustules, it did not have a statistically significant effect on other kinds of lesions, particularly open comedones.

Reference

(1) OTC Volume 070283.

c. *Other Category III combination products.* The Panel is unaware of any clinical trials on the following combinations which compared the combination to the individual active ingredients and to the vehicle. Although studies were submitted and reviewed by the Panel for some of these combinations, none of them met the Panel's criteria.

The Panel concludes that the following combinations are of questionable effectiveness because of inadequate data. One of these combinations contains an ingredient on which there are inadequate safety data (thymol). The safety of this ingredient must be established before the combination can move from Category III to I.

(1) Sulfur-resorcinol-alcloxa.

(2) Sulfur-resorcinol-thymol-zinc oxide.

(3) Sulfur-salicylic acid.

(4) Salicylic acid-resorcinol.

(5) Salicylic acid-resorcinol-alcloxa.

(6) Salicylic acid-resorcinol-sodium thiosulfate.

(7) Benzoic acid-boric acid-zinc oxide-zinc stearate.

E. Guidelines for Safety and Effectiveness Studies

The following guidelines are for studies that the Panel recommends be conducted in order to move a Category III topical acne drug product into Category I. These guidelines are in accord with the present state of the art but do not preclude the use of any future advances or improved technology.

The Panel's approach has been to completely study the potential toxicity of active ingredients used in topical acne products. Even though these ingredients are to be used topically, their oral toxicity should be studied first to identify the target organ or system and then to determine the safety factor which permits safe use when absorption and systemic toxicity occur.

1. *Safety guidelines.* The Panel recommends that the following studies be performed as appropriate to evaluate topical acne ingredients classified in Catogory III because of inadequate safety data.

a. *Acute studies in animals.* (1) Determine the acute oral toxicity of the total formulation in an appropriate species to define the response curve and allow determination of the LD_{10}, LD_{50}, and LD_{90}. Short-term topical toxicity tests on the total formulation should be done on both intact and abraded skin.

(2) Conduct an appropriate rabbit skin irritation study on intact and abraded skin on the vehicle and total formulation.

(3) Conduct an appropriate rabbit eye irritation study on the vehicle and total formulation.

b. *In vitro screening for carcinogenic potential.* (1) A bacterial mutagenesis assay would be a logical first step in screening for carcinogenic potential. One of the assays using the *Salmonella* histidine auxotroph back mutation, such as that described by Ames (Ref. 1) or Frantz and Malling (Ref. 2), would be suitable. Because the compounds in question are likely to be antibacterial, parallel dose-response curves for viability must be done. Where obvious antibacterial activity occurs, other cellular testing procedures should be used.

(2) Depending on the properties of the chemical tested and the results of the bacterial mutagenesis assay, other in vitro tests could be conducted for clarification. These tests should use a mammalian cell culture system designed to test either mutagenicity or transformation. Strategies for selecting

tests in this rapidly developing field can be found in current literature.

c. *Subchronic studies in animals.* (1) Conduct a 28-day dermal toxicity study in the rabbit or other appropriate species on abraded skin at suitable dose levels to ensure adequate exaggeration of normal "use" levels. At the conclusion of this study, conduct a full pathological assessment on vital organs and skin. It would be desirable to evaluate the direct effects on the skin following application for a longer period of time, but the Panel is not aware of a suitable model for such a study.

(2) Conduct a subchronic (90 days or longer) feeding study with the total formulation. Determine blood levels and conduct full pathology at termination of the study. This study should attempt to determine the "no effect" blood level of the total formulation. Determine the target organ(s) for toxic effects.

d. *Chronic studies in animals.* (1) Conduct a 1-year chronic feeding study with at least two dose levels. Monitor blood levels at 3-month intervals. Conduct a full pathology evaluation at conclusion of study.

(2) A carcinogenicity evaluation following dermal application will be necessary only if the appropriate in vitro screening assays are positive or have yielded questionable results. For example, acne agents may have antibacterial activity which can cause false-negative or misleading results in the *Salmonella* mutagenicity test because the assay procedure involves bacterial enumeration.

e. *Studies in humans.* (1) Determine the irritation potential of the vehicle and total formulation using the best current procedures.

(2) Conduct an appropriate sensitization potential study on the total formulation using the most reliable procedure for identifying both potent and weak sensitization potential(s).

(3) Because absorption studies in animals do not necessarily parallel those in humans, appropriate transepidermal studies should be conducted in humans. These studies should be conducted only where the safety of the ingredient has been adequately established in animals.

References

(1) Ames, B. N., J. McCann, and E. Yamasaki, "Methods for Detecting Carcinogens and Mutagens with the *Salmonella*/Mammalian-Microsome Mutagenicity Test," *Mutation Research*, 31:347–364, 1975.

(2) Frantz, C. N., and H. V. Malling, "The Quantitative Microsomal Mutagenesis Assay Method," *Mutation Research*, 31:365–380, 1975.

2. *Effectiveness guidelines*—a. *Guidelines for clinical trials.* To move a Category III ingredient into Category I, the ingredient must be shown to be effective in the treatment of of acne in a well-designed clinical trial that meets the following criteria:

(1) The trial should involve a sufficient number of subjects established by using accepted statistical procedures.

(2) An objective measure of the severity of acne should be decided before the study. This method should be precisely defined.

(3) Patients should be randomly assigned to total formulation or control group. The control is the vehicle (total formulation minus the active ingredient (s)). When comparing total formulation to vehicle, the use of parallel groups of patients is preferable to half-face comparisons. The comparability of groups should be established by analyzing pertinent variables, such as age, sex, severity of acne.

(4) The study should be double-blind.

(5) No concomitant therapy (other than soap and water) should be allowed.

(6) The trial should last at least 8 weeks. The investigators should state which calendar months were included in the study because acne lesions generally clear up somewhat in the summer.

(7) The patients should be evaluated at least three times: before treatment, at final examination, and at one other time. The method of evaluation should be lesion counts grouped by type of lesion (closed comedones, open comedones, papules, pustules, and total lesions). A global assessment of patients may also be helpful. Local adverse effects and patient compliance should be noted and systematically recorded.

(8) Results should be statistically evaluated. The total formulation should be significantly more effective than the placebo in reducing lesion counts.

b. *In vitro testing of acne ingredients*—(1) *Background.* The Panel has included an optional in vitro testing procedure. Before a manufacturer tests an ingredient for clinical effectiveness in acne or determines in vivo activity for an antibacterial claim, it would be helpful to determine activity against *P. acnes* in an in vitro test. With in vitro testing the minimal inhibitory concentration (MIC) of an ingredient can be determined against *P. acnes.* With this information one can determine whether the ingredient has antibacterial activity under these testing conditions. MIC determination can also be used to compare different ingredients tested against the same pure culture under the same conditions. Another use is to find whether antibacterial activity varies when an ingredient is tested against various strains of bacteria.

Ingredients often show activity in vitro which cannot be shown in vivo. Although the reverse is not so often true, it can happen when the conditions of the MIC test differ significantly from the availability of the antibacterial agent in vivo. In vitro antibacterial activity may also be affected by the interaction of the antibacterial ingredients or other components in the formulation with one of the components of the medium used to determine the MIC. Obviously this will not affect the in vivo activity.

Because the in vitro availability of the ingredient may be altered in formulation, it is often advisable to determine the MIC for the formulation as well as for the ingredient alone. The optimal multiple of the MIC of an ingredient in a topical dosage form is often very high, ranging from a hundred times to thousands of times the MIC. This high multiple is often necessary because of formulation binding, partition of the ingredients on the skin, and differential absorption into the skin. Absorption into the follicle is critical in formulations for acne treatment.

Therefore, the information derived from in vitro data may be helpful in trying to make the most effective formulations or in reaching a decision about whether to proceed with testing. Although the in vivo data ultimately determine the validity if the antibacterial claim, the MIC test is a helpful guide to potential activity and availability. In some cases it can also be useful in quality control. The following discussion illustrates how the MIC data can be used.

The MIC of benzoyl peroxide was reported as approximately 78 μg/mL against *P. acnes.* The minimal bactericidal concentration (MBC) was reported as approximately 156 μg/mL.

If these figures are applied to actual use of a formulation on the skin and some assumptions are made, useful information can be derived. The amount of drug material applied is 2 mg/cm² or 2,000 μg/cm². If an average lotion or cream product contains 10 percent benzoyl peroxide, then the amount applied could be in the range of 200 μg/cm².

If an average volume of a single follicle is assumed to be 2 microliters (μL) and it is estimated that there are 200 follicles/cm², then the total follicular volume could be estimated at 400 μL (0.4 mL) for each cm² of involved epidermis. Based on this estimate and assuming complete and uniform follicular penetration, the concentration of benzoyl peroxide at the site of the

organism would be 200 μg/0.4 mL or 500 μg/mL benzoyl peroxide. To obtain the multiples, the estimated concentration of benzoyl peroxide at the site is derived using the MIC or the MBC. The multiples for various concentrations of benzoyl peroxide would be as follows:

Concentration of benzoyl peroxide (percent)	MIC	MBC
10	6×	3×
7	4×*	2×*
5	3×	1.5×
2.5	1.5×	.75×

These data and calculations suggest that appropriate availability of the benzoyl peroxide from 2.5 percent formulations will be important to their effectiveness.

(2) *Testing procedures.* The Panel suggests the following procedures for testing ingredients in vitro for possible bactericidal or bacteriostatic activity against *P. acnes* (although other procedures may be used): (i) *Materials*—(*a*) Double-strength brain-heart infusion agar, containing 104 g/L.

(*b*) Single-strength brain-heart infusion agar, containing 52 g/L.

(*c*) Double-strength brain-heart infusion broth, containing 74 g/L.

(*d*) Single-strength brain-heart infusion broth, containing 37 g/L.

The brain-heart infusion agar and broth are commercial preparations to which double-distilled water is added to make the working preparations.

(ii) *Basic P. acnes culture.* An ATCC *P. acnes*-type culture or a well-characterized *P. acnes* facial isolate is reconstituted and then grown anaerobically under hydrogen/carbon dioxide or equivalent, in brain-heart infusion or a similar broth at pH 7, for 5 to 7 days, until good growth is obtained as evidenced by turbidity.

(iii) *Determination of the minimal inhibitory concentration for agents insoluble in water by the agar dilution method.* The agar dilution test is used for products that are insoluble or precipitate in broth, rendering culture media cloudy and making turbidimetric measurements of microbial growth difficult.

The test is run in duplicate. The following should be prepared and sterilized: 2 test tubes (18 mm×150 mm) with 5 mL of double-strength brain-heart infusion agar, 22 test tubes containing 5 mL of single-strength brain-heart infusion agar, and 2 test tubes containing 9 mL of brain-heart infusion broth. The agar in these test tubes is melted and kept in a 45° C water bath to prevent solidification during the test. Next, 5 mL of the concentrated test ingredient is placed into the test tubes containing the double-strength brain-heart infusion agar and mixed well for 10 seconds. Then the tubes are returned to the water bath. (This is a 1:2 dilution.)

Five mL from each one of these tubes is transferred into each of two of the single-strength brain-heart infusion agar tubes, mixed, and returned to the water bath. (This is a 1:4 dilution.) This procedure is continued until a 1:1,024 dilution has been prepared. From the last dilution tube, 5 mL is discarded so that all tubes contain a total of 5 mL of agar. The last two agar tubes will be kept undiluted and uninoculated as negative controls. The contents of each tube are mixed well and poured into 25 mm×10 mm petri dishes. The agar is allowed to solidify.

Two serial tenfold dilutions from the *P. acnes* broth culture are made using the two brain-heart infusion broth tubes. The 1:100 dilution constitutes the inoculum. The duplicate set of plates (from the 1:2 dilution to 1:1,024 dilution) is seeded with one drop of the diluted *P. acnes* culture. Two plates with inoculated brain-heart infusion agar, two plates containing a 1:2 dilution of the sample but no inoculum seeding, and two uninoculated brain-heart infusion plates serve as controls. The plates are incubated anaerobically at 35° C for 1 week and examined for growth. The end point of bacteriostatic activity is between the last plate with no growth and the first plate with growth. The titer is the dilution of the last clear plate before the first plate growth.

A piece of the agar from the plates showing no growth is subcultured in brain-heart infusion broth tubes to determine the bactericidal titer of the antimicrobial agent. An effective neutralizer should be included.

The MIC is calculated from the titer and the original concentration of the test compound in the suspending agent.

(iv) *Determination of the minimal inhibitory concentration for agents soluble in water by the broth dilution method.* The test is run in duplicate. Twenty-four test tubes (18 mm × 150 mm) are set up. Into the first four test tubes, 5 mL of a double-strength brain-heart infusion broth is pipetted. Five mL of the single-strength broth is placed into each of the other tubes.

Next, 5 mL of sterile saline is pipetted into each of the first two test tubes of double-strength broth and mixed. These will be the positive control tubes. Five mL is removed from each of these control tubes and discarded, leaving a total volume of 5 mL in each tube.

A known amount of the acne ingredient is mixed in a suspending medium and 5 mL of this dispersion is pipetted into each of the next two test tubes and mixed for 10 seconds. This is a 1:2 dilution.

Five mL of the content of each 1:2 dilution tube is transferred into the next two test tubes and mixed for 10 seconds. This is a 1:4 dilution.

This procedure is continued until a 1:1,024 dilution is obtained. Five mL from each test tube with the highest dilution is discarded, leaving a 5 mL total volume in each of the test tubes. The last two tubes will not be diluted or inoculated and will serve as negative controls. The culture of *P. acnes* in brain-heart infuson broth is mixed well to suspend the cells evenly and 1 mL is added to 9 mL of single-strength broth and mixed well. This is a 1:10 dilution.

One mL from this 1:10 diluton is added to 9 mL of single-strength brain-heart infusion broth to obtain a 1:100 dilution. This dilution constitutes the inoculum.

One-tenth mL of the inoculum is added to each of the sample dilutions and to the positive control tubes. All tubes are incubated at 35° C anaerobically for 1 week and then examined for growth.

(v) *Interpretation of the results.* The more concentrated suspensions of the test agent should completely inhibit the growth of *P. acnes*, and the broth should be clear. At higher dilutions the concentration of the active agent will be too low to completely inhibit the growth of the organism. These tubes should be turbid. The end point of activity is between the last clear and the first turbid adjacent tube. The titer is the dilution of the last clear tube.

When the test is concluded, a loopful of broth from each tube not showing turbidity should be streaked on brain-heart infusion agar plates and incubated at 35° C anaerobically for 1 week to determine whether the test compound is bacteriostatic or bactericidal at a given concentration. An effective neutralizer should be included. Knowing the titer (bacteriostatic and bactericidal) and the initial concentration of the dispersion tested, an MIC for this ingredient can be calculated by the following formula:

$$\text{Minimal inhibitory concentration } (\mu g/mL) = \text{Initial concentration } (\mu g/mL) \times \frac{1}{\text{Bacteriostatic titer}}$$

c. *In vivo testing of acne ingredients.* The Panel recommends the following testing guidelines to determine antimicrobial activity in an in vivo test. Ingredients which demonstrate in vivo activity and meet the criteria may use antibacterial claims in their labeling.

(1) *Study design.* Either parallel or half-face groups may be used. The half-

face design is permitted for drugs that are not sufficiently absorbed to result in antibacterial effects. When a drug is absorbed to a degree that systemic activity occurs, the untreated side of the face may be affected, thus invalidating the test. Reliability and extent of application are particularly important in a half-face test. For this reason, technicians should apply the drug when this study design is used. If translocation of the medication is known to occur, the half-face design should not be used.

All studies should be double-blind with the formulation containing the active ingredient compared with the vehicle control.

(2) *Subjects.* A minimum of 15 subjects for a half-face study and 30 for a parallel group study should be used. The groups should include males and females 15 years of age or older. The subjects may or may not have active acne, but they must have significant follicular fluorescence indicating an adequate density of *P. acnes* on the skin. The subjects must have a *P. acnes* baseline count of 1×10^5 to 1×10^6 organisms per cm^2.

(3) *Treatment.* The forehead and cheeks should be used as treatment sites. The method of application should be that specified in directions for use. The drug should be applied twice daily. The duration of treatment should usually be 4 weeks unless the study is intended to show that a product can meet the criteria in a shorter time. In that case the treatment time may be shortened.

(4) *Measurements.* The sample site should be specified by the investigator. To reduce error the same sample site should be used on each individual each time. The *P. acnes* count should be determined using the Williamson and Kligman scrub technique (Ref. 1). The Panel believes that the Williamson and Kligman scrub technique is the best method presently available to determine *P. acnes* counts. However, if other methods that are equivalent or superior to the Williamson and Kligman scrub technique are developed, they may be used after the agency has approved a petition to amend the monograph.

Three separate determinations of the baseline *P. acnes* count should be made. The values may be averaged to obtain a single baseline value for each subject. Measurements to determine reduction should be made weekly thereafter.

The free fatty acids determination is an optional confirmatory test. However, if it is used, the free fatty acids concentration should be carefully assessed by thin-layer chromatography, such as the method described by Downing (Ref. 2).

(5) *Criteria.* For an ingredient to be considered effective in demonstrating antibacterial activity against *P. acnes*, the following criterion must be met:

A reduction in *P. acnes* counts of 0.75 log must be shown. This reduction should be statistically significant at the $p < 0.1$ level. Therefore, the hypothesis test should be framed to test whether there is a 0.75-log reduction from baseline.

If it is desirable to show that the reduction is significant at the $p < 0.05$ level, the number of subjects should be increased appropriately.

To confirm antibacterial activity, an optional test to show reduction of free fatty acids may also be done. A 30-percent reduction in free fatty acids on the skin surface should be shown. The reduction should be statistically significant at the $p < 0.1$ level. The free fatty acid determination is included to ensure that the antimicrobial agent has penetrated and is acting at the follicular level.

(6) *Methodology*—(i) Microbiological sampling of the skin should be by the Williamson and Kligman detergent scrub technique or an equivalent technique. The following culture techinques should be observed:

a. Brain-heart infusion medium should be used to culture *P. acnes.* If another medium is developed that is shown to be equivalent or superior to brain-heart infusion, it may be used.

b. The sample retrieved from the scrub technique should be vortexed for 10 seconds prior to enumeration.

c. Anaerobic incubation should be at 35° C for 7 days.

d. A neutralizer adequate for the antimicrobial ingredient being tested should be added to the scrubbing fluid. The toxicity of the neutralizer must be determined for *P. acnes.* The presence of any residual antimicrobial agent in the sampling fluid must be investigated using adequate microbiological tests.

(ii) *Free fatty acids determination.* Samples of skin lipids should be obtained by swabbing the area with a hexane-saturated sponge (Ref. 3). Lipid analysis should be performed using a thin-layer chromatography technique, such as the one described by Downing (Ref. 2). Another method of lipid analysis that may be used is infrared spectoscopy, described by Anderson and Fulton (Ref. 4).

References

(1) Williamson, P., and A. M. Kligman, "A New Method for the Quantitative Investigation of Cutaneous Bacteria," *Journal of Investigative Dermatology*, 45:498–503, 1965.

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(3) Yeung, D., and W. Smith, "Method for the In Vivo Collection of Skin Lipids," memorandum to S. Nacht, June 4, 1980, OTC Volume 070279.

(4) Anderson, A. S., and J. E. Fulton, Jr., "Sebum: Analysis by Infrared Spectroscopy," *Journal of Investigative Dermatology, 60:115–120, 1973.*

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

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)), under 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, (see 46 FR 26052; May 11, 1981), 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 in Part 333, a new Subpart D, to read as follows:

Subpart D—Topical Acne Drug Products

Sec.

333.301 Scope.
333.303 Definitions.
333.310 Acne active ingredients.
333.320 Permitted combinations of active ingredients.
333.340 Testing procedures to determine antibacterial activity of acne active ingredients.
333.350 Labeling of acne drug products.

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); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart D—Topical Acne Drug Products

§ 333.301 Scope.

(a) An over-the-counter acne drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this subpart and each general condition established in § 330.1.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 333.303 Definitions.

As used in this part:

(a) *Acne.* An inflammatory skin disease involving the oil glands and hair follicles of the skin.

(b) *Acne drug product.* A drug product used to reduce the number of acne lesions.

(c) *Blackhead.* An acne lesion characterized by a black tip.

(d) *Follicle.* A minute cavity with an opening on the surface of the skin.

(e) *Lesion.* A characteristic area of a skin condition. Lesions in acne include blackheads and pimples.

(f) *Pimple.* A small, prominent inflamed elevation of the skin.

§ 333.310 Acne active ingredients.

The active ingredients of the product consist of any of the following when labeled according to § 333.350.

(a) Benzoyl peroxide 2.5 to 10 percent.

(b) Resorcinol 2 percent when combined in accordance with § 333.320.

(c) Resorcinol monoacetate 3 percent when combined in accordance with § 333.320.

(d) Sulfur 3 to 10 percent.

(e) Sulfur 8 percent when combined in accordance with § 333.320 (a) and (b).

§ 333.320 Permitted combinations of active ingredients.

(a) Resorcinol identified in § 333.310(b) when combined with sulfur identified in § 333.310(e) provided the product is labeled according to § 333.350.

(b) Resorcinol monoacetate identified in § 333.310(c) when combined with combined with sulfur identified in § 333.310(e) provided the product is labeled according to § 333.350.

§ 333.340 Testing procedures to determine antibacterial activity of acne active ingredients.

(a) *Study design.* Either parallel or half-face groups may be used. The half-face design is permitted for drugs that are not sufficiently absorbed to result in antibacterial effects. When a drug is absorbed to a degree that systemic activity occurs, the untreated side of the face may be affected, thus invalidating the test. Reliability and extent of application are particularly important in a half-face test. For this reason, technicians should apply the drug when this study design is used. If translocation of the medication is known to occur, the half-face design should not be used. All studies should be double-blind with the formulation containing the active ingredient compared with the vehicle control.

(b) *Subjects.* A minimum of 15 subjects for a half-face study and 30 for a parallel group study should be used. The groups should include males and females 15 years of age or older. The subjects may or may not have active acne, but they must have significant follicular fluorescence indicating an adequate density of *Propionibacterium acnes* (*P. acnes*) on the skin. The subjects must have a *P. acnes* baseline count of 1×10^5 to 1×10^6 organisms per square centimeter.

(c) *Treatment.* The forehead and cheeks should be used as treatment sites. The method of application should be that specified in directions for use. The drug should be applied twice daily. The duration of treatment should usually be 4 weeks unless the study is intended to show that a product can meet the criteria in a shorter time. In that case the treatment time may be shortened.

(d) *Measurements.* The sample site should be specified by the investigator. To reduce error the same sample site should be used on each individual each time. The *P. acnes* count should be determined using the Williamson and Kligman scrub technique (*Journal of Investigative Dermatology*, 45:498–503, 1965). Other methods of measuring *P. acnes* counts may be used if they are shown to be equivalent or superior to the Williamson and Kligman method. Such methods may be used only after the agency has approved a petition to amend the monograph. Three separate determinations of the baseline *P. acnes* count should be made. The values may be averaged to obtain a single baseline value for each subject. Measurements to determine reduction should be made weekly thereafter. The free fatty acids determination is an optional confirmatory test. However, if it is used, the free fatty acids concentration should be carefully assessed by thin-layer chromatography, such as the method described by Downing (*Journal of Chromatography*, 38:91–99, 1968).

(e) *Criteria*—(1) *Required.* For an ingredient to be considered effective in demonstrating antibacterial activity against *P. acnes*, the following criterion must be met: A reduction in *P. acnes* counts of 0.75 log must be shown. This reduction should be statistically significant at the $p<0.1$ level. Therefore, the hypothesis test should be framed to test whether there is a 0.75-log reduction from baseline. If it is desirable to show that the reduction is significant at the $p<0.05$ level, the number of subjects should be increased appropriately.

(2) *Optional.* To confirm antibacterial activity, an optional test to show reduction of free fatty acids may also be done. A 30-percent reduction in free fatty acids on the skin surface should be shown. The reduction should be statistically significant at the $p<0.1$ level. The free fatty acid determination is included to assure that the antimicrobial agent has penetrated and is acting at the follicular level.

(f) *Methodology*—(1) Microbiological sampling of the skin should be by the Williamson and Kligman detergent scrub technique or an equivalent technique. The following culture techniques should be observed:

(i) Brain-heart infusion medium should be used to culture *P. acnes*. If another medium is developed that is shown to be equivalent or superior to brain-heart infusion, it may be used.

(ii) The sample retrieved from the scrub technique should be vortexed for 10 seconds prior to enumeration.

(iii) Anaerobic incubation should be at 35° C for 7 days.

(iv) A neutralizer adequate for the antimicrobial ingredient being tested should be added to the scrubbing fluid. The toxicity of the neutralizer must be determined for *P. acnes*. The presence of any residual antimicrobial agent in the sampling fluid must be investigated using adequate microbiological tests.

(2) *Free fatty acids determination.* Samples of skin lipids should be obtained by swabbing the area with a hexane-saturated sponge as in the method by Yeung and Smith (contained in a memorandum to S. Nacht, dated June 4, 1980, in OTC Volume 070279, on file in the Dockets Management Branch, HFA–305, Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857). Lipid analysis should be performed using a thin-layer chromatography technique, such as the one described by Downing (*Journal of Chromatography*, 38:91–99, 1968). Another method of lipid anlysis that may be used is infrared spectroscopy, described by Anderson and Fulton (*Journal of Investigative Dermatology*, 60:115–120, 1973).

§ 333.350 Labeling of acne 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 "acne medication."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" and is limited to the following:

(1) *For products containing any ingredient identified in § 333.310 for the treatment for acne.* The indications consist of one or more of the following statements:

(i) "For the management of acne."

(ii) "For the treatment of acne."

(iii) "Anti-acne formula."
(iv) "Anti-acne medication."
(v) "Anti-acne formulation."
(vi) "Dries and clears acne blemishes."
(vii) "Dries and clears acne pimples."
(viii) "Dries acne blemishes and allows skin to heal."
(ix) "Dries acne pimples and allows skin to heal."
(x) "Dries up acne pimples."
(xi) "Helps clear acne pimples."
(xii) "Clears up most acne pimples."
(xiii) "Clears up most acne blemishes."
(xiv) "Reduces the number of acne lesions."
(xv) "Reduces the severity of acne lesions."
(xvi) "Reduces blackheads."
(xvii) "Clears up most blackheads."
(xviii) "Loosens blackheads."
(xix) "Helps clear up blackheads."
(xx) "Helps clear up acne pimples."
(xxi) "Helps remove blackheads."
(xxii) "Helps remove acne pimples."
(xxiii) "Dries up blackheads."
(xxiv) "Dries up acne blemishes."
(xxv) "Unclogs pores to help clear acne."
(xxvi) "Unplugs pores to help clear acne."
(xxvii) "Penetrates follicles to eliminate most blackheads and acne pimples."
(xxviii) "Penetrates pores to eliminate most blackheads and acne pimples."
(xxix) "Penetrates follicles to control blackheads and acne pimples."
(xxx) "Penetrates pores to control blackheads and acne pimples."
(xxxi) "Penetrates follicles to clear most blackheads and acne pimples."
(xxxii) "Penetrates pores to clear most blackheads and acne pimples."
(xxxiii) "Penetrates follicles to reduce blackheads or acne pimples."
(xxxiv) "Penetrates pores to reduce blackheads or acne pimples."

(2) *For products containing any ingredient identified in § 333.310 for the prevention of new acne lesions.* The indications consist of one or more of the following statements provided that the labeling also contains one or more of the indications identified in § 333.350(b)(1).

(i) "Helps keeps skin clear of new acne lesions."
(ii) "Helps keep skin clear of new acne pimples."
(iii) "Helps prevent new blackheads or acne pimples."
(iv) "Helps prevent new acne pimples."
(v) "Helps prevent new acne pimples from forming."
(vi) "Helps prevent acne lesions."
(vii) "Helps prevent the development of new acne lesions."
(viii) "Helps prevent new acne blemishes from forming."

(3) *For products that have shown antibacterial activity according to § 333.340.* The indications consist of one or more of the following provided that the labeling also contains one or more of the indications identified in § 333.350(b)(1).

(i) "Antibacterial."
(ii) "Kills acne bacteria."
(iii) "Kills the bacteria that can cause acne."
(iv) "Kills acne bacteria on the skin."
(v) "Kills acne bacteria in the skin."
(vi) "Kills acne bacteria and helps clear acne pimples."
(vii) "Works to kill bacteria that may cause pimple redness to spread."
(viii) "Works to kill bacteria that may cause inflammation to spread."
(ix) "Penetrates follicles to kill bacteria associated with acne."
(x) "Penetrates pores to kill bacteria associated with acne."
(xi) "Penetrates follicles to reduce bacteria associated with acne."
(xii) "Penetrates pores to reduce bacteria associated with acne."
(xiii) "Reduces *P. acnes*, bacteria associated with acne."
(xiv) "Reduces the bacterial products associated with the inflammation of acne."
(xv) "Reduces the bacterial products associated with the irritation of acne."

(4) *Product attributes.* Terms to describe certain physical and chemical qualities may be used, as long as these terms do not imply any therapeutic effect and are distinctly separated from the indications identified in § 333.350(b)(1), (2), and (3). These terms are intended to provide consumer information and relate to a product's color, odor, or feel.

The following or similar terms may be used:

(i) "Greaseless."
(ii) "Nonstaining."
(iii) "Odorless."
(iv) "Colorless."
(v) "Nontinted."
(vi) "Blends easily with skin."
(vii) "Disappearing foam."
(viii) "Drying."
(ix) "Dries excess skin oils."
(x) "Skin-softening."
(xi) "Cools and comforts hot, irritated skin areas."
(xii) "Cleans the skin and helps to remove oil."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing any ingredient identified in § 333.310.* (i) "For external use only."

(ii) "Other topical acne medications should not be used at the same time as this medication."

(2) *For products containing benzoyl peroxide identified in § 333.310(a).* "Do not use this medication if you have very sensitive skin or if you are sensitive to benzoyl peroxide. This product may cause irritation, characterized by redness, burning, itching, peeling, or possibly swelling. More frequent use or higher concentrations may aggravate such irritation. Mild irritation may be reduced by using the product less frequently or in a lower concentration. If irritation becomes severe, discontinue use; if irritation still continues, consult a doctor or pharmacist. Keep away from eyes, lips, mouth, and sensitive areas of the neck. This product may bleach hair or dyed fabrics."

(3) *For products containing sulfur identified in § 333.310 (d) and (e).* "Do not get into eyes. If excessive skin irritation develops or increases, discontinue use and consult a doctor or pharmacist."

(4) *For products containing any combination identified in § 333.320.* "Apply to affected areas only. Do not use on broken skin or apply to large areas of the body."

(d) *Directions.* The labeling of the product containing any ingredient identified in § 333.310 contains the following statements under the heading "Directions":

(1) "Cleanse the skin thoroughly before applying medication. Cover the entire affected area with a thin layer one to three times daily. Because excessive drying of the skin may occur, start with one application daily, then gradually increase to two or three times daily if needed or as directed by a doctor."

(2) The directions described in paragraph (d)(1) of this section are intended for products that are applied and left on the skin. Other products, such as soaps or masks, may be applied and removed and should have appropriate directions.

Interested persons may, on or before June 21, 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 July 21, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: January 19, 1982.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: March 16, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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Federal Register

Tuesday
March 23, 1982

Part III

Department of Health and Human Services

Food and Drug Administration

Topical Antifungal Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 333

[Docket No. 80N-0476]

Topical Antifungal 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) topical antifungal drug products are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review Panel on OTC Antimicrobial (II) Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by June 21, 1982 and reply comments by July 21, 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. Gilbertson, 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 February 23, 1980, a report of the Advisory Review Panel on OTC Antimicrobial (II) 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 topical antifungal drug products 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.

FDA is aware of the Panel's recommendation to make the prescription drugs haloprogin 1 percent and miconazole nitrate 2 percent available for OTC use as single ingredients for the treatment of athlete's foot, jock itch, and ringworm. Without addressing the merits of this recommendation, the agency wishes to point out that no final decision will be made without a careful and thorough evaluation of all comments that are submitted in response to the publication of this recommendation. Any persons marketing such OTC drug products before a final monograph is published in the **Federal Register** will do so at their own risk, since the agency may at any time adopt a position requiring relabeling, recall, or other regulatory action, as detailed in § 330.13 (21 CFR 330.13).

FDA is also aware of the Panel's recommendation that the prescription drugs haloprogin 1 percent, miconazole nitrate 2 percent, and nystatin 100,000 U/g as single ingredients be made available OTC for the indications of "treatment of external feminine itching associated with vaginal yeast (candidal) infection" and "treatment of superficial skin infections caused by yeast (*Candida*)." The agency is dissenting from this recommendation at this time. FDA believes that self-treating the symptoms of itching around the vagina without knowing or treating the underlying cause of the itching could create a serious health hazard. Infections caused by *Candida* must be diagnosed in the laboratory; they cannot be self-diagnosed by consumers. Some candidal infections may require both systemic and intravaginal treatment. Furthermore, itching around the vagina can be a symptom of serious systemic disease, such as diabetes, or of a serious gynecological disorder, including trichomoniasis or gonorrhea. Trichomoniasis and gonorrhea must be diagnosed in the laboratory and treated with appropriate systemic medicines, not with topical nystatin. FDA is soliciting comments on the Panel's recommendations that haloprogin, miconazole nitrate, and nystatin be available OTC for the treatment of candidal infections and particularly invites comments from gynecologists. Under § 330.13 (21 CFR 330.13), haloprogin, miconazole nitrate, and nystatin may not be marketed OTC with anticandidal claims at this time.

FDA is also aware that the Panel recommended that up to three Category I antifungal ingredients may be combined, provided that each ingredient broadens the antifungal spectrum, for the treatment of athlete's foot, jock itch, and ringworm. The agency is not aware of any such Category I combinations currently on the OTC market. At this time, the agency will continue to permit the marketing of combinations of antifungal ingredients already on the OTC market and will permit the reformulation of products to include Category I ingredients except where prescription to OTC switches are involved. However, under § 330.13 (21 CFR 330.13), no new combinations of antifungal ingredients containing an active ingredient limited to prescription use on or after May 11, 1972 may be marketed at this time. The agency invites comments and data on any combination of antifungal ingredients which the Panel recommended for Category I status.

The agency is also aware of the Panel's recommendation that, for the treatment of athlete's foot, jock itch, and ringworm, any single Category I antifungal ingredient, except nystatin, or any combination identified in proposed § 333.220(a) may be combined with any single antiperspirant which is generally recognized as safe and effective in an OTC drug final monograph. The agency is not aware of any combination product currently on the OTC market containing the Category I ingredients recommended by the Panel, nor were such combinations submitted to the Panel. Only two products containing an antiperspirant combined with one or more antifungal ingredients were submitted to the Panel. The agency notes that the Panel stated a belief that drying the affected area will aid in the treatment of athlete's foot. However, the Panel cited no data to support this theory. The agency advises that the Advisory Review Panel on OTC Antiperspirant Drug Products placed antiperspirants for use on the foot in Category III in its report published in the **Federal Register** on October 10, 1978 (43 FR 46727). Data are needed to establish the safety and effectiveness of

combinations of antifungal and antiperspirant ingredients. At this time, the agency will continue to permit the marketing of antifungal-anitperspirant combinations already on the OTC market and will permit the reformulation of products to include Category I ingredients except where prescription to OTC switches are involved. However, under § 330.13 (21 CFR 330.13), no new combinations of antifungal and antiperspirant ingredients containing an active antifungal or antiperspirant ingredient limited to prescription use on or after May 11, 1972 may be marketed at this time. The agency invites comments and data on any combination of antifungal and antiperspirant ingredients.

The agency is also aware that the Panel recommended that, for the treatment of athelete's foot, jock itch, and ringworm, any single Category I antifungal ingredient, except nystatin, or any combination identified in § 333.220(a) may be combined with any single keratolytic agent which is generally recognized as safe and effective in an OTC drug final monograph. The agency is not aware of any combination product currently on the OTC market containing only a keratolytic and the Category I antifungal ingredients recommended by the Panel. The agency points out that a number of currently marketed OTC products, some of which were submitted to the Panel, are combinations of anitfungals with salicylic acid as the keratolytic. The agency advises that the Miscellaneous External Panel reviewed salicylic acid as a keratolytic in its report on wart remover drug products published in the Federal Register of October 3, 1980 (45 FR 65609). Although that Panel classified salicylic acid as Category I, it expressed concern regarding the safety of salicylic acid on skin areas other than those being treated and proposed a warning to advise users to keep the product away from surrounding skin while treating warts. In addition, the agency notes that the Antimicrobial II Panel stated that theoretically an effective keratolytic agent could remove the outer layers of the stratum corneum, thus better exposing the infecting fungus to the action of the antifungal ingredients, and cited salicylic acid as an example of such an agent. However, the Panel provided no data to support its recommendation. Further, there was no evidence submitted to the Panel to show that a keratolytic agent would be useful or safe in treating fungus conditions. At this time the agency will continue to permit the marketing of antifungal-keratolytic combinations already on the OTC market and will permit the reformation of products to include Category I ingredients except where prescription to OTC switches are involved. However, under § 330.13 (21 CFR 330.13), no new combinations of antifungal and keratolytic ingredients containing an active antifungal or keratolytic ingredient limited to prescription use on or after May 11, 1972 may be marketed at this time. The agency invites comments and data on any combination of antifungal and keratolytic ingredients.

The agency is aware that the Panel also recommended that combinations of up to three Category I antifungal ingredients and hydrocortisone or hydrocortisone acetate 0.5 to 1 percent be available for OTC use for the treatment of athlete's foot, jock itch, and ringworm. The agency is dissenting from this recommendation at this time. The agency recognizes that the Panel reviewed data for two marketed products which are currently available by prescription only. The agency advises that both of these prescription products, containing hydrocortisone combined with either iodochlorhydroxyquin or calcium undecylenate as the antifungal, are currently classified by FDA as lacking adequate evidence of effectiveness. (See 37 FR 12171, June 20, 1972; 37 FR 12856, June 29, 1972; and 39 FR 36365, October 9, 1974.) These products are in various stages of administrative review and remain on the prescription market pending final resolution and review of available data. The agency further points out that the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products recommended that hydrocortisone and hydrocortisone acetate 0.25 to 0.5 percent be allowed OTC as single ingredients, but not in any combination. (See the External Analgesic Drug Products report published in the Federal Register on December 4, 1979 (44 FR 69813)). The agency is currently reviewing that Panel's recommendation and the comments to that report, but has not made a final decision on whether hydrocortisone should be an OTC drug. Under § 330.13 (21 CFR 330.13), no combinations of antifungal ingredients and hydrocortisone or hydrocortisone acetate may be marketed OTC at this time. The agency invites comments and data relating to the Panel's recommendation that these combination products be available OTC. The agency specifically invites comments on adequate directions for use, appropriate warnings, and duration of use for these products before a physician should be consulted.

After reviewing all comments submitted in response to the agency's statements above and to the Panel's recommendations and conclusions, FDA will issue in the Federal Register a tentative final monograph for OTC topical antifungal 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.

In the preamble to this report, the agency comments on a number of the Panel's recommendations. Because of these agency comments, certain prescription to OTC drug switches recommended by the Panel will not be permitted at this time; other such switches will not be permitted. In the case of some combinations, the agency will permit the reformulation of products to include Category I ingredients as long as no prescription to OTC drug switches are involved. This means that one currently marketed OTC ingredient in a combination drug product may be replaced by another currently marketed OTC ingredient. Because these actions do not restrict the previously existing marketing conditions of OTC drug products, the agency has determined that there is no regulatory impact of these actions at this time.

The agency's position on OTC topical antifungal drug products will be stated initially when the tentative final monograph is published in the Federal Register as a notice of proposed rulemaking. In that notice of proposed rulemaking, the agency also will announce its initial determination whether the proposed rule 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 if 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 notice of proposed rulemaking is published. At that time FDA also will consider whether the proposed rule 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 antifungal 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 antifungal 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 topical antifungal 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 April 22, 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 authorized 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 results of that testing or any other data, would need to 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 products 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 monograph 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 introduced 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 monograph regardless of the date the product was initially introduced 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 antimicrobial active ingredients for the treatment and prevention of specific disorders such as seborrhea, dandruff, acne, athlete's foot, vaginitis, and otitis externa (swimmer's ear) was issued in the **Federal Register** of December 16, 1972 (37 FR 26842). (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 or 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 than an 'active ingredient.'")

A subsequent request for data and information on topical antibiotic active ingredients used in OTC drug products for the treatment and prevention of infections in minor skin wounds was published in the **Federal Register** of September 7, 1973 (38 FR 24391). The Panel's conclusions and recommendations for topical antibiotic drug products were published in the **Federal Register** of April 1, 1977 (42 FR 17642).

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

Wallace Guess, Ph. D., Chairman
Frank B. Engley, Jr., Ph. D.
Paul D. Stolley, M.D., M.P.H. (resigned June 1977)
William F. Schorr, M.D. (resigned July 1977)
W. Kenneth Blaylock, M.D.
E. Dorinda Loeffel Shelley, M.D.
Margaret Hitchcock, Ph. D. (resigned September 1974)
David R. Brown, Sc. D. (appointed March 1975, resigned March 1976)
Eula Bingham, Ph. D. (appointed July 1976, resigned June 1977)
James E. Rasmussen, M.D. (appointed October 1976)
George B. Youngstrom, M.D. (appointed June 1977, resigned October 1979)
Anne Tucker, Ph. D. (Panel consultant from July 1978 to March 1979; appointed as a Panel member March 1979)
Zenona Mally, M.D. (appointed October 1979)

The Panel first convened on July 26 and 27, 1974 in an organizational meeting. Working meetings which dealt with the topic in this document were held on January 9, 10, and 11, February 13, 14, and 15, March 12, 13, and 14, June 25, 26, and 27, July 23, 24, and 25, August 20, 21, and 22, October 29, and 30, November 19, 20, and 21, 1976; January 7 and 8, February 18 and 19, April 15 and 16, May 20 and 21, June 24, 25, and 26, August 26 and 27, October 8 and 9, November 18 and 19, 1977; January 13 and 14, February 10 and 11, March 17 and 18, April 14, and 15, August 18 and 19, September 29 and 30, November 10 and 11, 1978; January 19 and 20, March 23 and 24, April 27 and 28, June 8 and 9, July 20, August 17 and 18, October 12 and 13, 1979; January 18 and 19, and February 22 and 23, 1980.

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

The following nonvoting consultants assisted the Panel: Brenda M. Brandon,

Sc. M., from October 1977 to June 1979, and Kazuo M. Kimura, M.D., Ph. D., from October 1977 to June 1978.

The following nonvoting liaison representatives served on the Panel: James D. Lawrence, M.D., Ph. D., served as an industry liaison in October 1976. Gavin Hildick-Smith, M.D., nominated by the Cosmetic, Toiletry and Fragrance Association, served as an industry liaison until April 1978. Michael Winrow, Ph. D., nominated by the Proprietary Association, served as an industry liaison until April 1979, followed by Kenneth Johannes until January 1980, followed by C. Elizabeth McKinivan, M.D. Ms. Sarah Newman, nominated by an ad hoc group of consumer organizations, served as the consumer liaison.

The following FDA employees served: Mary K. Bruch served as Executive Secretary; Michael Kennedy served as Panel Administrator in July 1974, followed by Armond M. Welch, R.Ph., until August 1978, followed by Lee Geismar. Melvin Lessing, R.Ph., M.S., served as Drug Information Analyst until October 1974, followed by Joseph Hussion, R.Ph., until July 1976, followed by Anne W. Eggers, R.Ph., M.S., until June 1978, followed by Elaine G. Euchner, R.Ph.

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

A. M. Allen, M.D.
Harvey Blank, M.D.
Eugene A. Conrad, Ph. D.
James D. Cope
David Cram, M.D.
Stanley Cullen, M.D.
R. Sherman Detrick
Eugene Farber, M.D.
Beverly Foster
Kare Gundersen, M.D.
Larry Gundersen, Ph. D
Dietrich Hoffman, Ph. D.
William Hubregs, Ph. D.
Arthur Isbit, Ph. D.
Herman Jass, Ph. D.
Albert Kligman, M.D., Ph. D.
John Leer, M.D.
Leonard Levy, M.D.
James Leyden, M.D.
Edward Marlowe, Ph. D.
William Merz, M.D.
John Middleton, Ph. D.
Sigfrid Muller, M.D.
Gerbert Rebell, M.D.
Robert I. Schattner, D.D.S.
Vithal Shetty, Ph. D.
Donald Smith
David Taplin
Frederick Urbach, M.D.
George Warren, Ph. D.
Peyton Weary, M.D.
Nardo Zaias, M.D.

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

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent data and information submitted through February 23, 1980, in arriving at its conclusions and recommendations.

In this document the Panel presents its conclusions and recommendations on antifungal drug products used for the treatment of jock itch and ringworm and for the treatment and prevention of athelete's foot. The Panel believes that some of these drug products are also effective in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*). Thus, these indications for use have been included where appropriate.

The Panel's findings for acne drug products will be presented in a future issue of the **Federal Register.**

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

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

Category II. Conditions under which OTC topical antifungal 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 33 active antifungal ingredients. Six ingredients were placed in Category I for use in treating athlete's foot, jock itch, and ringworm. The Panel placed 9 ingredients in Category II and 18 ingredients in Category III for the treatment of athlete's foot, jock itch, and ringworm. One of the six ingredients placed in Category I for the treatment of athlete's foot, jock itch, and ringworm was also placed in Category I for the prevention of athlete's foot. Three of the ingredients placed in Category I for treating athlete's foot, jock itch, and ringworm were also reviewed for treating feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*) and were placed in Category I for these uses.

I. Submission of Data and Information

A. Submissions by Firms

Firms	Marketed products
Ayerst Laboratories, New York, NY 10017.	Enzactin Aerosol, Enzactin Cream, Enzactin Power Pack.
Buckman Laboratories, Inc., Memphis, TN 38108.	Buderma First Aid Ointment.
Chattem Drug and Chemical Co., Chattanooga, TN 37409.	Blis-To-Sol Aerosol Power, Blis-To-Sol Liquid, Blis-To-Sol Medicated Gel, Blis-To-Sol Power.
Ciba-Geigy Corp., Summit, NJ 07901.	Vioform Antiseptic Dusting Power, Vioform Cream, Vioform Ointment, Vioform-Hydrocortisone Cream, Vioform-Hydrocortisone Mild Cream, Vioform-Hydrocortisone Ointment, Vioform-Hydrocortisone Mild Ointment, Vioform-Hydrocortisone Lotion.
Clapp, Otis, and Son, Inc., Cambridge, MA 02139.	Obtundia Antiseptic Swab Pads, Obtundia First Aid Spray, Obtundia Surgical Dressing.
Cramer Products, Inc., Gardner, KA 66030.	Cramer Foot Ointment, Fung-O-Spray.
Gaddy, R. L., Tallahassee, FL 32302.	Ez-It Liquid.
Gillette Medical Evaluation Laboratories, Rockville, MD 20850.	Foot Guard Power, Foot Guard Spray.
Laboratory Robaina, Inc., Hialeah, FL 33010.	Acetolia Robaina.
La Wall and Harrisson Research Laboratories, Inc., Philadelphia, PA 19103.	Ecco Medicated Powder.
Magnesia Products, Inc., Dayton, OH 45404.	Sporodyne.
Norwich Pharmacal Co., Norwich, NY 13815.	NP-27 Aerosol, NP-27 Cream, NP-27 Liquid, NP-27 Powder.
Pennwalt Corp., Rochester, NY 14603.	Cruex Medicated Cream, Cruex Medicated Spray-On Powder, Desenex Ointment, Desenex Powder, Desenex Solution, Desenex Spray-On Foot Powder, Ting Antiseptic Medicated Cream.
Plough, Inc., Memphis, TN 38151.	Aftate Antifungal Gel, Aftate Antifungal Powder, Aftate Antifungal Spray Liquid, Aftate Antifungal Spray Power.
Purdue Frederick Co., Norwalk, CT 06856.	Isodine Athlete's Foot Solution.
Red Foot Products Co., Inc., Detroit, MI 48228.	Red Foot Powder.
Rilox Co., New Orleans, LA 70122.	Geneva Ointment.
Rorer, William H., Inc., Fort Washington, PA 19034.	Carfusin.
Rystan Co., Inc., Little Falls, NJ 07424.	Prophyllin Ointment, Prophyllin Powder.
Schattner, R., Co., Washington, D.C. 20016.	Chloraderm.
Schering Corp., Bloomfield, NJ 07003.	Tinactin Cream, Tinactin Powder, Tinactin Powder Aerosol, Tinactin Solution, Tinactin Solution Aerosol.
Scholl, Inc., Chicago, IL 60610.	Solvex Athlete's Foot Liquid, Solvex Athlete's Foot Ointment, Solvex Athlete's Foot Powder, Solvex Athlete's Foot Spray Powder, Solvex Athlete's Foot Spray.
Smith, Kline, and French Laboratories, Philadelphia, PA 19101.	Pragmatar.
Sterling Drug, Inc., New York, NY 10016.	Campho-Phenique Liquid, Campho-Phenique Powder.
Stiefel Laboratories, Inc., Oak Hill, NY 12460.	Salicylic Acid and Sulfur Soap.
Texas Pharmacal Co., San Antonio, TX 78296.	Verdefam Cream, Verdefam Solution.
Upjohn Co., Kalamazoo, MI 49001.	Fluid Salicresin, Medicated Foot Powder.
Wade Chemical Corp., Shreveport, LA 71103.	Jim Wade Foot Powder.

Firms	Marketed products
Westwood Pharmaceuticals, Inc., Buffalo, NY 14213.	Halotex Cream, Halotex Solution.
Wyeth Laboratories, Inc., Philadelphia, PA 19101.	Sopronol Ointment, Sopronol Powder, Sopronol Solution.
Young, W. F., Inc., Springfield, MA 01101.	Absorbine Athlete's Foot Powder, Absorbine Jr.
In addition, the following firms or groups provided related information:	
Carbisulphoil Co., Dallas, TX 75204.	Sulfur.
Clairol Research Laboratories, Stamford, CT 06902.	Resorcinol.
Dermik Laboratories, Inc., Syosset, NY 11791.	Coal tar.
Ferro Corp., Washington, D.C. 20014.	Chloroxylenol.
Givaudan Corp., Clifton, NJ 07014.	Dichlorophen.
Johnson and Johnson, New Brunswick, NJ 08903.	Miconazole nitrate, Miconazole nitrate/hydrocortisone, talc.
Norcliff Thayer, Inc., Tuckahoe, NY 10707.	Tolindate.
Pennwalt Corp., Rochester, NY 14603.	Calcium undecylenate/hydrocortisone, chloroxylenol, fungicidal testing.
Purdue Frederick Co., Norwalk, CT 06856.	Povidone-iodine.
Proprietary Association, Washington, DC 20006.	OTC labeling terminology, use of a guinea pig model in product testing.
Reckitt and Colman, Hull, England.	Chloroxylenol.
Richardson-Merrell, Inc., New Rochelle, NY 10801.	Resorcinol.
Schattner, R., Co., Washington, DC 20016.	Phenol/phenolate sodium.
Schering Corp., Bloomfield, NJ 07003.	Tolnaftate/nystatin, professional labeling.
Schuylkill Chemcial Co., Philadelphia, PA 19132.	Alcloxa, allantoins.
Sterol Controls Co., East Northport, NY 11731.	Candicidin.
U.S. Borax Research, Anaheim, CA 92801.	Boric acid.
Warner-Lambert Co., Morris Plains, NJ 07950.	Methyl salicylate.
Westwood Pharmaceuticals, Inc., Buffalo, NY 14213.	Professional labeling.
Young, W. F. Inc., Springfield, MA 01101.	Chloroxylenol, in vivo guinea pig studies.

B. Ingredients Reviewed by the Panel

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

Acetone
Alcohol
Aluminum chlorhydroxyallantoinate
Aluminum potassium sulfate
Aluminum sulfate
Aluminum sulphate
Anhydrous ethanol
Aromatic oils
Basic fuchsin
Bentonite
Benzethonium chloride
Benzocaine
Benzoic acid
Benzyl alcohol
Boric acid
Calcium silicate
Calcium undecylenate
Camphor
Cetyl alcohol-coal tar distillate [1]
Chlorophyll
Chlorothymol
Chloroxylenol
Chlorthymol
Cinnamaldehyde
Coal tar
Copper undecylenate
Corn starch
Dichlorophene (G–4)
Diethyl sebacate
Dioctyl sodium sulfosuccinate
Essential oils
Eucalyptol
Glycerin
Glycerine
Hexadecyl alcohol
Hydroxoquinoline
8-Hydroxyquinoline
8-Hydroxyquinoline benzoate
8-Hydroxyquinoline sulfate
Iodochlorhydroxyquin
Isopropyl alcohol
Magnesium carbonate
Magnesium stearate
Menthol
Meta-cresol
Methylparaben
Methyl salicylate
Oil of pine
Orthochloromercuriphenol
Orthohydroxyphenylmercuric chloride
Oxyquinoline
Oxyquinoline sulfate
Parachlorometaxylenol
Petrolatum
Phenol
Phenyl Salicylate
Polyethylene glycol 400
Polyethylene glycol 4000
Polyvinylpyrrolidone
Polyvinylpyrrolidone-iodine
Potassium sulfate
Propionic acid
n-Propyl alcohol
Propyl alcohol
Propylene glycol
Propylparaben
Resorcinol
Salicylic acid
Secondary amyltricresols
Sodium borate
Sodium caprylate
Sodium dioctylsulfosuccinate
Sodium phenolate
Sodium propionate
Starch
Sulfur
Sulphur
Talc
Talcum
Tannic acid
Thymol
Tincture benzoin compound
Tolnaftate
Triacetin
Trimethyloctadecadienyl ammonium chloride
Trimethyloctadecenyl ammonium chloride
Undecylenic acid
Wormwood
Zinc caprylate
Zinc oxide
Zinc propionate
Zinc stearate
Zinc undecylenate

2. *Other ingredients reviewed by the Panel.*

Candicidin
Haloprogin
Hydrocortisone
Hydrocortisone acetate
Miconazole nitrate
Nystatin
Tolindate

C. Classification of Ingredients

1. *Ingredients identified by the Panel as active antifungal ingredients.* The Panel has adopted the following nomenclature for the active ingredients reviewed in this document. Where applicable, other nomenclature has been included in parentheses for purposes of clarification.

Aluminum salts
  Alcloxa (aluminum chlorhydroxyallantoinate)
  Aluminum sulfate (aluminum sluphate)
  Potassium alum (aluminum potassium sulfate)
Basic fuchsin
Benzethonium chloride
Benzoic acid
Borates
  Boric acid
  Sodium borate
Camphor
Candicidin
Caprylates
  Sodium caprylate
  Zinc caprylate
Chlorothymol (chlorthymol)
Chloroxylenol (parachlorometaxylenol)
Coal tar (coal tar distillate)
Cresols
  m-Cresol (*meta*-cresol)
  Secondary amyltricresols
Dichlorophen (dichlorophene (G–4))
Haloprogin
Iodochlorhydroxyquin
Menthol
Miconazole nitrate
Nystatin
Oxyquinolines
  Benzoxiquine (8-hydroxyquinoline benzoate)
  Oxyquinoline (8-hydroxyquinoline and hydroxoquinoline)
  Oxyquinoline sulfate (8-hydroxyquinoline sulfate)
Parabens
  Methylparaben
  Propylparaben
Phenolates
  Phenol
  Phenolate sodium (sodium phenolate)

[1] In this document, this mixture will be considered as two separate ingredients—coal tar and cetyl alcohol.

Phenyl salicylate
Povidone iodine
Propionic acid and its salts
  Sodium propionate
  Zinc propionate
Resorcinol
Salicylic acid
Sulfur (sulphur)
Tannic acid
Thymol
Tolindate
Tolnaftate
Triacetin
Undecylenic acid and its salts
  Calcium undecylenate
  Copper undecylenate
  Zinc undecylenate

2. *Ingredients identified by the Panel as inactive or pharmaceutically necessary ingredients.* The following ingredients have been carefully reviewed by the Panel as possible antifungal agents. Based on the available literature and in some cases based on concentrations reported in a submission, the Panel considers the following to be inactive ingredients when used in products labeled for fungal infections of the foot, body, or groin. In general, most are used as pharmaceutical aids (solvent, vehicle, dispersant, or preservative) or as product identification materials.

Acetone
Alcohol
Aromatic oils
Bentonite
Benzyl alcohol
Calcium silicate
Cetyl alcohol (hexadecyl alcohol)
Chlorophyll
Cinnamaldehyde
Compound benzoin tincture (tincture benzoin compound)
Corn starch (starch)
Dehydrated alcohol (anhydrous ethanol)
Diethyl sebacate
Dioctyl sodium sulfosuccinate (sodium dioctylsulfosuccinate)
Essential oils
Eucalyptol
Glycerin (glycerine)
Isopropyl alcohol
Magnesium carbonate
Magnesium stearate
Methyl salicylate
Oil of pine
Petrolatum
Polyethylene glycol 400
Polyethylene glycol 4000
Polyvinylpyrrolidone
Propyl alcohol (*n*-propyl alcohol)
Propylene glycol
Talc (talcum)
Trimethyloctadecadienyl ammonium chloride
Trimethyloctadecenyl ammonium chloride
Wormwood oil (wormwood)
Zinc oxide
Zinc stearates

3. *Nonantifungal ingredients reviewed under combination products.* See part III. paragraph D. below—Combination Products Used in the Treatment of Athlete's Foot, Jock Itch, and Ringworm.

Benzocaine
Hydrocortisone
Hydrocortisone acetate

4. *Ingredient referred to the Advisory Review Panel on OTC Miscellaneous External Drug Products.*

o-Mercufenol chloride (*ortho*-chloromercuriphenol and *ortho*-hydroxyphenylmercuric chloride)

5. *Products referred to other advisory review panels.*

Products for the treatment of swimmer's ear were referred for review to the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Products. Products for the intravaginal treatment of vaginitis were referred for review to the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products. Products for the treatment of dandruff and seborrhea were referred for review to the Advisory Review Panel on OTC Miscellaneous External Drug Products.

A notice of transfer of responsibility for the review of OTC drug products for the treatment or prevention of dandruff or seborrhea was published in the **Federal Register** of March 6, 1979 (44 FR 12271).

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons in response to the call-for-data notice published in the **Federal Register** of December 16, 1972 (37 FR 26842). 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 April 22, 1982, in the Docket Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statement and Recommendations

A. Definitions

The Panel adopted the following definitions related to the use of topical antifungal drug products:

1. *Antifungal agent.* An agent which either kills or inhibits the growth and reproduction of fungal cells.

2. *Athlete's foot.* In common usage the term "athlete's foot" is applied to any chronic, acute, or recurrent rash occurring on the soles of the feet or between the toes, regardless of cause. In this document, however, the term "athlete's foot" is restricted to infections of the feet caused by dermatophytic fungi. The active rash is usually itchy, red, and scaling. Often, the toewebs (spaces between the toes) are white and soggy and painful cracks may occur between the toes. There may be small water blisters and pustules on the soles. The term "jungle rot" is also used to describe athlete's foot, particularly by men who developed the condition during military service in hot, humid climates. Secondary bacterial infections often accompany the underlying fungal infection.

3. *Dermatophytes.* A group of taxonomically related fungi which normally live in soil, where they metabolically decompose organic keratinous debris through the enzymatic digestion of keratin (a fibrous protein also found in cornified epidermis). Many of these fungi cause superficial skin infections including athlete's foot, jock itch, and rignworm in humans and in animals by invading and living in the cornified epidermis or in the hair or nails. These fungi are subdivided and classified according to their usual source of isolation from soil, from animals, or from man.

The dermatophytic fungi most commonly mentioned in this document include *Trichophyton rubrum* (*T. rubrum*), *Trichophyton mentagrophytes* (*T. mentagrophytes*), and *Epidermophyton floccosum* (*E. floccosum*). These organisms are the most frequent causes of human infections in the United States, but other strains may be involved.

4. *Dermatophytosis.* Any superficial infection in humans or animals caused by dermatophytic fungi. In this document, athlete's foot, jock itch, and ringworm represent types of dermatophytosis.

5. *Fungicidal agent.* An agent that kills fungi.

6. *Fungistatic agent.* Traditionally, an agent that inhibits the growth or reproduction of fungal cells, but allows later culturing of viable fungal cells when contact with the agent is removed. However, more modern approaches to the destruction of microbial cells have emphasized that agents described as either fungicidal or fungistatic kill the exposed fungal cells, but at different rates. A fungicidal agent kills the fungal cells more rapidly, whereas a fungistatic agent may permit cell reproduction for several generations before cell death is observed.

7. *Fungus.* The term "fungi" or the plural "fungi" encompasses a diverse group of organisms which includes yeasts and molds. Although the general term is used, this document most often refers to a specific group, the dermataphytic fungi. This group includes yeastlike and moldlike organisms and some with the morphological characteristics of both.

8. *Intertrigo.* An inflammatory skin eruption occurring in any skin-fold area. Intertrigo develops when opposing skin surfaces, such as those of the upper thigh and lower abdomen surrounding the groin, rub against each other and trap moisture, creating a warm, moist environment that favors the proliferation of microorganisms, including bacteria and fungi.

9. *Jock itch.* In common usage the term "jock itch" refers to a chronic and recurrent rash, regardless of cause, which occurs on the upper inner thighs of men and sometimes extends into the groin and pubic areas. Jock itch is usually caused by dermatophytic fungi, and in this document jock itch is limited to dermatophyte infections. This rash may also be referred to as "crotch rot" or "Dhobie itch." When active, the rash is usually red, scaling, and itchy, with a well-defined border along the inner thigh.

Women may develop the same rash, but much less commonly than men. The Panel is not aware of any common designation given to this skin condition in women. The general term "intertrigo" could be used to describe the condition in women, although the use of this term is not strictly limited to the groin area.

10. *Potassium hyaroxide (KOH) preparation.* This laboratory test (called KOH preparation) is performed to help confirm a diagnosis of a superficial fungus infection of the skin, including one caused by dermatophytes and other types of fungi, such as *Candida albicans (C. albicans).* Although a positive KOH may mean the presence of a dermatophytic fungus, it will not distinguish between different genera or species of dermatophytes. And a negative KOH does not definitely rule out the presence of fungi. In performing the test, skin scrapings from recently formed, enlarging lesions are placed on a glass slide and treated with a few drops of 10 to 20 percent KOH. The slide is then gently heated and microscopically examined for fungal hyphae (threadlike filaments).

11. *Ringworm.* In common usage the term "ringworm" is applied to any ring-shaped lesion on the skin. This document, however, limits the term to skin infections caused by dermatophytic fungi. Such lesions usually have a clear center and an active border which is red and scaling. Ringworm may also be used generally to describe any superficial fungus infection of the skin, hair, or nails, even when individual skin lesions are not ring shaped. For example, "ringworm of the groin" refers to jock itch. A common misconception is that ringworm involves a "worm" in the skin.

In scientific usage the Latin word "tinea" is generally combined with another Latin word designating the location of the fungal infection, i.e., tinea capitis— ringworm of the scalp; tinea corporis—ring-shaped or other fungal lesion on the hairless parts of the body; tinea cruris—jock itch; tinea pedis—athlete's foot.

12. *Wood's light.* This light is used to help detect some fungal and bacterial infections on the skin. It consists of an ultraviolet light source which shines through glass composed mainly of barium silicate with nickel oxide. The transmitted light rays with a wavelength above 3,650 angstrom units cause some micoorganisms to fluoresce due to the chemicals they produce. The Wood's light is particularly useful in diagnosing ringworm of the scalp, since hairs infected by the dermatophytic fungi *Microsporum canis (M. canis)* and *Microsporum audouinii (M. audouinii)* fluoresce a brilliant green because the chemical, pteridine, is formed in the hair.

Ringworm lesions caused by these same organisms on the skin do not fluoresce under the Wood's light. Neither do the fungi that most commonly cause athlete's foot and jock itch. But the Wood's light can detect specific bacteria which induce conditions on the feet and in the groin that mimic athlete's foot and jock itch. The major types of bacteria thus detected include *Pseudomonas aeruginosa (P. aeruginosa),* which causes infection in macerated toewebs, and *Corynebacterium minutissimum (C. minutissimum),* which causes erythrasma in the toewebs and groin.

B. Types of Fungal Infections

Although all surfaces of the human body can be infected by one or another of the various microorganisms that cause fungal infections of the skin, the Panel has concentrated on fungal infections of the foot and the groin and on ringworm of the body excluding the scalp and nails. Fungal infections of the foot and groin often occur in the same individual.

The names of fungi in mycological literature number more than 200,000, according to Emmons, Binford, and Utz (Ref. *1*). Many are earlier names; many others are names that have been given to minor variations of fungi. For example, other names for *T. mentagrophytes* include *Microsporum mentagrophytes (M. mentagrophytes), Trichophyton gypseum (T. gypseum),* and *Trichophyton interaigitale (T. interdigitale).* This document will use the names that appear in the cited references.

The pathogenic fungi that cause athlete's foot are also commonly found in jock itch (Ref. *2*). The fungi most commonly isolated from the feet and the groin are *T. rubrum, T. mentagrophytes,* and *E. floccosum.* Of these, *T. rubrum* is more prevalent in infections of the feet; *E. floccosum* is more prevalent in the groin. These organisms may vary with a patient's sex, age, ethnic group, or geographic location.

1. *Tinea pedis (athlete's foot).* Athlete's foot usually begins in men between the ages of 15 and 40 years. It is uncommon in children before puberty. Women develop athlete's foot much less commonly than men. The infection may begin in the web spaces of the toes or on the sole. Itching and burning are the common symptoms, but the clinical picture varies from the moist web to the relatively dry soles.

In the toeweb, white scale is common especially between the fourth and fifth toe. Vesciles (blisters) and pustules (pus-filled sweat pores or hair follicles) may also occur. The skin may crack, probably causing the burning sensation.

On the sole, irregularly grouped vesicles and superficial scale are common, but athlete's foot rarely produces the "ringworm" shape that is considered characteristic of fungal infections in other sites. The disease may produce only slight scales and little significant inflammation (vesicles or erythema). With such a variety of lesions, a KOH preparation of skin scrapings is usually necessary to accurately differentiate tinea pedis from all the other diseases which mimic it and are sometimes called "athlete's foot." A fungal culture will confirm the presence of fungi and enable identification of the specific fungus.

If the infection persists, the appearance of the lesion can change and the infection may spread to other areas. Chronic athlete's foot usually produces either a superficial scale on both soles or white, scaling lesions in the web spaces. Sometimes both the soles and the web spaces are affected. The toenails are commonly involved, and fungus may invade and destroy the nail plate.

2. *Tinea cruris (jock itch).* Jock itch is most common in young men (ages 18 to 40 years) and is rarely seen in

prepubertal children. The initial infection occurs on the upper inner thigh near the genito-crural crease. It spreads downward, to the side, and onto the scrotum. Frequently the result is a semicircle and not a "ring." The expanding margin is slightly raised and scaling; the clearing center is stained a light brown by the resolving inflammation. Vesicles and pustules are uncommon.

3. *Tinea corporis (ringworm of the body).* Ringworm of the body is the most common type of dermatophyte infection before puberty. It is commonly caused by *M. canis,* an organism which can be carried by dogs and cats. Ringworm of the body usually forms ring-shaped lesions, erythema and scaling at the margins, and relatively clear centers.

4. *Tinea capitis (ringworm of the scalp) and tinea unguium (ringworm of the nails).* Fungal infections of the scalp and nails tend to be chronic. They respond poorly to topical thereapy, partly because of the thickness of the nails and the depth of the hair roots. Both sites of infection provide inaccessible locations for fungi, thus drastically decreasing the penetration of topical antifungals. For this reason, OTC topical antifungals must be labeled that they are not effective for the treatment of ringworm of the scalp or nails.

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C. Diseases That May Simulate Athlete's Foot or Jock Itch

There are several less common skin conditions that may affect the feet and the groin and cause symptoms that mimic athlete's foot and jock itch. These conditions may be misdiagnosed as athlete's foot or jock itch. Common examples of such conditions include the following: candidiasis, a yeast infection; allergic contact dermatitis; psoriasis; and hyperhidrosis (excessive perspiring) which may be associated with maceration of the skin and an inflammatory eruption known as dyshidrotic eczema.

1. *Candidiasis (moniliasis).* This infection is caused by *Candida* species, usually *C. albicans,* a yeast which is pathogenic under certain circumstances. The organism thrives on warm, moist areas of the body, such as the toewebs and groin. On the feet, the symptoms of candidiasis are redness, maceration, and fissuring of the toewebs. In the groin, the infection produces itchy, bright-red, exuding patches with numerous pustules along the outer edge. In men the eruption frequently spreads to involve the scrotum and the skin around the rectum. In women the eruption is similar but is usually associated with extreme itching and with a discharge if the vagina is infected. Candidiasis in the groin is often secondary to proliferation of *C. albicans* in the digestive tract following a disturbance of normal intestinal bacterial flora. Numerous factors predispose the patient to develop candidiasis, including diabetes, pregnancy, obesity, and profuse sweating. Birth control pills, oral corticosteroid drugs, or broad-spectrum antibiotics may also predispose to candidiasis.

The diagnosis of candidiasis is confirmed by finding the organism in a KOH preparation of skin scrapings, where it appears as long pseudohyphae associated with clusters of oval, budding, thin-walled yeast cells. The organism may be easily cultured on Dermatophyte Test Medium (DTM), Mycosel ®, Sabouraud's Glucose Agar, or equivalent media.

2. *Allergic eczematous contact dermatitis.* Allergy to shoes is usually caused by the rubber in the insoles. It can, however, be caused by dyes or tanning agents. The area of dermatitis will correspond to the part of the shoe containing the allergen. For persons who are allergic to the sponge rubber insoles, the usual pattern of dermatitis is on the arch of the foot, with less involvement on the thickly keratinized sole. At this site, there may be erythema, scale, and visible blistering. The toewebs are not involved and unless the disease is severe and longstanding, the toenails will remain normal.

3. *Bacterial infection of the feet.* Bacterial infection of the feet is usually limited to the toewebs. It is a common secondary infection occurring with fungal disease. The bacterial infection may be acutely inflammatory and is usually caused by gram-negative bacteria, such as *Pseudomonas.* Odor, pus, and a yellowish-green color are all suggestive of a gram-negative infection of the toewebs.

4. *Erythrasma.* Erythrasma is a common bacterial infection which causes macerated scale in the toewebs (Ref. 1). It is frequently seen in adolescence and young adulthood, where it tends to involve the third and fourth toewebs bilaterally (Ref. 2). The infection is caused by *Corynebacterium minutissimum,* an aerobic gram-positive diphtheroid, or by several other fluorescent diphtheroids. Erythrasma is diagnosed by exposing the foot to a Wood's light and detecting a bright coral-red color, resulting from the fluorescence of porphyrin pigments produced by the bacteria (Ref. 3). Skin scrapings with staining of the scales will reveal gram-positive slender rods, filaments, and coccoid forms.

Erythrasma may also involve the inner thighs, where it is often misdiagnosed as jock itch. The eruption appears as irregular, well-circumscribed, reddish-brown patches with fine scales and slight wrinkling of the skin. Here, too, the diagnosis is confirmed by Wood's light.

5. *Psoriasis.* Psoriasis, a disease of unknown cause, may cause lesions of the feet and groin which closely resemble athlete's foot and jock itch. On the feet, psoriasis usually produces dry, red, scaly plaques which are sharply marginated and symmetrical, and often limited to pressure points. Maceration is sometimes present between the toes. The toenails are likely to be pitted and thickened, and may resemble toenails infected by fungus. In the groin, psoriasis usually produces red plaques which may be either scaly or macerated.

Psoriasis of either the feet or groin can be more readily diagnosed if the typical red, scaly lesions are also found on the knees, elbows, and scalp.

6. *Dyshidrosis.* Dyshidrosis is a recurrent noninflammatory eruption of the palms and soles. Occasionally it may involve only the feet and is difficult to distinguish from athlete's foot. Although most people with dyshidrosis also have hyperhidrosis of the hands and feet, the relationship between dyshidrosis and abnormal functioning of the underlying sweat glands remains unclear. Attacks of dyshidrosis tend to be worse during warm weather and are sometimes precipitated by emotional stress.

Dyshidrosis begins suddenly with crops of itchy, deeply set, clear or white blisters on the palms and soles and on the sides of the fingers and toes. Involvement on the feet is usually symmetrical and favors the high part of the instep. The blisters sometimes merge to form large blisters, which may rupture, ooze fluid, and develop secondary bacterial infection. An attack of dyshidrosis usually subsides spontaneously after 2 to 3 weeks, resolving with peeling.

In contrast to most cases of athlete's foot, dyshidrosis does not cause the sole to become red and scaly. Nevertheless, the presence or absence of fungi in dyshidrosis should be determined with a KOH preparation and fungal culture.

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D. Factors That May Affect the Development of Fungal Infections

The development of a fungal infection, such as athlete's foot or jock itch, depends on multiple factors that influence susceptibility to these diseases. Primary among these factors is exposure to *T. mentagrophytes, T. rubrum,* and *E. floccosum.* These fungi are common in homes, offices, and atheletic facilities; yet most adults and children do not have chronic athlete's foot or jock itch. the rate and prevalence of these superficial fungal infections are obviously related to many factors other than exposure to pathogenic organisms. Two important factors are local environmental and climatic conditions and the body's natural immunity.

1. *Environmental factors.* Fungal infections are difficult to establish naturally or experimentally on normal, dry skin. Conversely, skin damage (cracks, blisters, other infections) and increased moisture (from tight shoes, excessive sweating, humid summer weather, tropical climate) contribute to the development and continuation of athlete's foot and jock itch (Ref. *1*). Some fungal infections can be prevented and others terminated simply through control of the local environment and improvement in the patient's hygiene.

2. *Natural immunity.* Fungal skin infections can be established in natural or experimental settings when those exposed have never had a fungal skin infection (Ref. *2*). Such individuals are called nonimmune or "virgin" in medical parlance. Once a fungal infection has been established in the skin, certain fungal components (antigens) diffuse through the skin where they are exposed to the white blood cells. These antigens sensitize the white blood cells so that further exposure to fungal antigens attracts white blood cells to the site of skin infection.

When the sensitized white blood cells are in the area of fungal infection, they act as "killer cells" to destroy the fungi, producing a spontaneous clinical "cure." The previously infected host is now immune and repeated exposure to fungi results in either no infection or in a very brief inflammatory one (Ref. *2*). Immunity can be detected with the trichophytin (fungal antigen) skin test; a hard, red papule occurs 24 to 48 hours following injection into the skin. Because the immunity is mediated by the white blood cells, it is called cell-mediated immunity.

Not all individuals develop cell-mediated immunity during their first fungal infection so that spontaneous clinical "cures" are rare in this group. Many of these people have asthma, hay fever, or atopic eczema and do not develop 48-hour reactions to injected fungal antigens (Refs. *2* and *3*). However, they will develop immediate reaction (wheal and flare) to trichophytin, a reaction which represents the presence of antibodies. Apparently, antibodies are not effective in destroying superficial fungi, possibly because they cannot reach the outer surface of the skin. Such individuals commonly develop chronic athlete's foot or jock itch.

There are other factors, such as circulating inhibitory agents, which influence the host's immunity, but these are not well understood (Ref. *4*).

a. *Dermatophytid ("id").* The dermatophytid reaction is a response of the skin to a localized fungal infection caused by dermatophytes. The original concept of the "id" response was that a hapten (partial antigen) moved from the feet through the bloodstream to the skin of the body, causing a skin reaction similar to contact dermatitis. The eruption was free of the fungi noted in the original focal infection. Current data, however, suggest that sensitized T-cells (thymus-influenced lymphocytes sensitized to trichophytin) react to a carrier protein in the skin of the hands which is identical to the protein in the skin of the feet. This reaction results in the release of lymphokinin and the destruction of tissue. To date, trichophytin antigen has not been found in the bloodstream.

Symptoms of an "id" reaction may be fever, malaise, and loss of appetite. Enlarged lymph nodes, enlarged spleen, and an increased white blood cell count are occasionally noted. The skin lesions may be localized or generalized. The most common localized dermatophytid reaction is the vesicular dermatitis noted primarily between the fingers and on the palmar surface of the hands (Ref. *5*). When the eruption is widespread, the primary lesions are usually follicular papules (small bumps arising about hair follicules) which may become hard, leathery, and scaly. Other skin lesions may include erythema nodosum (tender, red nodules), urticaria (hives), and erythema annulare centrifigum (a chronic skin eruption in the form of rings). There may also be migratory superficial thrombophlebitis.

b. *Skin test for tinea infections: Trichophytin (T).* Trichophytin (T), a glycoprotein commercially prepared from the filtrate or broth used to grow several *Trichophyton* species, is used to determine immediate and delayed sensitivity to the *Trichophyton* haptens. Immediate reactions (20 minutes or less) may be noted in certain individuals who have chronic tinea infections. The immediate reaction may also be noted in persons with hives following acute infection, i.e., acute dermatophytosis. The delayed reaction to trichophytin is more common and may be noted in persons who have clinical symptoms and signs of active infection as well as in those without clinical infection. This kind of reaction may be most intense when a person has a kerion (massive acute inflammatory infiltrate in the skin) or a dermatophytid.

The delayed reaction to trichophytin can be used as a tool to evaluate a portion (efferent links) of cell-mediated immunity; it may also be helpful in studies of the epidemiology of tinea infections. But the delayed reaction cannot be used therapeutically to reduce the risk of infections by these organisms.

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E. Consumer Use of Topical Antifungal Drug Products

The Panel recognizes that safe and effective topical medications for the treatment of athlete's foot, jock itch, and ringworm are useful to the general public and should be available on the OTC market.

To illustrate the scope of the problem of treating athlete's foot, the Panel offers the following quotation by Mitchell (Ref. *1*):

It is an interesting fact that some patients have had a macerations [sic] and the fissures about the toes for so many years that they have come to regard the condition as perfectly normal, and will sometimes be somewhat indignant when it is pointed out to them that they have an infection.

Although no information was submitted on factors that influence the consumer's choice of topical antifungal drug products, the Panel suspects that there are several. Among these factors are media advertising, advice of a pharmacist, and suggestions from friends and acquaintances. The Panel also believes that most cases of athlete's foot, jock itch, and ringworm are self-diagnosed and self-treated by the consumer before a physician is consulted. The severity of symptoms, along with physician availability and cost, probably influence the duration of self-medication. Often the symptoms are mild enough to be little more than a nuisance, and the consumer may even accept them as "normal." The Panel suspects that many consumers do not realize that athlete's foot, jock itch, and ringworm are caused by fungi.

The Panel is concerned that many of these antifungal products may be used daily for months or even years with questionable benefit and possibly harmful side effects. For example, prolonged application of medication to chronic, persistent athlete's foot can produce skin sensitization and irritation without eradicating the underlying fungus. Such prolonged use on soggy toewebs or in a macerated groin with areas of broken skin can lead to the absorption and accumulation in tissue of certain ingredients that eventually could produce toxic effects. The Panel is also concerned that some products used to treat jock itch may be applied inappropriately over large areas of skin, thus leading to increased absorption of certain potentially toxic ingredients.

The Panel realizes that consumers' habits of self-medication and personal hygiene vary greatly. For example, some consumers may continue to use a product indefinitely that gives only symptomatic relief instead of looking for a more effective product. Others would probably discontinue any form of medication as soon as the signs and symptoms improve or disappear. Some consumers routinely use a foot powder to decrease sweating and promote drying. Consumers also choose varying types of footwear: some wear heavy shoes and occlusive socks or stockings that increase sweating and favor the development of athlete's foot; others wear lightweight, nonocclusive shoes or sandals which promote drying of the feet.

The Panel concludes that in order to best serve all consumers, an OTC product must provide more than temporary symptomatic relief of athlete's foot, jock itch, and ringworm. Such products must contain a Category I antifungal ingredient capable of killing the fungus.

Reference

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F. Availability of Antifungal Agents From Ointments, Creams, Powders, and Aerosol Sprays

Most antifungal materials are active in low concentrations and are usually incorporated into suitable vehicles for convenient application. Vehicle selection depends on many factors including consumer acceptance. But deviations from the theoretical ideal vehicle may tend to decrease the effectiveness of an antifungal agent in vivo. The following discussion, which is included to review the effects of vehicles and possible problems relating to availability of the active antifungal agent, is based on the Panel's general knowledge. Accordingly, there may be exceptions to the statements made, and none of the statements should be interpreted as reflecting adversely on any product which uses the kind of vehicle under discussion. Data on vehicles were not submitted to the Panel. (For a more detailed discussion of drug release from topical preparations, see the report on topical antibiotic products in the **Federal Register** of April 1, 1977 (42 FR 17647).)

Most antifungal agents are designed to be used on broken, denuded, diseased, or infected skin. The objective of any form of treatment is to deliver the antifungal chemical to the fungus in sufficient concentration to exert its antifungal activity. In athlete's foot, jock itch, and ringworm, the skin may be intact, or it may be inflamed, scaly, irritated, or fissured. In general, the most effective way to deliver an antifungal agent is to have the agent solubilized in an appropriate vehicle. Then the only obstacle to reaching an adequate concentration at the site of action is the rate at which the agent moves through the vehicle to reach the site (rate of diffusion). The rate of diffusion of an antifungal agent in solution in a nonviscous (watery) vehicle is fast enough so that there would be no obstacle to reaching an adequate concentration at the site of action.

Other factors, however, must be considered when choosing a vehicle for a given product. For example, an aqueous solution of an antifungal agent would not necessarily be the best for treating jock itch or athelete's foot because it would tend to run off the site of application so rapidly that contact time would be too short and action would be slight. A semisolid (viscous) dosage form, however, tends to hold an antifungal agent at the site somewhat longer than aqueous solutions.

Ointments have been popular vehicles for antifungal agents for many years. The term "ointment" at one time connoted a thick, greasy, water-repellent preparation as typified by white petrolatum. More modern pharmaceutical references to ointments include materials such as polyethylene glycols, which have varying viscosities and are water soluble. Ointments differ in degree of water solubility and miscibility. Petrolatum is water insoluble and immiscible; polyethylene glycols, to a varying degree, are water soluble and miscible. The major similarity between these vehicles is their viscosity. Between these extremes are other preparations with their own solubility and miscibility characteristics.

Vehicle solubility also influences the effectiveness of antifungal agents. Water-insoluble or repellent vehicles may tend to retard the release of medicaments to the skin. Water-insoluble or repellent vehicles may not adhere if the skin is broken and has serum in a fissure or wound. They may also be repelled from intact skin that is moist with sweat. In such vehicles moisture and serum may reduce the intimate contact of the medication with the infected site. Once the product contacts the skin, the antifungal agent must diffuse to the interface between the product and skin. It must then move from the vehicle to the aqueous milieu, where it can exert its antifungal activity.

In contrast, if the vehicle is a water-soluble polyethylene glycol type, both the vehicle and the antifungal agent dissolve in the serum or moisture and no partitioning needs to take place. Then the controlling factor becomes solely the rate of diffusion. Thus water-soluble vehicles may have certain advantages over water-insoluble vehicles in delivering the drug to the site of action. However, considerations such as solubility of the drug in the vehicle, site of application, type of skin condition, patient preference, and other factors also influence the final decision on which vehicle should be used for a given product.

The viscosity of a vehicle may simultaneously be an advantage and a disadvantage. For example, a viscous vehicle may adhere better to the application site, but its viscosity can also slow the diffusion of an antifungal agent through it. As a result, the concentration of drug at the interface with the skin can be rapidly depleted, with the possible result of a reduced concentration of drug at the site of action. With a viscous vehicle which is water soluble as well, diffusion is not such a major problem.

Powder formulations compose a large class of vehicles used in athlete's foot, jock itch, and ringworm products. Despite the wide use of these vehicles, there is little basic research on the bioavailability of drugs from powders, particularly on mixtures of powders.

To varying degrees, most powders used in these preparations are insoluble but wettable. The antifungal agent is usually dispersed uniformly throughout the powder vehicle by thorough mixing so that the antifungal agent is dispersed as a solid in a solid.

When a powder formulation is applied to diseased skin, the powder stacks in a layer. Some adheres to the site or if made to adhere by rubbing onto the site.

One way the antifungal agent can possibly reach intimate contact with the skin and the target fungus is for moisture to penetrate the powder by diffusion through interstitial spaces of the powder, solubilize or leach the antifungal agent, and carry the antifungal agent to the site. This process obviously requires sufficient moisture to effect the solubilization or leaching process. If a powder base is too absorbent, it may retard this process by absorbing too much moisture from the skin into the absorbent powder base. The resulting dry surface of the skin may interrupt diffusion of the antifungal agent from the powder to the skin.

One possible advanatage of a powder vehicle stems, however, from this same drying mechanism in that the fungus does not thrive well in a dry environment.

A number of products reviewed by the Panel contain volatile solvents as vehicles for the various antifungal agents. These include aerosol sprays and alcohol-acetone solutions. In general, these solvents evaporate quite rapidly, leaving the antifungal agent in immediate and intimate contact with the skin. Subsequent solubilization of the antifungal agent may then take place in moisture (sweat) or serum at the site. If the antifungal agent is sufficiently solubilized at the action site, it should carry out its designed effect.

G. Labeling

The Panel reviewed and concurs with the labeling requirements for OTC drugs (21 CFR 210.61 (a), (b), and (c)). The Panel also reviewed all submitted labels of preparations used for the treatment of athlete's foot, jock itch, and ringworm and the prevention of athlete's foot. The following general recommendations for labeling are based on these reviews. (For details see part III. paragraph A.2. below—Category I Labeling.)

1. *Pharmacological action.* In order to use the term "antifungal" in its labeling, a product must contain at least one ingredient with specific fungicidal or fungistatic action.

The Panel recognizes that many agents, especially those that promote drying of infected skin, such as alcohols, starch, talc, and acetone, may temporarily relieve symptoms of certain kinds of fungal infection. This is especially true if these ingredients are used on macerated skin. But these drying agents are not true antifungals. Drying alone will not produce clinical cures and negative cultures in most cases of athlete's foot and jock itch.

2. *Indications.* The indications for use should be simply and concisely stated. They should enable the consumer to clearly understand the results that can be anticipated from the use of the product. Any statement on the indications for use should be restricted to the conditions for which the product is recommended. There should be no reference, made or implied, to the relief of any symptoms unrelated to the condition accepted as an indication for use of the product.

For Category I ingredients the indications for use include the treatment of jock itch and ringworm and the treatment and prevention of athlete's foot. The Panel does not recommend the use of antifungal agents for the prevention of jock itch or ringworm. Because the groin is a much more sensitive area than the feet, antifungal agents should not be used indefinitely in the groin. Also, it would be impractical to use an antifungal agent prophylactically over large areas of the body to prevent ringworm of the body. The Panel believes that ingredients proven effective for the treatment of fungal disease may also be effective in the prevention of athlete's foot. But these ingredients may use the prevention labeling only after performing an appropriate clinical trial to demonstrate effectiveness in prevention. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

For some ingredients the indications for use also include the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*).

3. *Ingredients.* Antifungal drug products should contain only active ingredients plus such inactive ingredients as needed for formulation. The label should state the concentration of each active ingredient.

The Panel strongly recommends that all inactive ingredients be listed as such on the label in descending order of quantity. For a variety of reasons, such as allergies and idiosyncratic reactions, the consumer may need to know the product ingredients. The label, however, should not imply or claim that the product's inactive ingredients have a therapeutic benefit.

4. *Directions for use.* The directions for use should be clear and direct. They should provide the user with sufficient information to enable safe and effective use of the product. (See part III. paragraph A.2. below—Category I Labeling.)

Where necessary, the Panel has recommended specific directions under the ingredient statements in later sections of this document.

H. Evaluation of Safety and Effectiveness

1. *Sensitization by topical preparations—Contact dermatitis.* Believing that sensitization is an important consideration when determining the safety of antifungal ingredients, the Panel hs reviewed all submitted ingredients for sensitization potential, including those which might ordinarily be classified as weak sensitizers.

Some topical preparations contain ingredients that may sensitize only at low concentrations and only when applied frequently over long periods of time. But even this weak sensitization potential should be identified in ingredients tested for use as topical antifungals. Large numbers of people use these preparations, possibly over long periods of time and on body areas that may be occluded or may easily become sensitized, such as the feet and the groin.

Modified maximization tests or the original Draize test or one of its many modifications are the most commonly used procedures for predicting sensitization to chemicals or formulations applied to the skin (Ref. 1). (The original Draize test does not classify ingredients as weak sensitizers.) Weak sensitizers may easily be missed

in predictive testing. Maximization procedures or an increase in the number of subjects tested will increase the likelihood of identifying less potent or weak sensitizers. Grading an ingredient as a nonsensitizer based on zero positive reactions out ot 200 individuals tested is a less reliable procedure than, for example, the Kligman Maximization Test or modifications of it (Ref. *2*).

The Advisory Review Panel on OTC Antiperspirant Drug Products concluded that in testing, the following methods of enhancing the accessibility of the allergens to the skin are essential if any degree of predictability is to be attained: (1) stripping, cutting, or abrading the skin; (2) occlusion; (3) exposure to sodium lauryl sulfate or other material; and (4) raising the concentration of the ingredient to be tested (Ref. *3*).

When selecting testing procedures for an ingredient, the individual variation in the test subjects must also be considered. Induction of contact dermatitis is influenced by a variety of factors including:

(1) Genetic predisposition;
(2) Age and sex;
(3) Exposure time to antigen;
(4) Frequency of exposue to antigen;
(5) Antigen concentration;
(6) Antigen vehicle or adjuvant;
(7) Surface area of application on the skin;
(8) Site of application;
(9) Type of skin—diseased or healthy;
(10) Other factors, e.g., irritation.

The use of various maximization procedures that have been described in the literature increases the probability that the tester will identify weak sensitizers and thereby may provide a basis for predicting the number of sensitizations that may occur when the product is marketed.

For example, neomycin and benzocaine are similar in their ability to sensitize the skin of human subjects in circumstances like those of the modified maximization and Draize tests and in restricted populations, such as those in dermatology practices. This level of reaction, however, does not necessarily correlate with the prevalence of contact dermatitis attributed to neomycin and benzocaine in the general population. Likewise, this prediction of a sensitization rate does not necessarily translate to the sensitization rate of normal human skin in the testing of concentrations in predictive tests without maximization techniques or in circumstances of actual consumer use. These maximization tests will allow detection of materials that may not appear to have any risk of sensitization by some tests, but that actually do elicit responses in use situations.

The question of whether human skin can be sensitized with a low concentration of hapten needs further attention. It has been shown in animals that a low concentration of the hapten may induce tolerance. When low concentrations of haptens such as neomycin and benzocaine are applied to normal human skin, one might expect them to be low in sensitization potential. But when they are applied to irritated or inflammed skin, the sensitization potential increases.

The studies of Marzulli and Maibach (Ref. *4*) support the concept that the incidence of experimentally induced contact dermatitis is proportionate to the concentration of the hapten in question. Abnormally low concentrations may induce tolerance; excessive concentrations may cause irritation and also induce tolerance. Some haptens may sensitize only at low concentrations and only when applied frequently over prolonged periods of time.

References

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(*2*) Kligman, A. M., and W. Epstein, "Updating the Maximization Test for Identifying Contact Allergens," *Contact Dermatitis*, 1:231–239, 1975.

(*3*) Summary Minutes of the Advisory Review Panel on OTC Antiperspirant Drug Products, 5th Meeting, September 19, 20 and 21, 1974.

(*4*) Marzulli, F. N., and H. I. Maibach, "Antimicrobials: Experimental Contact Sensitization in Man," *Journal of the Society of Cosmetic Chemists*, 24:399–421, 1973.

2. *Criteria for evaluating safety.* To assess the safety data of topical antifungal ingredients, the Panel developed a set of flexible guidelines. Flexibility was needed to accommodate difficult chemical agents. Factors influencing the data assessment were the surface area and site of application, frequency and length of application, the vehicle, and the degree of occlusion.

To avoid needless repetition, the safety evaluation criteria are detailed later in this document. (See part III. paragraph E.1. below—Safety guidelines.)

Because many antifungal products had been marketed for extensive periods before this review was begun, the safety evaluation was based on limited historical data, new data obtained from various sources, and the expertise of the Panel.

3. *Criteria for evaluating effectiveness.* In evaluating the data submitted on antifungal ingredients, the Panel considered in vitro data, animal and human models, and clinical trials.

a. *In vitro data.* Antifungal activity should be demonstrated against *T. mentagrophytes, T. rubrum, E. floccosum, M. canis,* and, under certain conditions, *Candida* species. Data should include information on: (1) strains of microorganisms, (2) culture media, (3) neutralizers used, (4) type of inoculation, (5) temperature and time of incubation, (6) identification of isolates, and (7) procedures used.

b. *Animal and human models.* A variety of experimental cutaneous fungal infections can be induced in animals (Refs. *1* through *4*) and in humans (Refs. *5, 6,* and *7*).

The guinea pig is the usual animal studied (Ref. *8*). Fungi (usually spores of *T. mentagrophytes*) are applied and then occluded with tape after the animal's hair has been shaved. In a few days the infection is established and will progress until the test animal develops immunity to the fungi (usually 6 to 8 weeks). This is signaled by an increase in inflammation and a halt in peripheral spread. Once the animal is immune, it can no longer be used in the study.

Although the Panel concludes that animal models are important in testing the potential usefulness of topical antifungal agents, it does not accept animal model data as the sole criterion for initial categorization of effectiveness of these agents. Such proof of effectiveness must be derived from appropriate human clinical studies.

The methods of inducing experimental fungal skin infections in humans are similar to those used in animals. Applications of fungal spores under occlusion with plastic wrap produce a spreading infection followed by resolution in a variable period of time. To increase the likelihood that an infection will be induced, the skin may be abraded with chemicals, such as cantharadin which produces blisters, or may be stripped with tape.

Not all fungi can be studied in such models: some require a different environment or host, such as hair. But the animal and human models usually suffice for preliminary study of the pathogens commonly isolated from patients with athlete's foot, jock itch, and ringworm.

c. *Clinical data.* The Panel required each antifungal ingredient to have a least one well-designed clinical trial demonstrating its effectiveness in the treatment of athlete's foot in order to be classified as Category I. The Panel believes that ingredients that are effective in athlete's foot will also be

effective in jock itch and ringworm because the infecting organisms of these conditions are representative of the same groups as the organisms causing athelets's foot and have been shown to be susceptible to the same antifungal drugs.

In evaluating data, the Panel considered each study design and how it conformed to the following description of a well-designed trial. A well-designed clinical trial is usually double-blinded, randomized, and vehicle controlled. Test groups are of adequate size. Patients enter the study based on clinical signs and symptoms, such as redness, cracking, fissuring, scaling, swelling, pain, itching, and burning. Diagnosis of fungal infection is verified by positive KOH preparation and positive culture.

The dosing regimen is standardized. Athlete's foot and ringworm are more difficult to treat than jock itch. For this reason the treatment period should be at least 4 weeks for athlete's foot and ringworm and 2 weeks for jock itch. There should be followup examinations at specified intervals. (For details see part III. paragraph E.2.c. below—Effectiveness standards for labeling indications of antifungal products.) There should also be evidence of compliance of test subjects and statistical analysis of study results.

Antifungal ingredients effective in the treatment of athlete's foot should be equally effective in treating jock itch or ringworm. However, the Panel believes that the groin represents a more sensitive and easily irritated area than the feet and recommends that any antifungal products for the treatment of jock itch have a low potential for irritation.

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III. Topical Antifungal Drug Products

A. *Category I Conditions Under Which Topical Antifungal Products 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.**

1. Category I Active Ingredients

Haloprogin
Iodochlorhydroxyquin
Miconazole nitrate
Nystatin
Tolnaftate
Undecylenic acid and its salts
  Calcium undecylenate
  Copper undecylenate
  Zinc undecylenate

a. *Haloprogin.* The Panel concludes that haloprogin is safe and effective for OTC topical antifugal use in the treatment of athlete's foot, jock itch, and ringworm. Haloprogin is also safe and effective in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*).

Haloprogin, 1,2,4-trichloro-5-[(3-iodo-2-propynyl) oxy] benzene, was developed in Japan in 1962. It is a white or yellowish crystalline powder, practically odorless, and freely soluble in acetone and chloroform (Ref. *1*). Haloprogin is insoluble in water. It is stable against heat or ultraviolet rays (Ref. *2*).

Haloprogin is presently a prescription drug, and the Panel recommends that it be available for OTC use. New Drug Applications for 1 percent haloprogin cream and solution were approved by FDA in August 1971, and both dosage forms have been marketed on a prescription-only basis in the United States since 1972. Haloprogin has been available as an OTC drug in Japan (as tincture and ointment) since 1962 and in Canada (as solution and cream) since 1976.

(1) *Safety.* The acute toxicity of haloprogin was evaluated in mice, rats, dogs, and rabbits by using aqueous suspensions administered orally and intraperitoneally to determine the median lethal dose (LD_{50}) (Ref. *3*). The drug was much less lethal orally than intraperitoneally. The oral LD_{50} in milligrams per kilogram (mg/kg) was >3,000 in mice, >5,600 in rats, >3,000 in dogs, and 1,625 in rabbits. The intraperitoneal LD_{50} in mg/kg was 183 in mice, 152 in rats, 250 in dogs, and 137 in rabbits. The cause of death after intraperitoneal administration was not apparent, but irritancy was observed. The results suggested poor absorption from the gastrointestinal tract.

In an acute dermal toxicity test (Ref. *3*), the fur was clipped from rabbit skin before large doses of haloprogin were applied and held in place for 24 hours. No evidence of systemic toxicity was observed for the 2-week study period. However, dermal irritation was noted. Injected intradermally, 1 percent haloprogin caused irritation. When 1 percent haloprogin was instilled in the rabbit eye both as a solution and as a cream, it was observed that although the cream caused no significant irritation, the solution caused severe irritation because of the alcohol used in the solution vehicle (Ref. *3*).

Using C^{14}-labeled haloprogin in both animals and humans, researchers determined that the drug is absorbed into the skin and systemically distributed. (C^{14} is carbon-14, widely used as a tracer in metabolic research.) Using a ratio comparing excretion after topical application to excretion after intravenous administration, it was determined that humans absorb about 15 percent of a 1-percent cream and about 6 percent from a 1-percent topical solution (Ref. *4*). Distribution studies in rats also showed that about 4 hours after absorption, 62 percent had been excreted in the urine and by 24 hours, less than 3 percent remained in the tissues. Apparently most of the absorbed haloprogin is metabolized to 2,4,5-trichlorophenol, which is probably excreted as the sulfate salt in the urine (Ref. *3*).

A subacute dermal toxicity study of the Draize type (Ref. *3*) was conducted on 22 male and 22 female rabbits. A 1-percent haloprogin solution or cream was applied to intact or abraded skin in 0.5, 1.0, or 2.0 milliliters per kilogram (mL/kg) doses 5 days a week for 4 weeks. Appropriate hematologic and urinalysis studies were done. The rabbits were killed in either the fifth or seventh week of the study. Blood and vital organs were microscopically examined, and no distinct changes were noted. The only alterations noted were erythema and edema in intact as well as in abraded skin. Considerable recovery from these effects was noted during the 2 days a week when haloprogin was not applied. This study also included a 2-week "recovery" group, in which the

treated area of skin showed good hair regrowth and skin color.

A 90-day dermal toxicity study (Ref. *3*) was also conducted in miniature pigs. Three groups of four male pigs each were treated with either 0.5, 1.0, or 2.0 grams per kilogram (g/kg) per day of 1 percent haloprogin cream applied to about a 25-square centimeter (cm^2) area of skin. The area of application was then covered with plastic sheeting and bandages. A fourth group of four pigs served as nonmedicated controls. Hematologic studies, serum chemistry, and urinalysis studies were conducted. After the animals were killed, appropriate tissues were microscopically examined; no significant alterations were noted in the haloprogin-treated groups. No clear or consistent skin changes were noted in the pigs.

The effects on reproduction (Ref. *4*) in rats and rabbits were studied after topical application of 1 percent haloprogin cream during days 6 through 15 of presumed gestation. No difference was noted between the litters of the treated and the control animals.

Studies conducted on humans (Ref. *5*) used daily application of 1 percent haloprogin under occlusive dressing for 10 or 20 days in adult males. No evidence of significant irritation, allergic contact sensitization, or toxicity was noted. The allergic contact sensitization potential of 1 percent haloprogin cream was evaluated using both the Kligman maximization method (22 subjects) and the Draize-Shelanski method (219 subjects). There was no indication of allergic contact sensitization with either method of evaluation.

Two investigators used a total of 20 subjects to evaluate the phototoxicity potential of haloprogin. Although this number is far too small for the results to be conclusive, no evidence of phototoxicity was noted in these studies (Refs. *4* and *5*).

Allergic contact photosensitization was evaluated in 28 patients, and haloprogin was found to have minimal or no potential to induce photosensitization. However, the numbers in this study were also too small to produce conclusive results (Refs. *4* and *5*).

Body-inunction studies (Ref. *4*) were conducted in 16 persons (eight subjects per dosage form). Fifteen grams of cream of 15 mL of solution (1 percent haloprogin) was applied for 10 days to the entire body excluding the head. No signs of toxicity were noted, and only trace amounts of unchanged haloprogin were recovered in the urine.

The Panel calculated a "safety factor" based on data mentioned above. Although no studies were performed to support the validity of the calculation below, the Panel suggests that it represents a maximal load or exaggerated use condition. Assuming that 15 percent of an applied dose is absorbed (Ref. *4*), the following calculation may be made. If 15 g of a 1-percent cream were applied, then total exposure to the body would be 150 mg. Assuming 15 percent absorption, and assuming rapid, instantaneous absorption, the total amount in systemic circulation would be 22.5 mg. This amount of haloprogin distributed into 7 L of blood results in a maximum blood concentration of about 0.3 mg/100 mL. This blood level is far below any expected acute toxicity level that would result from exaggerated use. Also, elimination studies show little or no accumulation of the drug over 24 hours.

In view of the above summary, the Panel concludes that haloprogin is safe for OTC topical antifungal use.

(2) *Effectiveness.* Seki et al. (Ref. *6*) reported the in vitro test results of haloprogin. These investigators concluded that haloprogin has strong antifungal and antibacterial activity "chiefly confined to *Trichophyton*, diplococci, streptococci, and staphylococci."

The in vitro antifungal activity of haloprogin was compared with tolnaftate using the two-fold tube dilution method in Sabouraud's liquid medium (Ref. *4*). Tolnaftate was probably selected because it has only antidermatophytic activity, while haloprogin is thought to have a broader spectrum. Several organisms were tested, many of which were fungi totally unrelated to the dermatophytic fungi. For many species haloprogin had a low minimal inhibitory concentration of 0.047 microgram per milliliter (μg/mL) or lower. However, for species such as *T. mentagrophytes* the values varied considerably. Tolnaftate showed essentially the same results against this group of organisms. It may be concluded that the minimal inhibitory concentrations are probably low for both drugs. However, a number of details of the testing procedures were not recorded; this could possibly alter the reported values.

The in vitro activity of haloprogin against yeasts was determined using growth comparison techniques (Ref. *4*). The minimal inhibitory concentrations were less than 1 μg/mL for haloprogin using a variety of yeasts. For tolnaftate, the minimal inhibitory concentration ranged from >25 μg/mL >100 μg/mL. The minimal fungicidal concentration of haloprogin against *C. albicans* was determined to be 20 to 40 μg/mL. Haloprogin has anticandidal activity in vitro which tolnaftate does not possess.

The minimal inhibitory concentration for several bacteria was determined by tube dilution in soybean-casein digest agar (Ref. *4*). This is not considered standard procedure. (Meuller-Hinton is the standard.) Although haloprogin has been considered active in vitro against staphylococci and streptococci, it showed variable activity in this test. Activity was shown against only a few strains of staphylococci and streptococci. It was not active against gram-negative bacteria. Because haloprogin has such a narrow spectrum of antibacterial activity in vitro, it cannot be considered an antibacterial agent.

In 1963, four separate studies (Refs. *2, 7, 8,* and *9*) published in Japanese journals concluded that 1 percent haloprogin is an effective antifungal ingredient. The Panel reviewed these studies and found that they lacked double-blinding, randomization, or placebo-controlled groups. For this reason these studes will not reviewed in detail.

Weitgasser (Ref. *1*) reported on the success of 1 percent haloprogin in the treatment of various tinea infections in both an "open" study and a double-blind study. The "open" study, by definition, was not blinded, randomized, or placebo controlled, and hence will not be discussed.

Weitgasser's double-blind, randomized study compared 1 percent haloprogin ointment and solution with 1 percent clotrimazole cream and solution in the treatment of 152 subjects with athlete's foot, ringworm of the body, or cutaneous candidiasis. (Clotrimazole is a recognized antifungal agent.) Diagnostic criteria for study inclusion are unclear. Treatment with either haloprogin or clotrimazole continued for "a maximum of four weeks." Outcome criteria included performing KOH preparations. No followup observations were made. Weitgasser concluded that there were no marked differences in the antifungal effectiveness of haloprogin and clotrimazole.

Hermann (Refs. *10* and *11*) compiled data from multiple investigators, in addition to the results of other haloprogin effectiveness studies. The reports, both published in December 1972, are similar in content. The author concluded in both instances that the effectiveness of 1 percent haloprogin was substantially greater than a placebo and similar to tolnaftate in the treatment of dermatophytoses.

Olansky (Ref. *12*) studied the effectiveness of 1 percent haloprogin cream in treating chronic dermatophytoses other than athlete's foot. Study design included double-blinding, randomization, and two placebo groups. Diagnosis and treatment outcome were based on clinical inspection confirmed by KOH preparations. Treatment continued for 28 days. Of the 31 patients in the study, 10 received the haloprogin cream. Only 5 of these 10 patients were diagnosed as having ringworm of the body or jock itch. Olansky concluded that 1 percent haloprogin cream was "significantly more effective ($p<0.005$) than placebo." Although the basic study design is sound, the Panel notes the small number of subjects receiving haloprogin. No followup observations were made.

Katz and Cahn (Ref. *13*) conducted a double-blind, randomized study comparing the effectiveness of 1 percent haloprogin and 1 percent tolnaftate in the treatment of 74 patients with dermatophytosis (athete's foot or ringworm of the body). Both the initial diagnosis and the treatment outcome were based on clinical inspection confirmed by KOH preparation. Treatment continued for 14 to 28 days. No followup observartions were made.

Table 1 shows that the results obtained with haloprogin are comparable to those obtained with tolnaftate. Haloprogin and tolnaftate proved to be significantly more effective than placebo ($p<0.05$).

TABLE 1.—RESULTS OF TREATMENT WITH HALOPROGIN, TOLNAFTATE, OR PLACEBO CREAM

Treatment group	Number of patients treated	Treatment outcome			
		Clinically improved (50 pct reduction in pretreatment lesion score)		Positive KOH reversed to negative	
		Number	percent	Number	percent
Haloprogin	27	20	(74)	17	(63)
Tolnaftate	20	16	(80)	13	(65)
Placebo	27	11	(40)	9	(33)

Katz and Cahn (Ref. *13*) further analyzed the results of treatment by specific disease, i.e., athlete's foot or ringworm of the body. The investigators noted the greatest clinical improvement occurred in ringworm of the body, regardless of treatment. The 11 patients treated with haloprogin and the 9 treated with tolnaftate improved. In the placebo group 55 percent (5/9) improved. In athlete's foot, however, improvement was noted in only 60 percent (9/15) of the patients treated with haloprogin, 64 percent (7/11) of those treated with tolaftate, and 35 percent (6/17) of those who received the placebo.

Van Dersarl and Sheppard (Ref. *14*) conducted a double-blind, clinical study comparing the effectiveness of clotrimazole solution with haloprogin solution for the treatment of jock itch. Sixty-six patients with clinical evidence of jock itch confirmed by positive KOH preparation and culture were randomly assigned to either 1 percent clotrimazole (34 patients) or 1 percent haloprogin (32 patients). Treatment contained for 14 days with a 4-week assessment period following treatment. Treatment outcome was based on clinical improvement, KOH preparation, and culture results.

After 2 weeks of treatment, the mycologic evaluation was negative (i.e., negative KOH preparation and negative culture), and the fungal infection was considered cured in 85 percent of the patients treated with clotrimazole as compared to 62 percent of the patients treated with haloprogin. Four weeks after treatment stopped, mycologic evaluation was negative in 57 percent of the clotrimazole group as compared to 31 percent of the haloprogin group.

At the end of the 14-day treatment, there was no statistically significant difference between the number of patients clinically cured with clotrimazole (65 percent) or haloprogin (56 percent). Four weeks later, however, 63 percent of those treated with clotrimazole remained free of disease, whereas only 34 percent of the group treated with haloprogin had no clinical signs of disease. From these data, Van Dersarl and Sheppard (Ref. *14*) concluded that clotrimazole was significantly more effective than haloprogin for the treatment of jock itch.

In 1972, Carter (Ref. *15*) published the results of a double-blind, clinical study evaluating the effectiveness of three 1 percent haloprogin products and a 1-percent tolnaftate solution in the treatment of 82 patients. All patients had a diagnosis of athlete's foot determined by clinical inspection, KOH preparations, and cultures. Patients were randomly assigned to one of the following four treatment groups: 1 percent haloprogin solution, 1 percent haloprogin cream, 1 percent haloprogin foam, or 1 percent tolnaftate solution. Treatment lasted 27 days. Ah 8-day post-treatment assessment was also included in the study protocol. Treatment outcome was based on clinical improvement, KOH preparations, and culture results.

Clinical observations revealed no significant differences in the effectiveness of 1 percent haloprogin and 1 percent tolnaftate. Of the group treated with haloprogin, 92 percent (56/60) were clinically improved after 27 days of treatment and remained improved at the assessment 8 days after treatment. Of the group treated with tolnaftate, 85 percent (17/20) were clinically improved after 27 days of treatment, and 80 percent (16/20) remained improved 8 days later. However, KOH preparations and cultures showed that the patients treated with haloprogin had a significantly greater 27-day cure rate and maintenance of cure 8 days after therapy was discontinued: 90 percent (56/62) of the haloprogin group and 60 percent (12/20) of the tolnaftate group had negative KOH examinations after 27 days of treatment.

One week after treatment, 80 percent (50/62) of the patients treated with haloprogin maintained negative KOH examinations, compared to 25 percent (5/20) of those treated with tolnaftate. This difference is significant at the $p<0.001$ level. After 4 weeks of treatment, 88 percent (46/52) of the patients treated with haloprogin and 65 percent (11/17) of those treated with tolnaftate had negative cultures.

The 1-week posttherapy culture of these patients showed that 79 percent (41/52) of the patients treated with haloprogin and 41 percent (7/17) of those treated with tolnaftate maintained negative cultures. This difference is significant at the $p<0.01$ level. Carter concluded that there was no difference between haloprogin and tolnaftate in curing athlete's foot as measured by clinical inspection. KOH preparations and cultures, however, showed a significantly higher cure rate and lower relapse rate with haloprogin than with tolnaftate.

Several studies (Refs. *16, 17,* and *18*) have reported the use of haloprogin in the treatment of cutaneous candidiasis. In 1973, Montes (Ref. *16*) reported a pilot study in which 10 patients with cutaneous candidiasis applied 1 percent haloprogin cream twice daily. The eight patients in this group with common forms of candidiasis had "excellent results," including negative post-treatment cultures (post-treatment time unspecified). Two patients with chronic mucocutaneous candidiasis, a form of fungal infection often resistant to treatment, also experienced a "dramatic response," although *C. albicans* could still be recovered after several weeks of treatment.

In 1974, the use of "megadosage" haloprogin was reported in the treatment of another case of unremitting chronic mucocutaneous candidiasis in a

4-year-old child (Ref. *17*). The disease was controlled, although not cured, with 1 percent haloprogin cream and solution applied three times daily over a 3-year period. No toxicity developed from the administration of 12,090 g during seven treatment periods totalling 460 days.

In a double-blind parallel comparison study, 1 percent haloprogin cream was compared with nystatin ointment 100,000 units/gram (U/g) in 68 patients with cutaneous candidiasis (Ref. *18*). The treatment period was 13 days, and each product was applied twice daily. Followup KOH preparations and cultures were obtained 1 day after treatment stopped and repeated 2 weeks after treatment was discontinued. The overall cure rate exceeded 80 percent in both groups, with 29 of 35 haloprogin-treated patients responding "satisfactorily."

From this review of the available literature, the Panel concludes that Haloprogin is effective for OTC topical use in the treatment of athlete's foot, jock itch, and ringworm. Haloprogin is also effective in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*).

(3) *Dosage*—(i) *Concentration.* Haloprogin 1.0 percent.

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

(4) *Labeling.* The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm, and in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*). Category I labeling may also be used for antifungal products with activity against both dermatophytes and yeast. (See part III, paragraph A.2. below—Category I Labeling.)

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b. *Iodochlorhydroxyquin.* The Panel concludes that iodochlorhydroxyquin is safe and effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Iodochlorhydroxyquin is a yellowish-white or brownish-white powder with a slight characteristic odor. Its chemical formula is 5-chloro-7-iodo-8-quinolinol. It is practically insoluble in water and alcohol, but soluble in hot ethyl acetate and hot glacial acetic acid (Ref. *1*).

(1) *Safety.* The acute toxicity of iodochlorhydroxyquin has been reported in the form of oral lethal doses. Female mice appear to be more sensitive than male mice to the lethal effects of iodochlorhydroxyquin. The oral LD_{50} in mice is reported to be about 1,800 mg/kg in males and 800 mg/kg in females (Ref. *2*). The oral LD_{50} in guinea pigs is 175 mg/kg; in cats it is 400 mg/kg (Refs. *2* and *3*).

In a 3-month oral toxicity study of iodochlorhydroxyquin, daily doses of up to 30 mg/kg were administered to rabbits. No adverse effects on the animals' behavior or laboratory chemistry values were noted. Histopathologic examination of the tissue indicated no treatment-related changes in any tissues. In a followup study, half of the high-dose group was followed for 90 days and observed for delayed toxic effects. There were no behavioral or gait changes that suggested neurologic disorders or any histopathologic changes in tissues (Ref. *3*).

In another toxicity study (Ref. *3*), beagles were treated with daily oral doses of 100 mg/kg or 300 mg/kg iodochlorhydroxyquin for 4 months. There were no adverse effects noted in the group receiving 100 mg/kg. However, among the six dogs receiving 300 mg/kg iodochlorhydroxyquin, two deaths occurred: a male died on day 6 of treatment and a female died on day 12 of treatment. Autopsy of these two animals revealed acute congestion and diffuse edema of the lungs. Another female dog was killed on day 96 of treatment because of poor general condition. However, the three surviving animals were free of symptoms, and no pathological changes of organs or tissues were noted at autopsy.

In a second 90-day study (Ref. *3*) on beagles, iodochlorhydroxyquin was given orally once daily in doses of 30, 100, or 300 mg/kg to groups of six dogs each. A female dog receiving 300 mg/kg was killed because of poor health on the second day of treatment. Cerebral edema with acute neuronal lesions was attributed to anoxia (oxygen deficiency) judged to be unrelated to drug treatment. At autopsy after 90 days of dosing with iodochlorhydroxyquin, two dogs that had received low doses (30 mg/kg) and two that had received high doses (300 mg/kg) showed histological changes in the kidneys. These changes were considered unrelated to treatment. No other changes were noted in any of the tissues.

A third long-term toxicity study (Ref. *3*) in beagles was conducted over 24 months using daily doses of 30, 100, or 200 mg/kg iodochlorhydroxyquin. In the high-dose (200 mg/kg) group, five animals died or were killed because of poor physical condition. These five deaths were attributed to nonspecific causes. A female dog in the 100-mg/kg group developed convulsions in the 84th week of the study and was also killed.

No gross or microscopical changes were evident in any tissues. All the other dogs survived the study with no changes which differed remarkably from the controls.

Two separate toxicity studies (Ref. *3*) were conducted in monkeys. One study lasted for 6 months, the other, nearly 3 years. In the 6-month study, rhesus monkeys received daily oral doses of 60 or 200 mg/kg iodochlorhydroxyquin. One animal in each group was killed at the end of the first month of the study; the remaining animals were killed at 6 months. Standard laboratory tests revealed no changes in body chemistry either at 1 month or 6 months. At autopsy the only changes noted in any tissues were in the monkeys that had received high doses (200 mg/kg). Tubular dilation and protein casts in the kidneys were noted both after 1 month and after 6 months of dosing. These changes were considered reversible.

In a 33-month study (Ref. *3*), cynomolgus monkeys received daily oral doses of 50 or 200 mg/kg iodochlorhydroxyquin. No differences in behavior or motor function were noted between the controls and the treated animals. Autopsy and tissue examination revealed no tissue changes, and no changes was noted in various parts of the nervous system.

The Panel is aware of a serious adverse effect reported with the use of iodochlorhydroxyquin. This effect is called subacute myelo-optic neuropathy (SMON). However, data presented by two groups of investigators led the Panel to conclude that SMON is very unlikely to occur as a result of the topical application of iodochlorhydroxyquin. Tsubaki and Igata (Ref. *4*) presented data on oral doses of iodochlorhydroxyquin up to 2,400 mg per day given to humans. No evidence of SMON occurred. In addition, Gholz and Arons (Ref. *5*) reported on 4,000 patients taking 250 mg iodochlorhydroxyquin orally three times daily, among whom only 20 (0.5 percent) showed neurological symptoms. These data are further substantiated by long-term studies in monkeys as well as by the absorption data presented below.

Using radioactive tracers, researchers showed that orally administered iodochlorhydroxyquin is rapidly eliminated from the body (Ref. *3*). Within 120 hours after oral administration to a rat, 99.6 percent of the dose had been eliminated—15.3 percent in the urine and 84.2 percent in the feces. In the rat, dog, and human, more than 96 percent of the oral dose is eliminated within 72 hours. Distribution studies carried out in rats, rabbits, and dogs demonstrated that neither iodochlorhydroxyquin nor its metabolites accumulated in any organ or tissue. In humans, after single oral doses of 250 mg, 750 mg, and 1,500 mg, peak plasma levels of 5, 12, and 20 μg/mL, respectively, were reached about 4 hours after administration. Plasma half-life was calculated to be about 13 hours (Ref. *3*).

In one study, six human volunteers were given oral doses of 500 mg iodochlorhydroxyquin three times daily for 7 days; then 250 mg three times daily for 7 days. During the high-dose week, peak plasma levels reached about 30 μg/mL, later falling to 15 μg/mL when the dose was reduced. These results indicate good absorption of iodochlorhydroxyquin from the gut, and rapid elimination following discontiunance of the drug (Ref. *3*).

The panel is not aware of any specific data demonstrating the carcinogenicity of iodochlorhydroxyquin, although certain quinolines appear to be carcinogenic (Ref. *6*). One unpublished report suggests that iodochlorhydroxyquin has mutagenic potential in *Streptomyces coelicolor* (Ref. *7*), but this abstract contains no details. Using Ames' well-known in vitro mutagenesis test, researchers found that iodochlorhydroxyquin was negative at 1 μg per plate (Ref. *8*). At concentrations higher than this, toxicity precluded evaluation of mutagenicity. Neither the 24-month study in dogs nor the 33-month study in monkeys revealed a problem with tumorigenesis from the use of this drug (Ref. *3*).

In one percutaneous absorption study in two human volunteers, 1 g of cream containing 3 percent iodochlorhydroxyquin and 1 percent hydrocortisone was applied over an area of 200 cm^2 at the rate of 5 mg/cm^2. Occluding the area for 10 hours resulted in 2 to 3 percent absorption of the topically applied iodochlorhydroxyquin (Ref. *3*).

Fischer and Hartvig (Ref. *9*) treated four patients with widespread dermatitis with an ointment containing 3 percent iodochlorhydroxyquin and a corticosteroid. Forty percent of the body was treated with 15 to 20 g of the ointment twice daily. Within 4 hours the serum concentration of iodochlorhydroxyquin increased from 0.8 to 1.2 μg/mL and remained constant during treatment. In one patient the daily urinary excretion of iodochlorhydroxyquin amounted to 15 to 20 mg, estimated by the authors to represent a 3- to 4-percent absorption of the applied dose.

The Panel recognizes that in the above two percutaneous experiments, the corticosteroids in the test products may have interfered with the absorption of iodochlorhydroxyquin. Even though the above data suggest only a 3- to 4-percent absorption of iodochlorhydroxyquin after topical application, the Panel has calculated the following "worst case" situation in order to evaluate possible blood levels in humans following the topical application of iodochlorhydroxyquin to broken skin. The calculation is based on the following assumptions: (1) A 3-percent iodochlorhydroxyquin product is applied to a jock itch or ringworm condition (both of which represent a larger surface area than an athlete's foot condition); (2) a 2-g dose is applied twice a day, and (3) total and rapid absorption occurs after each application.

The highest possible amount of absorbed drug would be 30 mg iodochlorhydroxyquin distributed in 7,000 mL of blood twice a day, resulting in a blood level of approximately 4.5 μg/mL. This blood level is well below the reported 15 to 30 μg/mL blood levels obtained during the 2-week oral administration of iodochlorhydroxyquin in which no toxic symptoms were observed (Refs. *3* and *9*).

Considering the data summarized above, the Panel concludes that iodochlorhydroxyquin is safe for OTC topical use in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* In vitro activity of iodochlorhydroxyquin has been reported against a number of fungi, yeasts, and bacteria (Ref. *10*). The average minimal inhibitory concentrations are listed below. (The method was used to determine these values was not given.)

Microorganism	Minimal inhibitory concentration (μg/mL)
T. rubrum	10
M. Gypseum	20
C. albicans	10
S. aureus	2
P. aeruginosa	40

In vitro testing indicates that iodochlorhydorxyquin has some antibacterial activity. A series of isolates from patients with various dermatological conditions were tested for susceptibility to iodochlorhydroxyquin. Using gradient plate technique, the researchers tested 818 gram-positive and 263 gram-negative organisms. Soybean-casein digest agar was used, although Meuller-Hinton is the standard medium. Incubation was at 37° C; 32 to 35° C is considered optimal. The minimal inhibitory concentration for

staphylococci (estimated with cumulative percentage) ranged from 40 to 100 μg/mL. Most gram-negative organisms had a minimal inhibitory concentration of 100 μg/mL, but some could not be determined because the levels were not run above 100 μg/mL. The levels recorded with this testing are relatively high for therapeutic activity (Ref. *10*).

The minimal inhibitory concentration of iodochlorhydroxyquin was determined by agar dilution in Dermatophyte Sporulation Test Agar (DST) beginning at 128 μg/mL (Ref. *10*). In these tests, staphylococci and streptococci were inhibited at 16 to 32 μg/mL. Gram-negative strains generally had minimal inhibitory concentration values of 64 μg/mL (for 100 percent inhibition), but *P. aeruginosa* showed a minimal inhibitory concentration of > 128 μg/mL. Because the levels at which iodochlorhydroxyquin is therapeutically active are high, it can be concluded that this ingredient has little or no antibacterial activity.

Carpenter et al. (Ref. *11*) tested the effectiveness of iodochlorhydroxyquin with and without hydrocortisone in 277 patients diagnosed with inflammatory skin diseases associated with secondary bacterial or fungal infections. Seventy-nine patients had primary fungal infections. The study design was randomized and double-blinded. The initial diagnosis was established by cultures, but no KOH preparations were performed. Patients applied one of the following four treatments three times daily: (1) 3 percent iodochlorhydroxyquin and 1 percent hydrocortisone cream, (2) 3 percent iodochlorhydroxyquin cream, (3) 1 percent hydrocortisone cream, or (4) cream base. The authors noted that the distribution of organisms and disease severity did not differ appreciably among the four treatment groups. Patients were seen before treatment, after 2 to 3 days of treatment, and after 7 to 10 days of treatment. Cultures were taken at each visit, and symptomatic response and clinical improvement were evaluated.

At the final visit, cultures were negative in 51 percent (39/77) of the iodochlorhydroxyquin-treated patients as compared to 27 percent (18/68) of the placebo group. Negative cultures were reported in 31 percent (21/68) of the hydrocortisone group and 56 percent (36/64) of the patients receiving the iodochlorhydroxyquin-hydrocortisone combination. The iodochlorhydroxyquin-hydrocortisone combination results were statistically significant when compared to the placebo base or hydrocortisone alone. Iodochlorhydroxyquin appears much more effective than palcebo in the treatment of inflammatory skin diseases, but the investigator did not analyze this statistically.

In a double-blind, placebo-controlled study (Ref. *3*) conducted by a large group of dermatologists, the effectiveness of iodochlorhydroxyquin 3 percent used alone or combined with hydrocortisone 1 percent, was compared to hydrocortisone alone and a placebo vehicle base in the treatment of jock itch and ringworm. A total of 354 patients with KOH positive, culture-positive fungal infections were randomly assigned to one of the four previously mentioned treatment groups. The investigators noted that all four treatment groups were comparable in age, sex, isolated organism, and site and severity of infection. Patients were treated twice daily and were seen 2 to 3 days after the study began, and again after 6 to 8 days of treatment.

At the last visit, 65 percent of the patients treated with the iodochlorhydroxyquin-hydrocortisone combination had moderate to complete clearing compared to 46 percent of the patients treated with iodochlorhydroxyquin, 32 percent treated with hydrocortisone, and 25 percent treated with the vehicle. "The cultural conversion rate" (positive to negative culture) was 76 percent in the iodochlorhydroxyuin group, 67 percent for iodochlorhydroxyquin-hydrocortisone, 23 percent for hydrocortisone, and 30 percent for the placebo vehicle. The investigators concluded that iodochlorhydroxyquin was significantly more effective than the placebo vehicle in the treatment of cutaneous fungal infections ($p<0.05$). Also, the iodochlorhydroxyquin-hydrocortisone combination was found to be significantly more effective than either of its components or the vehicle in the relief of symptoms and in overall clinical response ($p<.01$).

A randomized, double-blind study (Ref. *3*) of 94 Texas prison inmates compared the effectiveness of 3 percent iodochlorhydroxyquin to a placebo in the treatment of athlete's foot. Athlete's foot was diagnosed by clinical appearance, positive KOH preparations, and positive cultures. Patients were treated twice daily and seen weekly for 4 weeks; then therapy was discontinued. The patients who remained in the study were reevaluated 2 weeks after therapy. Table 2 shows that iodochlorhydroxyquin was more effective than the placebo in the treatment of athlete's foot at both the 4-week and the 6-week evaluation. These results are statistically significant at the $p<0.05$ level.

TABLE 2.—COMPARISON OF IODOCHLORHYDROXYQUIN (ICHQ) AND PLACEBO IN ATHLETE'S FOOT

[In percentage]

	Results 4 weeks		Results 2 weeks post-therapy	
	3 percent ICHQ	Placebo	3 percent ICHQ	Placebo
Excellent/good	* 23(55)	* 16(31)	* 18(50)	* 10(21)
Fair/no change	18(43)	34(65)	18(50)	32(68)
Worse	1(2)	2(4)	0(0)	5(11)
Total	42(100)	52(100)	36(100)	47(100)

An asterisk indicates $p<0.05$.

Based on the above review of the literature, the Panel concludes that iodochlorhydroxyquin is effective for OTC topical use in the treatment of athlete's foot, jock itch, and ringworm.

(3) *Dosage*—(i) *Concentration.* Iodohlorhydroxyquin 3.0 percent.

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

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

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(*9*) Fischer, T., and P. Hartvig, "Skin Absorption of 8-Hydroxyquinolines," *The Lancet*, March 12, 1977, p. 603.

(*10*) OTC Volume 070233.

(*11*) Carpenter, C. L., Jr., et al., "Combined Steroid-Antiinfective Topical Therapy in Common Dermatoses: A Double-blind, Multicenter Study of Iodochlorhydroxyquin-

Hydrocortisone in 277 Patients," *Current Therapeutic Research*, 15:650–659, 1973.

c. *Miconazole nitrate.* The Panel concludes that miconazole nitrate is safe and effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. Miconazole nitrate is also safe and effective in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (Candida).

Miconazole nitrate is a white, crystalline powder. The chemical name of miconazole nitrate is 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl) methoxy] ethyl]-imidazole mononitrate. It is very slightly soluble in water and very slightly to slightly soluble in most organic solvents (Ref. *1*).

A New Drug Application for miconazole nitrate 2 percent cream was approved in January 1974. At present this ingredient is marketed in the United States as a prescription drug for the treatment of fungal infections and cutaneous candidiasis. The Panel recommends that miconazole nitrate be made available for OTC use.

(1) *Safety.* Acute oral toxicity studies have been conducted on miconazole nitrate suspensions in mice, rats, guinea pigs, and dogs. The oral LD_{50} for mice was 578 mg/kg. All rats survived oral doses up to 640 mg/kg, while the oral LD_{50} in guinea pigs was reported to be 276 mg/kg. All dogs survived a high oral dose of 160 mg/kg, but four of the six treated animals vomited shortly after receiving the dose. The acute intraperitoneal LD_{50} in mice from a miconazole suspension was 670 mg/kg (Ref. *2*).

Acute oral toxicity studies (Ref. *2*) in mice and rats used a 2-percent miconazole nitrate cream formulation with the cream base serving as placebo control. Acute oral LD_{50} values could not be obtained in mice because the maximum volume the animals could accept was 40 mL/kg (800 mg/kg miconazole). Although two deaths occurred at the 40-mL/kg dose, with symptoms of irregular respiration and general central nervous system depression, deaths were too few to establish an LD_{50}. Acute studies in adult rats were essentially the same as in mice, with no LD_{50} established because of the limit of 40 mL/kg which the rats could accept.

Subacute oral toxicity studies were conducted on miconazole nitrate suspensions in rats and dogs. In one well-controlled study (Ref. *2*), three groups of 20 adult Wistar rats (10 male, 10 female) received 5, 20, or 80 mg/kg miconazole nitrate daily in their diets for 13 weeks. Hematology, clinical chemistry, urinalysis, and body weight studies were conducted. No abnormal behavior was observed in any of the animals, and all survived the 13-week study.

At the end of the study, all animals were killed and autopsied and selected tissues examined for histological change. There were no significant differences in body weight among any of the animals in the different dosage groups. However, the intermediate dose level (20 mg/kg) group did show a slight, though not significant, decrease in body weight. There were no significant differences in the hematological data or in clinical chemistry data. Urinalysis data for male rats indicated an increase in specific gravity at the 80-mg/kg dose level and a decrease in pH in both the 20- and 80-mg/kg dose level groups. At the 80-mg/kg dose level, the absolute and relative liver weight of both males and females increased. Thymus gland weight decreased in males but increased in females. Spleen weight decreased in both males and females. Pathological evaluation of tissues showed mild variations in the liver and kidney evident only at the 80-mg/kg dose level.

Subacute studies were also conducted over a 13-week period in purebred beagles (Ref. *2*). Three groups of six dogs (three male, three female) received oral doses of miconazole nitrate by capsule 6 days per week at dose levels of 2.5, 10, and 40 mg/kg, respectively. Control dogs (three male, three female) received lactose capsules. Both treated and controlled animals exhibited infrequent periodic vomiting, loose or soft stools, and loss of appetite. However, there were no deaths due to toxicity.

Hematological, clinical, urological, and body weight studies were conducted. At autopsy, selected tissues were studied for pathological alterations. There was a slight decrease in body weight in the 10-mg/kg and in the 40-mg/kg dose groups. Hematocrit and hemoglobin showed a decline in the 40-mg/kg dose group, but all other hematological parameters were normal. Only slight changes in clinical chemistry patterns were noted. No significant variations occurred in the urinalyisis patterns. Relative and absolute liver weight increases were noted in the 40-mg/kg dose group. Only the livers of animals in the high-dose group showed any cloudy swelling, a pathological alteration considered to be reversible.

Chronic oral toxicity studies (Ref. *2*) were conducted in rats and in dogs. Three groups of 60 Wistar rats (30 male, 30 female) received miconazole nitrate at respective dose levels of 10, 40, and 160 mg/kg mixed in their diet for 18 months. A control group of 60 rats received a drug-free diet.

Hematological, clinical chemistry, and urinalysis studies were conducted on all test animals. No dose-related or drug-related effects on health, behavior, or physical appearance were observed. All hematological, clinical chemistry, and urinalysis values were similar for both groups.

At sacrifice, selected tissues were examined for pathological alteration. Mortality rates at 6, 12, and 18 months were considered normal for both the miconazole and control groups. No carcinogenic effects were noted. Organ weights were normal, except for liver weight increases in the 160-mg/kg dose group. Histological examination revealed changes in the liver only where centrilobular cloudy swelling or fatty changes were noted in the high-dose animals. The changes were slightly more pronounced in males and were considered reversible.

Three groups of six purebred beagles (three male, three female) received oral doses of miconazole nitrate by capsule 6 days a week for 52 weeks at respective dose levels of 1.25, 5, and 20 mg/kg. Six control dogs received oral capsules of 250 mg lactose. Hematological, clinical chemistry, and urinalysis studies were conducted. Hematological and urinalysis values for all of the study animals were within normal limits. A persistent increase in serum alkaline phosphatase and a slight increase in serum glutamic pyruvic transaminase values was noted in the 20-mg/kg group. All animals survived the 12-month study. No drug-related or dose-related effect on behavior, health, or appearance was detected. At sacrifice, selected tissues were examined histologically. No pathologic changes were noted in any tissues except a relative increase in liver weight in this group; histological examination failed to show tissue changes in the liver (Ref. *2*).

Teratology studies (Ref. *2*) were conducted in rats and rabbits after oral administration of miconazole nitrate. Rats received miconazole nitrate in the diet from day 6 to day 15 of pregnancy at levels of 80 or 160 mg/kg. No abnormalties were noted in the cesarean-delivered fetuses of the control or test animals. Rabbits were dosed orally with miconazole nitrate suspended in polyethylene glycol 200 from day 6 to day 18 of presumed gestation at dose levels of 40, 80, or 160 mg/kg. A few fetuses had skeletal abnormalities which were observed in both control and treated litters. In another study using rabbits, pregnant

females were dosed by gavage with miconazole nitrate suspended in 25 percent methylcellulose at levels of 20, 40, or 80 mg/kg from day 7 to day 19 of pregnancy. At the 80-mg/kg dose level there was evidence of maternal and fetal toxicity which could be secondary to maternal nutritional effects. No birth defects were noted, even in the high-dose group.

Several studies (Ref. *2*) of the excretion and metabolism of miconazole have been conducted in male rats. In each study, tritium-labeled miconazole nitrate in polyethylene glycol was given in oral doses of 40 mg/kg. In one such study, 90.1 percent of the administered dose was recovered from the feces and 9.4 percent from the urine after 96 hours. Another 96-hour study found 85 percent recovery from the feces and 10 percent recovery from the urine. Because most of the drug is excreted, relatively little absorption from the gut occurs. About 18 percent of the radioactivity excreted in the feces was unchanged miconazole. Most of the miconazole in the urine was the metabolite form, alpha-(2,4-dichlorophenyl)-imidazole-ethanol. Less than 2 percent of the radioactivity was recovered in the brain, lungs, kidneys, and bladder. Peak blood levels, consisting mainly of metabolites, never exceeded 0.4 percent of the administratered dose.

After oral dosing of tritiated miconazole in rabbits, the researchers found that absorption did occur and the labeled drug could be found systemically. It could also be found in the eye and in the skin. The amount of radioactivity due to unchanged miconazole was about 15 percent in the plasma, and 20 to 30 percent in the liver, muscle, and eye.

Three-month intravaginal irritation studies were conducted in rabbits and monkeys (Ref. *2*). Ten white rabbits received daily intravaginal suppositories of 2 percent miconazole (total dose 20 mg) in a carbowax vehicle for 90 days; 10 control rabbits received placebo suppositories. At sacrifice, the hematological, urological, and clinical chemistry data of test animals and controls were similar. Microscopic examination of the vaginal mucosa indicated more irritation in the test group than in the control group.

In a similar study (Ref. *2*), vaginal suppositories of 2 percent miconazole in a carbowax base were inserted daily into four cynomolgus monkeys. Four control monkeys received base suppositories only. All monkeys survived the study and remained in good health. Hematological and clinical chemistry values remained within normal limits for all study animals. Histological examination of the vaginal wall revealed a slight increase in the thickness of the vaginal squamous epithelium in both test and control animals, which was slightly more pronounced in the test animals.

Vaginal absorption and excretion studies (Ref. *2*) were conducted in rabbits and dogs after administration of miconazole either by polyethylene glycol suppositories or a vehicle composed of triglycerides derived from coconut and palm kernel oils. Higher levels of absorption and excretion were noted from the polyethylene glycol and miconazole combination than from the triglyceride and miconazole combination.

Eye irritation studies (Ref. *2*) in 12 rabbits using 0.1 mL of 2 percent miconazole cream resulted in negative or low potential to produce eye irritation, in both test cream and placebo.

In an acute topical toxicity study in rabbits (Ref. *2*), 2 percent miconazole nitrate cream was evaluated on intact and scarified (artifically scratched) skin under a 24-hour occlusive sleeve. Based on gross observation, hematology, and urology data, there was no evidence of local or systemic toxicity.

Two topical subacute studies (Ref. *2*) were conducted on rabbits using both intact and scarified skin. Two percent cream was applied at levels of 0.2, 1.0, or 2.0 g/kg daily for 4 weeks. Except for occasional minimal patchy redness, hyperkeratosis, and loss of skin elasticity, no evidence of skin irritation was observed. Histopathologic examination of tissues revealed no treatment-related lesions. In a similar study conducted over 3 and 6 months, certain minor hematological changes were noted, namely an increased neutrophil level and a decreased lymphocyte count correlating roughly with dosage. A slight tendency for the hemoglobin hematocrit to show depression proportionate with dosage was also observed. Other than local skin irritation occurring in both the test and placebo groups, no changes were noted.

Two separate photosensitivity and phototoxicity studies (Ref. 2) of 2 percent miconazole nitrate cream were conducted in 35 human volunteers using xenon solar-simulating radiation filtered through window glass. It was concluded that the cream did not induce allergic photosensitization or phototoxicity reactions in humans.

Topical application of 1 g of the 2-percent tritiated cream on the forearm under an occlusive bandage was studied in three volunteers. Blood chemistry indicated absorption was too low for accurate measurement (Ref. *2*).

In another study on 50 human subjects (Ref. *2*), the 2-percent cream was applied under occlusive patches for 24 hours. No reactions were observed at the 72-hour evaluation period.

Using a modified Draize test to determine the human allergic skin sensitization potential (Ref. *2*), the 2-percent cream was used on 220 healthy adult male volunteers between the ages of 21 and 65. The cream was applied to the same site with occlusive strips three times weekly for a total of 10 applications. A 2-week rest period was followed by a final 72-hour challenge application. Irritation occurred in 12 of the 220 subjects. Miconazole cream was not considered a contact sensitizer.

In a double-blind, subtotal inunction study, 10 human subjects has 2.5 g miconazole cream applied to the entire back twice daily for 28 days (Ref. *2*). Five subjects were given a placebo cream. No skin irritation occurred. Hematology and urinalysis indicated no significant differences.

Oral studies (Ref. *2*) were conducted in three humans who were each initially given 50 mg tritiated miconazole nitrate. After 1 week and after 3 weeks, the subjects took a capsule containing 250 mg labeled miconazole and 750 mg unlabeled miconazole. Between day 7 and day 28 they also took 1 g unlabeled miconazole nitrate three times daily. The researchers found that the relative absorption and metabolism were unrelated to the dosage and remained unchanged during chronic treatment. Only 10 to 20 percent of the administered dose could be recovered in the urine, while 40 to 55 percent was recovered in the feces.

In another study (Ref. *2*), vaginal instillation of 1 g cream in three women showed total plasma levels of miconazole and its metabolites reached a maximal blood level between 4 and 24 hours after administration. This level never exceeded the detection limit, 30 micrograms per liter (μg/L). The researchers reported that miconazole was scarcely absorbed when administered vaginally.

Vaginal instillation of 5 g tritiated miconazole cream in three volunteers resulted in blood levels too low for accurate measurement (Ref. *2*).

In an intravenous infusion study (Ref. *2*), four patients (three males, one female) were given a single dose of 174 mg of labeled miconazole base equivalent to 200 mg miconazole nitrate over a 1-hour period. Blood, urine, and feces samples were taken periodically. Maximum levels of unchanged

miconazole in plasma of 1.6 μg/mL were reached 1 hour after starting the infusion. The concentration in plasma rapidly diminished over 12 hours, with a half-life of 24 hours. About 14 percent of the total radioactive material was excreted in the urine, with the highest rate of excretion 2 to 8 hours after infusion. Thirteen to 35 percent miconazole was excreted in the feces. The researchers concluded that the excretion of miconazole and its metabolites after intavenous infusion is qualitatively very similar to excretion patterns after oral administration.

The Panel concludes that adequate, well-controlled, animal and human toxicity studies were conducted and that miconazole nitrate exhibits a low order of toxicity. The major indications of toxicity noted in the animal studies were cloudy swelling in the liver and some central nervous system effects. The only deficiency noted in the animal data base for toxicity is the blood levels of miconazole needed to produce these toxic symptoms. But considering the extensive studies presented, the Panel does not consider this to be a serious deficiency.

Even though a few cases of mild irritancy in humans in the modified Draize test have been reported, the Panel concludes that miconazole nitrate is safe for OTC topical antifungal use.

(2) *Effectiveness.* Miconazole is an antifungal agent with activity aganist fungi responsible for both systemic and superficial infection. It is also effective against gram-positive bacteria in vitro (Ref. *3*). Fungicidal action is believed to result from the effect of miconazole on the cell membrane, altering cellular permeability (Ref. *4*). At a concentration of 1 μg/mL, miconazole nitrate inhibits the following microorganisms: *T. mentagrophytes, T. rubrum, E. floccosum,* and *Candida* species (Refs. *2* and *3*).

The following studies conducted on human volunteers were random and double-blind (Refs. *5* through *9*). Only those subjects with positive KOH preparations and cultures were studied. Each study tested 2 percent miconazole against a placebo (vehicle) in twice-daily applications. Most of the studies also included a 4-week followup examination with cultures and KOH preparations.

A study was conducted on 62 dermatology clinic patients at a military hospital in Mississippi (Ref. *5*). On initial examination, all of the patients had a symptomatic infection clinically compatible with diagnoses of jock itch, ringworm of the body, or athlete's foot. The patients ranged in age from 17 through 39 years; the typical one was in his early twenties.

Thirty patients were treated with 2 percent miconazole. The 32 controls were treated only with the vehicle (placebo). Other than the twice-daily application of the cream, no changes were made in the patients' daily activities, work habits, dress, or personal cleanliness. Of the 30 miconazole-treated subjects, 18 were suffering from *T. rubrum* infections, 7 from *T. mentagrophytes,* 2 from *E. floccosum,* 2 from *C. albicans,* and 1 showed no culture growth. Culture results from the 32 controls revealed that 20 had *T. rubrum* infections, 10 had *T. mentagrophytes,* 1 had *E. floccosum,* and 1 had *C. albicans.*

At the end of the second and fourth weeks of therapy, clinical and symptomatic evaluations were repeated. KOH preparations and cultures were repeated only at the fourth-week visit to the clinic. Medication was stopped at least one day before the cultures were performed. At the end of the 4-week therapy, 28 (93.3 percent) of the 30 miconazole-treated patients were reported free of both signs and symptoms of the disease, while in the placebo group, only 6 of 32 patients (18.8 percent) were reported to have similar clearing. Persistence of symptoms (burning, itching, and pain) in the control group paralleled the poor clinical results. Of the miconazole-treated group, 75 percent obtained relief of symptoms within 3 days.

At the end of therapy (28 days), 21 of the 32 in the control group had positive KOH preparations and 23 had positive cultures. Only 2 of the 30 in the miconazole treatment group had positive KOH preparations, and 3 had positive cultures. Four weeks after treatment stopped, followup KOH preparations and cultures were obtained. Only one miconazole-treated patient showed evidence of recurrence of the disease with delayed growth of *T. rubrum* from the 28th-day culture. However, this patient was reported clinically clear and had a negative KOH preparation at followup.

The effectiveness of miconazole against endemic dermatophytosis was tested by Fulton (Ref. *6*) on 99 inmates (20 to 29 years old) in a crowded Florida prison. The patients were told to apply either the 2-percent miconazole cream or the control vehicle each morning and night. Of the 49 patients in the miconazole treatment group, 22 had a diagnosis of jock itch, 20 had athlete's foot, 4 had ringworm of the body, and 3 had mixed tinea infections. Of the 50 patients in the palcebo group, 26 had a diagnosis of jock itch, 18 had athlete's foot, 1 had ringworm of the body, and 5 had mixed tineas. Those having jock itch and ringworm of the body were treated for 2 weeks and clincially evaluated each week. Those with athlete's foot were treated for 1 month and evaluated biweekly. The following table summarizes the results:

TABLE 3.—ISOLATION OF PATHOGENS

Pathogen isolated	Patients treated with miconazole		Patients treated with placebo	
	Before	After	Before	After
T. rubrum	39	7	43	33
T. mentagrophytes	1	0	2	2
C. albicans	7	1	4	4
T. rubrum and C. albicans	2	0	1	1
No growth on culture	0	41	0	10
Total	49	49	50	50

Thirty-six (73.5 percent) of the 49 patients treated with miconazole cream showed symptomatic relief of itching within the first week of therapy compared to 5 (10 percent) of the 50 patients in the placebo group. After therapy was discontinued, 30 of the successfully treated test group subjects were followed up. Only one patient in this group has a recurrence of signs and symptoms of the original condition, with a positive KOH preparation and culture. In addition, *T. rubrum* was isolated from two other patients who were otherwise free of any evidence of infection.

Ducan (Ref. *7*) also studied 51 KOH positive and culture-positive patients in a Texas prison for 28 days of treatment plus 28 days of observation. Twenty-one inmates were treated with a 2-percent miconazole cream, and 30 were treated with the vehicle. *T. rubrum* was isolated in 14 of the miconazole-treated group, *T. mentagrophytes* in 6, and *E. floccosum* in 1. Ducan also noted a similar distribution of causative organisms in the control group.

The overall clinical effectiveness, judged by the disappearance of signs and symptoms, was significantly greater in the miconazole group (63 percent) than in the control group (18 percent). After 28 days, 82 percent of the treatment groups had negative KOH preparations. Ninety percent had negative KOH preparations at the end of the followup (56 days). In contrast, 62 percent of the controls were KOH negative after 28 days and 39 percent were KOH negative after 56 days. Patients who has *T. rubrum* infections on admission to the study showed the greatest clinical responses to miconazole with 93 percent obtaining a good to excellent response immediately after therapy (28 days). After the

followup, 64 percent had maintained a good to excellent result. The number of patients with *T. mentagrophytes* infections was not considered large enough for statistical analysis.

A study at the University of Glasgow tested the effectiveness of 2 percent miconazole cream and 2 percent miconazole powder against their vehicles (Ref. *8*). The study was done under relatively uncontrolled conditions to test the effectiveness of miconazole in self-treatment. The 45 young male subjects, all of whom had athlete's foot, were university athletes. They regularly trained in the gymnasium and used its showers. The most common dermatophytes isolated were *T. rubrum* in 27 subjects, *T. mentagrophytes* var. *interdigitale* in 10 subjects, and *E. floccosum* in 4 subjects. Twenty subjects received the miconazole and 25 received the placebo. Their instructions were to gently massage the cream onto the affected areas each evening and to use the powder every morning and after bathing.

After the 4-week treatment, 12 of the 20 miconazole-treated subjects were cleared of infection. Of the 25 who received the placebo, 6 had negative cultures. When 16 of the 18 infection-free subjects were examined 4 weeks after treatment, 11 of them remained culture negative. (Seven were on miconazole and four were on the placebo.) The authors report that "it is worth noting that, despite the adverse effects of intensive gymnasium activity in rubber soled shoe, the active preparation succeeded in eliminating the subjective symptoms in 100% and objective symptoms in 80% of cases compared to the placebo group in which they persisted in 47% and 60% of cases respectively."

A study of the effect of 2 percent miconazole cream on dermatophytosis, skin candidiasis, pityriasis versicolor (also called tinea versicolor) and erythrasma revealed definite cures (defined as negative cultures) in 31 patients (93.9 percent) in the miconazole group. Only six patients (21.4 percent) of the placebo group were cured ($p < 0.0005$). The mean time in which the definite cure was obtained was 1.6 weeks in the miconazole group and 1.8 weeks in the placebo group (Ref. *9*).

Additional studies have shown the effect of miconazole nitrate on the treatment of mycotic vulvovaginitis. A Belgian study (Ref. *10*) reported the results on 230 patients whose ages ranged from 12 to 75 years with a median of 27 years. Most of them had *C. albicans* cultured on the first visit. Altogether, nine different yeasts were isolated from the patients before treatment. Symptoms included itching.

Of the 230 patients, 194 returned for a post-treatment examination 4 days after the completion of treatment. Of 165 women treated with miconazole, 147 were cured (negative cultures). The most successful treatment appeared to be 2 percent miconazole cream applied intravaginally once daily for 2 weeks; 54 out of 57 women were cured. After this treatment, "all patients who were mycologically cured and most patients treated with miconazole 2 percent from whom yeasts were grown after treatment were free from symptoms * * *" The least effective treatment was 1 percent cream, with only 18 patients out of 25 cured. In comparison, 7 out of 21 women treated with nystatin were cured, and 1 out of the 8 who used only the vehicle was cured.

Between 1974 and 1977, three studies compared miconazole nitrate 2 percent cream with nystatin vaginal tablets in the treatment of vulvovaginal candidiasis (Refs. *11, 12,* and *13*). (For details of these studies see part III. paragraph A.1.d. below—Nystatin.) Cure rates with miconazole cream were 91.1 percent, 76 percent, and 92.9 percent, respectively, with a pooled patient population of over 300 cases of candidiasis.

In view of these studies, the Panel concludes that miconazole nitrate is effective for OTC topical antifungal use in the treament of athlete's foot, jock itch, and ringworm. Miconazole nitrate is also effective in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*).

(3) *Dosage*—(i) *Concentration.* Miconazole nitrate 2.0 percent.

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

(4) *Labeling.* The Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm; and in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*). Category I labeling may also be used for antifungal products with activity against both dermatophytes and yeast. (See part III. paragraph A.2. below—Category I Labeling.)

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d. *Nystatin.* The Panel concludes that nystatin is safe and effective for OTC topical antifungal use in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast *(Candida).* The Panel concludes that nystatin is also safe and effective in the treatment of athlete's foot, jock itch, and ringworm, but only in combination with Category I antifungal ingredients. (See part III. paragraph D. below—Combination Products Used in the Treatment of Athlete's Foot, Jock Itch, and Ringworm.)

New Drug Applications for nystatin were approved in February 1957. Nystatin is currently marketed on a prescription-only basis for the treatment of infections caused by *C. albicans* and other *Candida* species. The Panel recommends that this ingredient be made available for OTC use in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections

caused by yeast *(Candida)*. The Panel also recommends that nystatin be made available for OTC use in combination with antifungals for the treatment of athlete's foot, jock itch, and ringworm.

Compared with the limited use of nystatin reported in the literature in treating dermatophyte infections, the use of topical, oral, and intravaginal nystatin in the treatment of candidiasis has been extensively reported for over 20 years. Marketing experience revealed that topical nystatin was the most frequently prescribed single-ingredient topical product for candidiasis in 1977 (Ref. *1*).

Nystatin is a polyene antibiotic obtained from *Streptomyces noursei* (*S. noursei*), an actinomycete originally found in a dairy farm pasture in Virginia. First isolated in 1949, nystatin was the first antifungal antibiotic to be found. Originally, 1 mg nystatin was arbitrarily assigned an activity value of 1,000 units (U), but later purification methods enabled production of the antibiotic with activity of 2,500 to 3,500 U/mg (Ref. *2*).

Nystatin inhibits the growth of yeasts and some other fungi, but has no activity against bacteria and viruses (Ref. *3*). It is a yellow to light tan hygroscopic powder with an odor resembling cereal. It is very slightly soluble in water, slightly soluble in alcohol, and insoluble in chloroform, ether, and benzene. Nystatin deteriorates on long exposure to light, heat, and air (Ref. *4*), and even in a dry state may lose 25 percent of its microbiologic activity in 6 months (Ref. *5*). In neutral solutions at room temperature in ordinary sunlight, nystatin may lose 50 percent of its activity after 2 weeks (Ref. *6*).

(1) *Safety.* Nystatin has been used extensively for over 20 years in the treatment of candidal infections of the skin, mucous membranes, vagina, and intestinal tract. Reports of adverse effects are rare. Topical application does not irritate the skin and mucous membranes (Ref. *3*).

The intraperitoneal LD_{50} of nystatin in mice is between 29,450 and 50,040 U/kg. In rats it is 85,068 to 93,440 U/kg. The mouse can tolerate a single oral dose of 12.5×10^6 U/kg without adverse effects (12-day observation). Absorption is negligible by this route, as an oral dose of 2.7×10^6 U/kg yields only 9.8 U/mL in plasma. Rats can tolerate a single oral dose of 8.34×10^6 U/kg (25-day observation). When an oral dose of 450,000 U/kg was administered to a dog, less than 1 percent was recovered in the urine after 24 hours, whereas 23 percent of a 3,200 U/kg intravenous dose could be recovered in the urine, again demonstrating poor absorption from the gastrointestinal tract (Ref. *7*).

When nystatin was applied topically to rats, no reaction was observed on intact skin, but abraded skin showed slight erythema. This preparation was 0.2 to 0.8 percent nystatin in an oleaginous ointment base (1,280 U/mg) (Ref. *7*).

Chronic testing of nystatin was carried out in rats by daily oral administration of 121,000 to 810,000 U/kg for 90 days. The only indication of drug intolerance in rats given 202,500 to 540,000 U/kg was a depression in the rate of growth of male rats. At the highest dose (810,000 U/kg), gastrointestinal distress, dehydration, and diarrhea were observed in both male and female rats. A few deaths occurred from pulmonary hemorrhage, but no gross or microscopic pathological lesions were found (Ref. *7*).

Dogs tolerated 90,000 to 450,000 U/kg daily for 217 days; the only adverse effect noted were a few cases of vomiting during the first few weeks (Ref. *7*).

In humans, daily oral doses of 10×10^6 U nystatin are well tolerated, with only a few cases of a mild, transitory nausea (Ref. *7*). The amount of nystatin absorbed from the gastrointestinal tract is negligible. Levels of only 1 to 2.5 μg/mL in plasma were found in persons with normal kidney function (Ref. *3*).

Topical application of creams containing 100,000 U/g nystatin are without adverse effect. Nystatin is not absorbed from the skin. Allergic contact dermatitis from nystatin is extremely uncommon, with the first case not reported until 1970, about 15 years after nystatin was introduced for the treatment of *C. albicans* infections (Ref. *2*). In this report a woman apparently became sensitized through contact with a cream medication containing nystatin which her husband had used for 2 weeks to treat jock itch. She developed a strongly positive patch test to nystatin 100,000 U/mL in 70 percent ethanol (Ref. *8*). Further patch testing in this patient revealed positive tests to nystatin in 10 percent propylene glycol in concentrations as low as 5,000 U/mL (1/20 the usual therapeutic concentration). A strongly positive patch test also developed with nystatin 100,000 U/g in petrolatum, although a concentration of 50,000 U/g failed to cause a positive reaction. It was suggested that a commercially available ointment containing 100,000 U/g in a plasticized hydrocarbon gel be used for routine patch testing a nystatin (Ref. *9*).

A few other case reports of nystatin sensitivity appeared in 1971. Coskey reported the case of a man who had chronic itching of the perianal area and who developed positive patch tests to several ingredients, including nystatin. These ingredients were contained in a cream that he had used intermittently for 6 months. He was not rechallenged with the product containing nystatin (Ref. *10*). Two later cases reported by Coskey also had positive patch tests to nystatin. One patient developed sensitivity after treating jock itch with a nystatin-containing cream for 30 days. The other patient first developed a widespread skin eruption after using nystatin vaginal suppositories. She later developed dermatitis of the hand after applying a cream containing nystatin (Ref. *11*).

The Panel is not aware of any other reports of contact sensitivity to nystatin. It concludes that allergic contact dermatitis caused by nystatin probably is very rare and not a significant hazard to the users.

The Panel concludes that nystatin is safe for OTC topical antifungal use in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*).

(2) *Effectiveness.* Although nystatin inhibits various dermatophytic fungi in vitro, it is particularly active against *C. albicans* and is primarily used for the treatment of candidiasis. The mechanism of action appears to be the ability of nystatin to bind to sterols in the cell membrane, thus rendering the membrane leaky to water and small molecules and ions, such as potassium (Ref. *12*). Nystatin induces the formation of microscopic aqueous pores in thin cell membranes containing cholesterol. These pores act as single ionic channels and also induce changes in the electrical conductance of the cell membranes (Ref. *13*).

In 1951, Hazen and Brown (Ref. *14*) described two antifungal agents which were produced by *Streptomyces;* these agents were nystatin and actidione. They listed the minimal inhibitory concentration of nystatin as 3.12 μg/mL against *C. albicans* and 6.25 μg/mL against *T. mentagrophytes*. They noted that nystatin is strongly fungicidal.

According to Pansy et al. (Ref. *15*), the minimal inhibitory concentration of nystatin is 1.1 μg/mL against *C. albicans*, 0.5 μg/mL against *M. canis*, and 2.8 μg/mL against *T. mentagrophytes*.

DiPalma (Ref. *16*) lists the following minimal inhibitory concentrations:

Microorganism	Minimal inhibitory concentration (U/mL)
C. albicans	7.8
M. canis	15.6
M. audouinii	15.6
E. floccosum	7.8
T. rubrum	31.2

Shadomy (Ref. *17*) studied the in vitro activity of numerous topical antifungals including nystatin. Table 4 shows his findings on nystatin.

TABLE 4.—THE MINIMAL INHIBITORY CONCENTRATION OF NYSTATIN AGAINST MULTIPLE STRAINS OF FUNGI

Microorganism	Number of strains	Mean (μg/mL)	Range (μg/mL)
T. mentagrophytes	3	12.5	3.13 to 25.
T. rubrum	5	1.56	0.39 to 1.56.
M. canis	3	0.78	0.78 to 1.56.
M. gypseum	3	0.78	0.39 to 1.56.
E. floccosum	3	1.56	0.78 to 12.5.

Hashimoto and Blumenthal (Ref. *18*) tested the in vitro activity of several antifungal agents including nystatin, clotrimazole, griseofulvin, and miconazonitrate. They studied the survival rates of arthrospores of *T. mentagrophytes* after a 24-hour exposure to the various ingredients. Nystatin proved to be the most effective of the antifungal tested.

Resistance to nystatin has been observed in mutant yeasts which do not contain cholesterol in their cell membranes (Ref. *2*). However, such resistance is difficult to induce in the laboratory and, as reported in 1955, repeated efforts had failed to develop strains of *C. albicans* resistant to nystatin by incorporating the antibiotic in agar and broth dilution tubes (Ref. *19*). In this same study, preliminary efforts to obtain nystatin-resistant strains of the dermatophytes *M. canis* and *T. mentagrophytes* also failed. In later studies, however, resistance of *Candida* species to nystatin was produced in the laboratory, although such strains are nonpathogenic (unable to cause infection). Significant natural resistance to *C. albicans* has not been observed in clinical isolates (Ref. *2*).

Clinical studies using nystatin to treat dermatophytic fungal infections have not been extensive. In 1955, nystatin was used to treat 93 patients with culture-positive dermatophytosis (Ref. *20*). Although the types of fungal infections were not specified, cultures revealed 60 cases of *T. rubrum*, 26 cases of *T. gypseum*, 3 cases of *Microsporum lanosum* (*M. lanosum*), and 4 other fungi.

Most patients with *T. rubrum* infections were treated for at least 3 months, after which all but one patient still had positive cultures. The results were rated as excellent in 1, good in 3, fair in 28, and no change in 28. Similar results were reported in patients with *T. gypseum* infections. These results were: 1 excellent, 20 fair, and 5 unchanged; 25 of 26 patients still had positive cultures after treatment. The results were more favorable in the three patients with *M. lanosum* infections, with good to excellent clinical improvement and negative cultures after treatment.

With all of the dermatophytes, clinical improvement generally occurred slowly, but cultures were still positive at the end of the treatment periods, which varied from 1 week to 8 months, with an average of 3 months.

The Panel is aware of only one other study in which nystatin as a single ingredient was used to treat dermatophyte infections (Ref. *1*). In this unpublished multicenter study, nystatin cream 100,000 U/g was compared with tolnaftate cream 1 percent and the combination of tolnaftate 1 percent/nystatin 100,000 U/g in cream base. The random, double-blind, controlled study involved 178 patients with jock itch caused by dermatophyte fungi (76 percent) or *C. albicans* (17 percent) or by both (7 percent). Types of dermatophytes were not specified. All patients had a positive KOH preparation or gram stain, and 90 percent had positive fungal cultures at the beginning of the study.

Among 47 patients with dermatophytic infections treated with nystatin cream, 30.4 percent (14/46) had positive KOH preparations and cultures at the end of 1 week. At the end of 2 weeks, 16.7 percent (6/36) were positive. This compared favorably with treatment with tolnaftate cream alone and the combination tolnaftate-nystatin cream. In each of these groups over 75 percent of the patients were either cleared or improved, and about 80 percent had negative KOH preparations and cultures. There were no significant differences between treatment groups in the overall success of treatment.

Nystatin has been used in double-blind, controlled studies to treat candidiasis of the skin in various anatomical areas, including the genital area (Refs. *21* through *24*). In a randomized, double-blind study by Alban (Ref. *21*), 50 infants (aged 6 days to 20 months) were treated for a variety of skin conditions with either nystatin topical cream (100,000 U/g) or placebo cream. These conditions included diaper rash, intertrigo, paronychia (inflammation of the folds of tissue around the fingernail), and perleche (inflammation and cracking of the lips). All patients had positive cultures before therapy and were recultured at the end of therapy. The creams were applied either three or four times daily for 2 to 8 days (average 6 days).

In the nystatin group, good to excellent results were seen in 21 of 25 (84 percent) infants compared with 8 of 25 (32 percent) in the placebo group. This difference is statistically significant ($p=0.001$). Positive cultures at the end of therapy were seen in only 8 (32 percent) of the nystatin cases, compared with 21 (84 percent) of the placebo group, a statistically significant difference ($p<0.001$).

Following this study, 18 infants who failed to repond to the placebo cream were treated with nystatin cream, with clinical clearing in 15 (83 percent) and mycologic clearing in 14 (78 percent) (Ref. *21*). Alban concluded that nystatin was "a rapid and convincing therapeutic agent for the treatment of cutaneous moniliasis (candidiasis) in infants when applied as a topical cream several times daily for six days."

Nystatin ointment 100,000 U/g was compared with 1 percent haloprogin cream in a double-blind parallel comparison method in 68 patients with cutaneous candidal infections (sites not stated) (Ref. *22*). Two institutions in the southeastern United States cooperated in the study. All skin lesions were rated 1 (mild) to 4 (severe) in clinical severity prior to treatment. Except for one child, all patients were adults, and all had positive pretreatment KOH preparations and cultures for *C. albicans*. Each product was applied twice daily for 13 consecutive days. One day later and again 2 weeks after discontinuing treatment, the clinical lesions were scored and followup KOH preparations and fungal cultures were obtained. Clinical improvement was considered to have occurred if lesion scores were reduced by 50 percent or more. Objective improvement was considered confirmed if cultures after therapy were negative for *C. albicans*. There was no significant difference in clinical improvement between the two groups, as 28 of 33 nystatin-treated patients and 29 of 35 haloprogin-treated patients responded satisfactorily to treatment. The overall cure rate exceeded 80 percent in both groups, including clinical and mycologic cures.

Another double-blind study compared nystatin ointment 100,000 U/g with 1 percent clotrimazole cream in a group of 10 patients with cutaneous candidiasis of the toewebs (7 patients) and groin (5

patients). Before therapy all patients had positive KOH preparations and cultures for *C. albicans*. Treatments were applied twice daily.

The patients were reexamined with microscopy and culture after 4 weeks of treatment and again 4 weeks after treatment stopped. Although the numbers of patients in the study were too small to be significant, the preparations seemed to be equally effective. Four weeks after the end of therapy, all three nystatin-treated patients and six of seven clotrimazole-treated patients were clear of infection as judged by cultures (Ref. *23*).

A multicenter, double-blind trail compared nystatin cream with nystatin/triamcinolone acetonide combination cream in the treatment of 31 patients with bilateral *Candida* infections of the flexural folds (Ref. *24*). (Triamcinolone acetonide is a corticosteroid anti-inflammatory drug.) In this bilateral paired comparison study, the patients (20 males and 11 females) applied nystatin cream on one side and nystatin/triamcinolone acetonide cream on the other side for 14 days. Before treatment all patients had positive cultures for *Candida*.

During the first 7 days of treatment, each patient completed a daily self-assessment form pertaining to symptoms of itching, irritation, and pain. This enabled a preference assessment to be made of the effectiveness and speed of action of the two creams. Both treatments proved equally effective in terms of clinical improvement and mycological cure. Mycological cure occurred in 27 patients on the nystatin-treated side and 26 patients on the nystatin/triamcinolone-treated side. Clinical improvement occurred on both sides in 29 patients.

Although 13 patients had no preference between the two creams, 13 other patients preferred the nystatin/triamcinolone combination and 5 preferred the nystatin alone. Physician assessment of the two creams, based on the rapidity of symptomatic relief, preferred the nystatin/triamcinolone combination 14 times; nystatin alone, 6 times; and no difference, 11 times. Although these numbers were too small to be statistically significant, patients and physicians tended to prefer the nystatin/triamcinolone combination. The study concluded that "the addition of a steroid may be desirable for a more rapid relief of the symptoms while a mycological cure is being achieved."

A series of 76 consecutive cases of vaginitis seen in office practice was reported in 1956 (Ref. *25*). *C. albicans* was demonstrated by culture in 59 patients, of whom 31 were pregnant. All patients complained of itching. Treatment consisted of the insertion of either one or two vaginal tablets containing nystatin 100,000 U at bedtime for either 7 or 14 days. No controls were included in the study. Evaluation was based on clinical improvement and culture results obtained at examinations 1 week later and 2 to 3 months later. Nystatin therapy was successful in 58 of the 59 patients. Vaginitis recurred with symptoms and positive cultures for *C. albicans* in 10 pregnant patients and 4 nonpregnant patients 2 to 5 weeks after therapy stopped. Repeat courses of nystatin gave excellent results in all cases. Itching was relieved within the first 48 hours of nystatin treatment.

Another uncontrolled study in 1956 reported the "successful" use of both oral and vaginal nystatin in combined therapy for candidal vulvovaginitis in 50 patients (Ref. *26*). Nystatin was said to be the "treatment of choice." Oral nystatin was used to reduce the candidal population in the gastrointestinal tract, often the source of the candidal infection. The report stated that patients should be warned to expect soreness and pain a day or so after treatment is started. This discomfort is probably caused by the dissolution of the yeast curds in the vagina with resulting raw eroded areas. The intensification of symptoms after treatment is started was said to be "almost diagnostic" of a yeast infection.

A randomized, double-blinded, controlled study in 1973 compared nystatin vaginal cream 100,000 U/g with placebo cream in 50 adult female patients (Ref. *27*). All patients had *C. albicans* vaginitis documented by positive KOH preparations and fungal cultures. The creams were applied in 5 g doses twice daily with 14-day treatment in most cases. Followup examinations were made after 4 to 7 days of therapy and 4 to 7 days after completion of therapy. The overall response was significantly better in the nystatin treatment group; 92 percent of these patients had good to excellent clinical results and positive cultures remained in only 26 percent. In contrast, positive cultures remained in 79 percent of the placebo-treated group; 60 percent had good to excellent clinical responses.

Two randomized, double-blinded studies in Europe compared nystatin with clotrimazole in the treatment of candidal vaginitis. In Germany, 120 patients with culture-proven candidal vaginitis were treated with a 7-day course of vaginal tablets containing either nystatin 100,000 U or clotrimazole 100 mg (Ref. *28*). None of these patients was pregnant. Followup examinations and cultures were performed 1 week and 4 weeks after beginning treatment. In the nystatin-treated group, 47 of 60 patients were "cured" at the 4-week followup, whereas 54 of 60 of the clotrimazole-treated group were "cured." A cure was defined as a clinical cure combined with negative cultures. There was no statistically significant difference between the results of the two treatment regimens. However, the symptoms of itching, burning, and vaginal discharge were mentioned much less frequently in the clotrimazole-treated group. Clotrimazole was concluded to be as effective as nystatin in treating vaginal candidiasis (Ref. *28*).

In Scotland, 62 pregnant patients were treated with either two vaginal suppositories of nystatin (100,000 U each) or one vaginal suppository of clotrimazole (100 mg) daily for 6 days (Ref. *29*). All patients had positive cultures for *Candida* species before beginning the study, and followup cultures were obtained 1 week and 5 weeks after ending therapy. The symptoms including itching. The treatment groups included 29 patients using nystatin and 33 patients using clotrimazole.

Five weeks after the end of therapy, 91 percent of the clotrimazole-treated patients and 32 percent of the nystatin-treated group had negative cultures. This difference between the two therapies was highly significant (<0.005). Both treatments reduced signs and symptoms including itching. Although clotrimazole resulted in a greater reduction of symptoms than nystatin, the researchers report that the difference was significant only in the reduction of vaginal discharge. Neither drug adversely affected the pregnancy, with all infants normal at birth. Clotrimazole was concluded to be superior to nystatin in the local treatment of candidal vaginitis during pregnancy.

Three studies compared nystatin with miconazole nitrate in the treatment of vulvovaginal candidiasis. In 1974, 116 pregnant or nonpregnant women with KOH and culture-positive vulvovaginal candidiasis were randomly assigned to two treatment groups (Ref. *30*). In one group of 60 women, treatment was one nystatin vaginal tablet (100,000 U) twice daily for 15 days. In the second group of 56 patients, 2 percent miconazole nitrate cream was inserted vaginally at bedtime for 14 days, with each applicator containing 0.1 g miconazole nitrate.

A "cure" was defined as clearing of signs and symptoms, including itching, as well as negative KOH preparation and fungal culture at least 30 days after

completion of therapy. In the nystatin-treated group, 46 of 60 (76.7 percent) were cured, compared to 51 of 56 (91.6 percent) cured with miconazole. A second course of nystatin treatment given to nine patients who were not cured after the first course resulted in cures in five of these nine patients. This gave an overall cure rate of 85 percent with nystatin.

Although the cure rate with miconazole was significantly higher than with nystatin, the Panel concludes that nystatin was still an effective therapeutic agent, curing over 75 percent of the cases of candidiasis.

A similar study (Ref. *31*) compared the nystatin vaginal tablets (100,000 U) and the 2-percent miconazole cream preparations in 94 pregnant patients with vulvovaginal candidiasis. The patients were randomly assigned to treatment groups. Among 42 culture-positive patients treated with nystatin tablets, 31 (75 percent) considered themselves subjectively cured at the end of the treatment period. However, 18 (44 percent) still had positive cultures for *Candida*. In contrast, only 8 of 37 (22 percent) of the miconazole-treated group had positive cultures at the end of treatment, while 34 (91 percent) considered themselves subjectively cured.

Among patients who had negative cultures at the end of treatment and who were followed for up to 16 weeks, the recurrence rate of vulvovaginal candidiasis was 48 percent in the nystatin group and 24 percent in the miconazole group. The recurrence rate was significantly lower in the miconazole-treated group (Ref. *31*). The Panel concludes that vulvovaginitis in pregnancy is often persistent and difficult to treat and that a "subjective" cure rate of 75 percent for nystatin would be acceptable for OTC use, despite the persistence of *Candida* on culture in many cases.

Nystatin vaginal tablets and 2 percent miconazole nitrate cream were again compared in pregnant women with vulvovaginal candidiasis in a multicenter comparative randomized study involving 33 investigators using a common protocol (Ref. *32*). Nystatin tablets were inserted twice daily for 15 days; miconazole cream was inserted once daily at bedtime for 14 days.

Followup clinical examinations with KOH preparations and cultures were done 8 to 10 days and 30 to 35 days after completion of therapy. A second course of therapy was offered to patients whose first course had failed. After the first couse of therapy, 53.3 percent of 244 patients were cured with nystatin, compared with 83.5 percent of patients treated with miconazole nitrate. After two courses of therapy, the combined cure rate was 66.1 percent for nystatin and 92.9 percent for miconazole. Although the cure rate for nystatin was significantly lower than that of miconazole, the Panel still regards an overall cure rate of 66 percent as acceptable in showing clinical effectiveness of nystatin.

The Panel is particularly interested in the use of nystatin for feminine itching that is usually associated with vaginal yeast infection. This infection is usually caused by *C. albicans*, unlike jock itch in males which usually a dermatophytic infection. In reviewing the efficacy of nystatin, the Panel also carefully reviewed the use of intravaginal nystatin in treating vulvovaginitis. Vaginal discharge is the most common pelvic complaint seen in office practice and is usually associated with vaginal itching (Ref. *25*). In vulvovaginitis due to *Candida* infection, the entire vulva may become moist, red, and raw; itching of the vulva may become so intense that the patient must seek emergency medical treatment. There may also be a white vaginal discharge. Of the two microorganisms most often responsible for vaginal itching and discharge, *C. albicans* is far more common than *Trichomonas vaginalis*. In 1956 the ratio of patients seen with *Candida* compared to *Trichomonas* was estimated to be 7:1 in nonpregnant patients and 15:1 in pregnant patients (Ref. *25*).

The Panel recognizes that the most successful treatment of vulvovaginitis caused by *Candida* involves combined therapies designed to eradicate the yeast infection from the vulva, vagina, and gastrointestinal tract (Ref. *4*). Such ideal therapy includes an appropriate anticandidal medication for each of these three areas, including a cream, lotion, ointment, or powder for the skin and mucous membranes of the vulva; intravaginal creams or tablets for the vagina; and oral tablets for the gastrointestinal tract. The Panel also recognizes, however, that women with *Candida* vulvovaginitis are bothered most by the itching and by the moist, raw, red eruption of the vulva. The Panel believes that this discomfort could be rapidly relieved by the application of OTC nystatin cream or ointment until more definitive treatment with oral and intravaginal anticandidal medications could be obtained from a physician.

The Panel concludes that nystatin is effective for OTC topical antifungal use in the treatment of superficial skin infections caused by species of *Candida*. Nystatin is also effective in the types of athlete's foot and jock itch (in males) caused by yeast infection. However, because most causes of athlete's foot and jock itch are caused by dermatophytes, the Panel recommends that nystatin not be used alone to treat these conditions. But nystatin would be useful in the treatment of mixed infections (candidal-dermatophytic) of the feet and groin. For this reason the Panel recommends the use of nystatin combined with a Category I antifungal ingredient in the treatment of athlete's foot, jock itch, and ringworm. (See part III. paragraph D. below—Combination Products Used in the Treatment of Athlete's Foot, Jock Itch, and Ringworm.) The Panel also concludes that nystatin is effective for the treatment of external feminine itching associated with vaginal yeast (candidal) infection.

Candidal or yeast infection of the vagina is extremely common and recurrent, and is the most common cause of intense itching and erythema of the vulva associated with a white vaginal discharge. The Panel believes that most women are familiar with this condition, particularly if they have ever been treated for it by a physician. The Panel believes that OTC treatment of the vulva with nystatin cream or ointment will often provide rapid symptomatic relief of itching through eradication of *Candida* on the vulva. The Panel recognizes that this treatment alone is insufficient to "cure" the yeast infection (because it does not eradicate the fungus in the vagina and gastrointestinal tract). For this reason the Panel recommends that labeling for nystatin used as a single ingredient for the treatment of external feminine itching associated with vaginal yeast (candidal) infection include a warning limiting use to 14 days if there is no improvement. Nevertheless, the Panel concludes that the use of topical nystatin is a rational and well-accepted part of the treatment of yeast vulvovaginitis.

(3) *Dosage*—(i) *Concentration.* Nystatin 100,000 μ/g.

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

(4) *Labeling.* The Panel recommends the Category I labeling for antifungal products used in the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*). For nystatin combined with up to two Category I antifungal ingredients, provided these ingredients broaden the spectrum, the Panel recommends the Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and

ringworm. For such combinations, Category I labeling may also be used for antifungal products with activity against both dermatophytes and yeast. (See part III. paragraph A.2. below—Category I Labeling.)

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e. *Tolnaftate.* The Panel concludes that tolnaftate is safe and effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm and in the prevention of athlete's foot.

The chemical name of tolnaftate ($C_{19}H_{17}$ NOS) is methyl (3-methylphenyl)-carbamothioic acid 0–2–naphthalenyl ester. Tolnaftate is a fine, white, odorless powder with a melting point of 110° to 113° C. It is practically insoluble in water, slightly soluble in alcohol, and freely soluble in chloroform (Ref. *1*).

(1) *Safety.* Acute toxicity studies (Ref. *2*) indicate that in rats, dogs, and rabbits, tolnaftate 1 percent displays a good therapeutic index (the ratio between the toxic dose and the therapeutic dose). An oral LD_{50} could not be obtained in mice, rats, guinea pigs, rabbits, or dogs, even with doses as high as 14 g/kg.

Acute dermal and eye irritation studies in rabbits revealed no changes. Subacute and chronic toxicity studies lasting from 3 weeks to 1 year and performed in a variety of animals showed no toxicity due to tolnaftate. Dosage forms tested included powder, solution, and cream with the highest concentration being a 3-percent solution. A 1-year, chronic dermal study in rats and mice showed no evidence of carcinogenicity or adverse reaction after application of tolnaftate in acetone (Ref. *2*).

Reproduction studies were conducted in rabbits, guinea pigs, mice, and rats. The researchers found no teratogenic effects from tolnaftate administered orally, topically, or subcutaneously (Ref. *2*).

In humans, some uncontrolled studies of tolnaftate have reported an insignificant incidence of mild dermatitis, including irritation, erythema, and itching (Ref. *2*). But numerous other studies confirm an absence of toxicity potential from the use of this ingredient.

Several controlled studies (Refs. *3* through *6*) using 1 percent tolnaftate solution or powder showed an absence of toxicity potential. Lubowe and Wexler (Ref. *3*) tested tolnaftate solution in 25 patients with athlete's foot and jock itch. The solution was applied two to three times daily for an average of 3.5 weeks. The investigators found "no evidence of primary irritation or secondary sensitization."

Tolnaftate solution was also used by Kurban et al. (Ref. *4*) in 49 patients; 27 had ringworm of the body and 22 had tinea versicolor. Treatment was twice daily for 2 to 3 weeks. The researchers reported no local side effects and no apparent hematologic or renal toxicity from tolnaftate.

Charney et al. (Ref. *5*) conducted a double-blind, multicenter trial to test tolnaftate powder in the treatment and prevention of athlete's foot. The study population consisted of 635 adults from

four different institutions. During the 12-week treatment period, one-half of the subjects received applications of tolnaftate powder twice daily. The other half received the vehicle. The treatments were given 5 days a week for 12 weeks with one investigator completing the scheduled 60 treatment days over an 8-week period by treating 7 days a week.

The researchers wrote that "there was no documented instance of hypersensitivity to any component of the medication." At one institution, however, two subjects who received the vehicle complained of irritation. Charney et al. believed these side effects were caused by "exacerbation of the disease process."

In a double-blind study, 50 subjects applied tolnaftate powder or vehicle twice daily during the 5-week to 6-week test period (Ref. *6*). None of these subjects had any clinical signs or symptoms of irritation due to tolnaftate or the vehicle.

After reviewing the data presented, and considering the area of use of tolnaftate preparations, the Panel concludes that tolnaftate is safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm, and in the prevention of athlete's foot.

(2) *Effectiveness.* Tolnaftate was submitted to the Panel at a concentration of 1 percent in powder, cream, solution, spray powder, and spray solution. Most of the relevant clinical data available pertain to the powder, cream, and solution forms of the drug. Very little information is available on the effectiveness of the spray powder and the spray solution.

The in vitro antifungal activity of tolnaftate was tested against 29 strains of fungi grown in Sabouraud's liquid medium (Ref. *7*). Using the tube-dilution method, the fungistatic concentration against *T. mentagrophytes* was 0.008 μg/mL, and the fungicidal concentration was 0.08 μg/mL. Tolnaftate was found to be "highly active and specific in vitro" against 19 strains of the following genera: *Trichophyton, Microsporum,* and *Epidermophyton.* Tolnaftate showed no activity against *C. albicans* (Ref. *7*). As stated earlier, the in vitro activity of tolnaftate against dermatophytes compared favorably with haloprogin, but tolnaftate did not show anticandidal activity. (See part III. paragraph A.1.a. above—Haloprogin.)

Tolnaftate has been studied in animal models (Ref. *7*), in induced human infections (Ref. *6*), and in natural human infections (Ref. *4*). In guinea pigs, tolnaftate has been shown to be effective in treating superficial fungal infections caused by *T. mentagrophytes.*

Weinstein, Oden, and Moss (Ref. *7*). reported on the antifungal properties of tolnaftate in an in vivo animal model system. Male guinea pigs were infected with *T. mentagrophytes.* Three days after infection, eight animals were treated with either a 1 percent tolnaftate solution, cream, or powder; 12 were treated with a control vehicle, and 8 were untreated controls. Animals were evaluated on days 1, 3, 7, 9, 11, and 21 after treatment was begun. By day 11, all tolnaftate-treated animals were clear of lesions both on examination and by culture. Conversely, after 21 days of therapy, neither the animals treated with the powder, solution, or cream bases alone nor the untreated animals were free of lesions.

In treating human dermatophytoses, tolnaftate has been shown to be far more effective than the placebo vehicle. In a double-blind controlled trial, Kurban et al. (Ref. *4*), studied 88 consecutive patients with superficial mycoses of the skin. Only patients with positive KOH preparations and cultures were included in the study. This discussion pertains to the 43 patients diagnosed with ringworm of the body. These 43 patients were instructed to apply either 1 percent tolnaftate solution or its vehicle twice daily and to use no other medications during the 2- to 3-week treatment. During this time the patients were seen for a weekly or biweekly evaluation including the patient's objective comments, clinical assessment, KOH preparation, and culture.

Twenty-seven patients received tolnaftate; of these patients, 25 (93 percent) had clinical cures and negative cultures. Of 16 patients treated with placebo vehicle, only 1 was cured. The authors concluded that tolnaftate was an effective topical antifungal agent.

Adam and Craig (Ref. *8*) in a double-blind, controlled study of 38 patients also illustrated the effectiveness of tolnaftate. The study population consisted of 23 cases of athlete's foot, 12 of jock itch, and 3 of ringworm of the body. KOH preparations were positive in all patients and cultures showed *T. rebrum, T. mentagrophytes,* or *E. floccosum.* Patients were treated with 1 percent tolnaftate in a cream base or the cream base alone. Observations were recorded at weekly intervals over a 3-week period and at a reevaluation visit 1 to 4 weeks after treatment was stopped. Lesions were cultured, and KOH preparations were performed at each visit.

Of the 29 patients treated with tolnaftate, 18 (62 percent) were cleared and 3 (10 percent) were failures. Of the 9 patients treated with the placebo, 2 (22 percent) were cleared and 5 (56 percent) were failures. The remaining 10 patients represented partial responses. Drawbacks in the study design include the apparent lack of randomization and failure to match patients and cultures.

Tolnaftate has been used extensively in controlled studies as a standard against which other topical antifungals have been compared and rated. Carter (Ref. *9*) compared the effectiveness of tolnaftate and haloprogin in a double-blind, clinical trial. A 1-percent solution of tolnaftate was compared to 1 percent haloprogin in 82 patients with athlete's foot. The diagnosis of cutaneous infection was determined by clinical inspection, KOH preparations, and cultures. Patients were randomly assigned to treatment groups and treated twice daily for 27 consecutive days. Of the 20 tolnaftate-treated patients, 17 (85 percent) showed clinical improvement; 56 (92 percent) of the 61 patients treated with the various forms of haloprogin showed improvement. Eighty percent of the tolnaftate-treated group and 91 percent of haloprogin-treated group maintained or further improved lesion scores 8 days after treatment.

Hermann (Ref. *10*) conducted three double-blind studies in which he compared 1 percent tolnaftate cream with 1 percent haloprogin cream in patients with dermatophyte infections. Haloprogin was also compared to its cream vehicle. Only patients with a clinical diagnosis confirmed by a positive culture and KOH preparation were included in the study. Patients applied the drugs twice daily and were observed at 7-day and 14-day intervals with repeated inspection and KOH determinations. These studies were carried out over a 28-day period. Of the 22 patients receiving tolnaftate, 20 (91 percent) improved and 2 (9 percent) did not improve. Of the 18 patients treated with haloprogin, 11 (61 percent) improved and 7 (39 percent) did not improve. From these data the author concluded that tolnaftate and haloprogin were comparable in effectiveness.

A double-blind study compared the effectiveness of 1 percent tolnaftate and 1 percent clotrimazole creams in 54 patients with superfical dermatophytoses (Ref. *11*). Each treatment group contained 27 patients, with *E. floccosum* and *T. rubrum* cultured from all patients. patients applied either tolnaftate or clotrimazole twice daily for 21 days. Clinical, microscopic, and culture examinations were performed at weekly intervals during therapy and at 1, 3, and 5 weeks after completing therapy. At the end of

the treatment period, 19 (70 percent) of the tolnaftate-treated patients were cured, compared to 21 (78 percent) of the clotrimazole-treated patients. This difference was not statistically significant.

Wethered and associates (Ref. *12*) conducted a double-blind, paired comparison, clinical trial in 24 patients with athlete's foot caused in most cases by *T. rubrum*. On microscopy, all patients demonstrated fungal elements on both feet. Patients were randomly assigned two tubes of ointment marked for the right or left foot. The tubes contained either 1 percent pecilocin ointment or its ointment base, or 1 percent tolnaftate cream or its base. (Pecilocin is an antifungal antibiotic used in Great Britain.) The ointments were applied twice daily for 28 days. Clinical assessment was made weekly. Seven days after the end of the trials, scrapings were taken from each foot for microscopy and culture. A similar examination was done 3 weeks later. Of the 12 patients in the tolnaftate treatment group, 5 showed greater clinical improvement on the untreated side and 2 showed greater improvement on the treated side. (Both sides were culture positive.) In most cases, the mycological findings were the same on both sides. The results of this study indicated that neither tolnaftate nor pecilocin has a clinical or mycological effect. The Panel considers that the paired-comparison study design is responsible for the lack of evidence of tolnaftate effectiveness.

A double-blind study by Smith and co-workers (Ref. *13*) tested both the effectiveness and the prophylactic activity of a 1-percent tolnaftate powder in the treatment and prevention of athlete's foot in a prison population. Before beginning treatment, the feet of all inmates were examined and clinical observations recorded. Scrapings of scale were taken for KOH preparation and for culturing on Sabouraud's media. This study included 317 men, 144 of whom had confirmed athlete's foot.

Of these 144 subjects, 71 were treated with 1 percent tolnaftate powder applied twice daily to the feet and toes. As a control, 49 inmates were treated twice daily with the talc-cornstarch vehicle. Twenty-four subjects were left untreated. No other topical or systemic therapy was given.

At the end of 8 weeks a series of final examinations of the subjects began. At the end of the study, 26 of the 71 subjects treated with tolnaftate had clinical cures and negative cultures. Five of the 49 men using the vehicle alone and 2 of the 24 men in the untreated group had clinical cures and negative cultures. Tolnaftate powder was shown to be superior both to the vehicle alone and to no treatment at all ($p<0.01$).

Seventy of the 317 patients had no sign of fungal infection when they began the above study. Twenty-eight of these subjects used tolnaftate powder prophylactically twice daily. At the end of the study period, 23 of these subjects still had normal clinical findings and negative cultures and KOH preparations. Of the 36 subjects who used the vehicle powder prophylactically, 20 remained "normal." Of the six subjects who were untreated, three remained free from the fungal disease at the end of this period. Statistical analysis of the study results revealed that tolnaftate powder was significantly more effective than the vehicle in preventing athlete's foot ($p<0.05$). There were not enough subjects in the untreated group to permit statistical analysis of the effectiveness of the talc-cornstarch vehicle alone in the prevention of athlete's foot (Ref. *13*).

Several other studies (Ref. *5, 6,* and *14*) have also examined the prophylactic effectiveness of tolnaftate.

An investigator (Ref. *6*) conducted a double-blinded study in 50 volunteers to test the prophylactic effectiveness of 1 percent tolnaftate powder in experimentally induced fungal infections of the foot. Preceding treatment, cantharidin was used to induce blisters on the feet of the test subjects before deliberate exposure to masses of *T. mentagrophytes* spores in foot baths. After the foot baths the subjects were instructed to apply either tolnaftate powder or the powder base to both feet twice daily throughout the 5-week to 9-week test period. Half of the subjects received tolnaftate powder, the others received the vehicle control. Of the 25 tolnaftate-treated patients, 20 remained clear of fungal infection throughout the study. Of the 25 vehicle-treated patients, 13 remained free of fungal infection. This difference is statistically significant ($p = 0.035$).

A double-blind, controlled study by Burrill and Nemlick (Ref. *14*) tested the prophylactic effectiveness of 1 percent tolnaftate powder in 86 patients for 12 weeks. The patients did not have athlete's foot before treatment. Diagnosis was established by clinical inspection, KOH preparations, and culturing. Response to treatment was evaluated in the same way. Six of the 45 patients treated prophylactically with tolnaftate developed new lesions while under study, although KOH preparations were negative. Of the 41 patients in the placebo group, 21 developed lesions during the treatment period and 16 of the 22 had positive KOH preparations. The difference between tolnaftate-treated and placebo-treated groups was statistically significant ($p<0.001$).

In the prophylactic segment of the multicentric study by Charney et al. (Ref. *5*) described above, a common protocol was employed at four institutions in California, Mississippi, Puerto Rico, and Texas. A total of 168 subjects entered the study with no evidence of fungal infection based on clinical and mycological examinations. These subjects were distributed among the four institutions with 69 receiving tolnaftate and 99, the vehicle control. They completed 60 prophylactic treatment days. Based on the pooled data, it was reported that 61 (88 percent) of the tolnaftate-treated subjects had no clinical evidence of athlete's foot at the end of the study, as compared to 68 (69 percent) of the vehicle-treated subjects. These results showed tolnaftate powder to be significantly more effective than the vehicle, talc-cornstarch, in preventing athlete's foot ($p<0.01$).

The Panel reviewed numerous other studies supporting the effectiveness of tolnaftate in the treatment and prevention of superficial fungal infections. These studies were found to be lacking in double-blinding, randomization, or placebo controlling. For this reason they are not presented here in detail.

Tolnaftate has been shown to be an effective drug in the treatment of athlete's foot, jock itch, and ringworm and in the prevention of athlete's foot. Its effectiveness has been demonstrated in both humans and laboratory animals by controlled, blinded studies in which tolnaftate was compared against its vehicle as well as against other known effective topical antifungals (e.g., haloprogin and clotrimazole).

The Panel concludes that tolnaftate may be used in the prevention of athlete's foot, but not in the prevention of jock itch or ringworm. Because the groin is a much more sensitive area than the feet, antifungal agents should not be used indefinitely in the groin. Also, it would be impractical to use an antifungal agent prophylactically over large areas of the body to prevent ringworm of the body.

Based on the foregoing clinical studies, the Panel concludes that tolnaftate is effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm, and in the prevention of athlete's foot.

(3) *Dosage—(i) Concentration.* Tolnaftate 1.0 percent.

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

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

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f. *Undecylenic acid and its salts (calcium undecylenate, copper undecylenate, and zinc undecylenate).* The Panel concludes that undecylenic acid and its salts (calcium undecylenate, copper undecylenate, and zinc undecylenate) are safe and effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm when used in a concentration of 10 to 25 percent.

Undecylenic acid is 10-undecenoic acid, an 11-carbon unsaturated fatty acid (Ref. *1*) which has been used topically as an antifugal agent since Peak et al. (Ref. *2*) first described its activity in 1939. It is a normal constituent of human sweat. Undecylenic acid is a yellow liquid with a characteristic unpleasant odor. It is almost insoluble in water, but is miscible with alcohol, chloroform, and ether (Ref. *1*). Undecylenic acid is most frequently used in combination with its salts (zinc, calcium, and copper). The concentration of undecylenic acid and its salts in marketed products ranges from 1.5 to 25 percent. Undecylenic acid is marketed as a powder, aerosol, ointment, solution, and gel, but is most commonly found as a dusting or aerosol powder, possibly because of its greater patient acceptance in these dosage forms.

(1) *Safety.* Years ago, undecylenic acid was administered by mouth for the treatment of psoriasis. Daily doses from 6 to 14 g produced transient adverse effects including gastrointestinal disturbances, headache, fever, dizziness, hives, folliculities, and conjunctivitis (Ref. *3*).

The LD_{50} in rats is reported to be between 2 g/kg (Ref. *4*) and 2.5 g/kg (Ref. *3*). The intraperitoneal LD_{50} is approximately 888 mg/kg (Ref. *4*). Up to 0.4 g/kg undecylenic acid in the diet of rats caused no toxicity even when continued daily for 6 to 9 months (Ref. *5*).

Undecylenic acid has a low incidence of topical irritation in humans. In 22 cases treated with undecylenate ointment, two cases of irritation were noted (Ref. *6*). Another study of 1,213 men using undecylenate powder prophylactically reported a complete lack of irritation and no adverse reactions (Ref. *7*).

A combination of 5 percent undecylenic acid and 20 percent zinc undecylenate in an ointment was applied to intact and abraded rabbit skin at a dose of 25.5 g. The area was occluded under plastic for 24 hours. Slight irritation was noted at the end of 24 hours. After 2 weeks the animals were killed and autopsied, and no evidence of organ toxicity was observed. Using the Draize test in rabbits, this same combination was rated as essentially nonirritating at a dose of 0.5 mL and was found to be slightly irritating to the rabbit's eyes at a dose of 0.1 mL (Ref. *4*).

Copper undecylenate-undecylenic acid solution was used topically to treat 28 children with ringworm of the scalp, 56 patients with dermatophytosis of the feet and hands, 6 patients with jock itch, and 5 patients with ringworm of the body. No evidence of toxicity or irritation was observed (Ref. *8*). The Panel notes that this study does not give the dose and does not indicate the degree of copper absorption or retention in the body.

The Panel concludes that undecylenic acid and its salts are safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* The minimal inhibitory concentrations of zinc undecylenate and of calcium undercylenate against laboratory strains of dermatophytic fungi were determined by broth dilution and gradient agar plate techniques (Ref. *4*). The gradient plate method is less accurate than broth dilution. *Candida* showed a minimal inhibitory concentration of 400 to 500 μg/mL by broth dilution, which should be considered resistant. Undecylenic acid was less active in these tests than the salts, but this could be a somewhat artificial result influenced by the pH of the test medium. The dermatophytes showed average values from 100 to 200 μg/mL. No data were submitted determining the antibacterial activity of the undercylenates.

A group of researchers tested the effectiveness of undecylenic acid-zinc undecylenate powder in 104 patients with athlete's foot verified by positive KOH preparation, positive culture (Sabouraud's agar), and clinical evaluation (Ref. *9*). Patients were assigned to one of four treatment groups with no substantial difference among the groups in age, sex, or race. There was also little variation in severity of disease or type of organism isolated. The types of organisms included *T. rubrum, T. mentagrophytes*, and *E. floccosum.*

The patients were treated twice daily with either 2 percent undecylenic acid and 20 percent zinc undecylenate; "old undecylenic acid powder," an OTC antifungal preparation with components similar to the undecylenic acid-zinc undecylenate preparation; or the vehicle of the undecylenate combination. A "no treatment" group was also included in the study. The patients were closely monitored for 6 weeks and evaluated with KOH preparations and cultures at 2, 4, and 6 weeks. However, there was no post-treatment examination. Two patients in the undecylenic acid-zinc undecylenate group with what was believed to be primary irritant dermatitis superimposed on allergic dermatitis were dropped from the study.

Fifty-nine percent (16/27) of the undecylenate group and 47 percent (14/30) of the "old undecylenic acid powder" group were clinically and mycologically cured after 6 weeks. This difference was not statistically

significant. However, both of these treatments resulted in a significantly higher cure rate than either the vehicle alone (4 percent) or the "no treatment" group (9 percent) ($p < 0.001$).

In another study (Ref. *7*) comparing a 20-percent zinc undecylenate-2.5 percent undecylenic acid powder aerosol with a placebo aerosol, 93 patients with clinical evidence of athlete's foot and positive KOH preparations and cultures were evaluated. Patients were randomly assigned to a treatment group; therapy was given twice daily for 2 weeks. *T. rubrum, T. mentagrophytes,* and *C. albicans* were the organisms recovered after culturing. Forty-nine percent (21/43) of the active aerosol group and 26 percent (13/50) of the placebo group were reported as showing greater than 75 percent improvement. This difference is significant at the $p < .022$ level when analysis is based on all patients in the trial. Results were also statistically significant when based on those individuals infected with *T. mentagrophytes* ($p < .012$). But results obtained from patients infected with *C. albicans* and *T. rubrum* were not significantly different from controls.

An unpublished study (Ref. *10*) examined the effectiveness of 10 percent calcium undercylenate in a talc aerosol product. Eight-two consecutive patients with jock itch, documented by clinical impression, positive KOH preparation, and positive culture, were observed in this randomized, double-blinded study. No substantial differences in the types of organisms isolated from patients in either of the groups were noted. The aerosols were used twice daily for 2 weeks, and the only other therapy was a daily soap and water wash. Weekly followups on each patient included an examination, KOH preparation, and culture. Results were presented as excellent, good, fair, or poor based on negative KOH, negative culture, and negative clinical examination. Fifty-three percent (23/43) of the patients in the active aerosol group and 5 percent (2/39) of the patients in the placebo control group were rated "excellent" (greater than 75 percent improvement) after therapy. This difference is statistically significant ($p < .001$).

The effectiveness of a 2-percent undercylenic acid-20 percent zinc undecylenate powder was compared with a 20-percent sodium propionate and talc powder in a large study on naval recruits (Ref. *7*). Patients were entered into the study after a diagnosis of athlete's foot by clinical examination. The diagnosis was not confirmed by KOH preparation or cultures. Patients received either active drug or placebo twice daily and were clinically evaluated weekly and at the end of the 10-week testing period. No followup examination after treatment was attempted. Of the 386 patients receiving the undecylenic acid powder, 76 percent (292/386) were cured or improved. A cure was defined as the absence of signs or symptoms. Sodium propionate cured or improved 47 percent (31/66). In the placebo group, 27 percent (80/297) were cured. The investigations concluded that the undecylenic acid powder was superior to the other agents tested.

In the same study, 133 patients with jock itch were treated with the undecylenic acid-zinc undecylenate powder or talc powder (Ref. *7*). Once again, neither KOH preparations nor cultures were done to confirm the diagnosis. All 50 of the patients treated with the active powder were cured or improved, whereas only 47 percent (39/83) of those treated with talc were cured. Undecylenic acid was concluded to be superior to the control.

Sulzberger and Kanof (Ref. *11*) evaluated the prophylactic activity of various topical preparations in athlete's foot. Length of treatment is unclear, but the study was run "throughout the summer." Admission to the study was based on a negative clinical examination. No KOH preparation or cultures were done. The effects of 20 percent zinc undecylenate-2 percent undecylenic acid powder, 15 percent calcium propionate-5 percent zinc propionate powder, and 20 percent sodium propionate powder were compared to no treatment in the prevention of athlete's foot. Table 5 shows the results.

TABLE 5.—PROPHYLACTIC EFFECT OF TOPICAL PREPARATIONS

Athlete's foot	Number of patients	Number and percentages new infections
No treatment	1,384	387(28%)
2% Undecylenic acid-20% zinc undecylenate	1,213	48(4%)
15% Calcium propionate-5% zinc propionate	814	64(8%)
20% Sodium propionate	135	20(15%)

Sulzberger and Kanof concluded that undecylenic acid used prophylactically reduced the incidence of infection by 85 percent. Undecylenic acid appears to be effective in the prevention of athlete's foot, but the Panel concludes that there are too many deficiencies in the study design (particularly the lack of cultures and KOH preparations) to permit a prophylactic assessment.

In a double-blind study, Roberts and Champion (Ref. *12*) evaluated 54 patients with athlete's foot, jock itch, and ringworm of the body as confirmed by positive KOH preparations or positive cultures of *T. rubrum, T. mentagrophytes,* and *E. floccosum.* Patients were treated twice daily with either 1 percent tolnaftate cream or 20 percent zinc undecylenate-5 percent undecylenic acid ointment. There was no control group. Seventy-three percent (19/26) of the tolnaftate group as compared to 68 percent (19/28) of the zinc undecylenate group were rated "good" at the end of the study. The criteria for a good rating included negative KOH, negative culture, and negative clinical examination. There was no post-treatment followup of patients. Although the authors presented no statistical evaluation of results, zinc undecylenate and tolnaftate appeared to be equally effective.

The Panel concludes that undecylenic acid and its copper, calcium, and zinc salts are effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

(3) *Dosage*—(i) *Concentration.* Undecylenic acid, calcium undecylenate, copper undecylenate, and zinc undecylenate may be used individually or in any ratio which provides a total undecylenate concentration of 10.0 to 25.0 percent.

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

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

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2. *Category I labeling*—a. *For products used for the treatment of athlete's foot, jock itch, and ringworm.* The Panel makes the following recommendations for the indications statements of products used for the treatment of athlete's foot, jock itch, and ringworm. In table 6, which follows, column A contains acceptable decriptions of product action. Column B contains acceptable phrases for specific conditions to which the product action applies. To accurately describe the indications to the consumer, one or more of the terms in Column A should be combined as appropriate with one or more of the terms in Column B.

TABLE 6.—TERMINOLOGY FOR INDICATIONS STATEMENTS

A. Product action	B. Conditions to which the product action applies
"Treats * * *"	"Athlete's foot."
For the treatment of * * *"	"Athlete's foot (dermatophytosis)."
"Cures * * *"	
"For the cure of * * *"	"Athlete's foot (tinea pedis)."
"Clears up * * *"	
"Proven clinically effective in the treatment of * * *"	"Tinea pedis (athlete's foot)."
"For effective treatment of * * *"	"Jock itch."
	"Jock itch (tinea cruris)."
"Kills * * * fungi"	
"Proven to kill * * * fungi.	"Tinea cruris (jock itch)."
	"Ringworm."
	"Ringworm (tinea corporis)."
	"Tinea corporis (ringworm)."

Based on the above lists, an example of acceptable labeling is: "Treats athlete's foot, jock itch, and ringworm."

b. *For products containing tolnaftate as a single antifungal active ingredient when used for the prevention of athlete's foot.* Table 7 contains two lists of acceptable phrases for athlete's foot prevention claims. Any one of the phrases in Column B may be inserted in any one of the phrases in Column A.

TABLE 7.—ATHLETE'S FOOT PREVENTION CLAIMS

Column A	Column B
"Clinically proven to prevent * * * with daily use".	"Athlete's foot."
"Prevents * * * with daily use".	"Athlete's foot (tinea pedis)."
"Proven effective in the prevention of * * * with daily use".	"Tinea pedis (athlete's foot)."
Helps prevent * * * with daily use".	"Athlete's foot (dermatophytosis)."
"For the prevention of * * * with daily use".	
"For the prophylaxis (prevention) of * * * with daily use".	
"Guards against * * * with daily use".	
"Prevents the recurrence of * * * with daily use".	

Based on the lists of terms in table 7, an example of acceptable labeling is: "Prevents the recurrence of athlete's foot with daily use."

The following labeling may also be used: "Clears up athlete's foot infection and with daily use helps keep it from coming back."

c. *For haloprogin, miconazole nitrate, or nystatin as single antifungal active ingredients in products used in the treatment of external feminine itching associated with vaginal yeast (candidal) infection.* Acceptable labeling is: "For the treatment of external feminine itching associated with vaginal yeast (candidal) infection."

d. *For haloprogin, miconazole nitrate, or nystatin as single antifungal active ingredients in products used in the treatment of superficial skin infections caused by yeast (Candida).* Acceptable labeling is: "For the treatment of superficial skin infections caused by yeast (*Candida*)."

e. *For products with activity against both dermatophytes and yeast.* For haloprogin or miconazole nitrate used alone or in combination, and nystatin used only in combination with up to two antifungal ingredients, the following phrases are optional:

"Kills dermatophytic fungi and yeast (causes of athlete's foot, jock itch, and ringworm)."

"Proven to kill dermatophytic fungi and yeast (causes of athlete's foot, jock itch, and ringworm)."

f. *Symptomatic relief.* Unlike other OTC products, OTC topical antifungal products treat disease rather than symptoms. Thus, symptomatic relief is the result rather than the aim of treatment.

"Relieves * * *," "for the relief of * * *," "for effective relief of * * *," and "soothes * * *" may be used with the following terms to describe the symptoms relieved by topical antifungal drug products and are to be used when appropriate only with the Category I phrases for treatment: "itching," "scaling," "cracking," "burning," "redness," "soreness," "irritation," "discomfort," "chafing associated with jock itch," "itchy, scaly skin between the toes," "* * * itching, burning feet."

Examples of acceptable labeling for symptomatic relief are: "Cures athlete's foot and relieves itching, scaling, and soreness."

"For the treatment of athlete's foot and for the relief of itching."

"For the treatment of athlete's foot; soothes itching, burning feet."

g. *Product attributes.* The Panel accepts the use of terms describing certain physical and chemical qualities of OTC topical antifungal drug products, as long as these terms do not imply any therapeutic effect and are distinctly separated from labeling indications.

Product attributes pertain to the inherent characteristics or the pharmaceutical elegance of the formulation. These properties are usually due to specific inactive (and in some cases active) ingredients included in the final product formulation. Product characteristics appear in the labeling for consumer information or product appeal and involve terms relating to the product's color, odor, and feel.

The Panel considers the following list and similar terms acceptable: "colorless," "odorless," "pleasantly scented," "greaseless," "usually does not sting," "non-staining," "drying," "cooling," "cools hot, tender feet," "helps keep feet dry."

h. *Warnings.* Labeling for all products should include the following warnings:

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

"For external use only."

Labeling for products used for the treatment of athlete's foot and ringworm should include the following warning:

"If irritation occurs or if there is no improvement within 4 weeks, discontinue use and consult a doctor or pharmacist."

Labeling for products used for the treatment of jock itch should include the following warning:

"If irritation occurs or if there is no improvement within 2 weeks, discontinue use and consult a doctor or pharmacist."

Labeling for products used for the treatment of external feminine itching associated with vaginal yeast (candidal) infection and superficial skin infections caused by yeast (*Candida*) should include the following warning:

"Do not use this product for more than 14 days without consulting a doctor or pharmacist if condition persists or recurs."

Labeling for products used for the prevention of athlete's foot should include the following warning:

"If irritation occurs, discontinue use and consult a doctor or pharmacist."

i. *Directions.* Depending on dosage form, manufacturers may vary directions for treatment or prevention, e.g., "Spray affected area * * *"

(1) *For products used for the treatment of athlete's foot, jock itch, and ringworm.* "Cleanse skin with soap and water and dry thoroughly. Apply a thin layer over affected area morning and night or as directed by a doctor. For athlete's foot, pay special attention to the spaces between the toes. It is also helpful to wear well-fitting, ventilated shoes and to change shoes and socks at least once daily. Best results in athlete's foot and ringworm are usually obtained with 4 weeks' use of this product and in jock itch with 2 weeks' use. If satisfactory results have not occurred within these times, consult a doctor or pharmacist. Children under 12 years of age should be supervised in the use of this product. This product is not effective on the scalp or nails."

(2) *For products used for the prevention of athlete's foot.* "To prevent fungal infection of the feet (athlete's foot), cleanse skin with soap and water and dry thoroughly. Apply a thin layer to feet once or twice daily, paying special attention to the toenails and the spaces between the toes. It is also helpful to wear well-fitting, ventilated shoes and to change shoes and socks at least once daily."

(3) *For products used for the treatment of external feminine itching associated with vaginal yeast (candidal) infection, and superficial skin infections caused by yeast (Candida).* "Cleanse skin with soap and water and dry thoroughly. Apply a thin layer over affected area morning and night or as directed by a doctor. If satisfactory results have not occurred within 2 weeks, consult a doctor or pharmacist."

j. *Professional labeling.* Professional labeling for any topical antifungal drug product may contain suitable information which has been approved by FDA through a new drug application for such antifungal drug. This information may be disseminated to health professionals but not to the general public.

B. *Category II Conditions Under Which Topical Antifungal Products Are Not Generally Recognized As Safe and Effective or Are Misbranded.* The safety and effectiveness of the following ingredients were classified on the basis of activity and use as antifungal agents. Ingredients that have been reviewed by the Panel and placed in Category II for antifungal effectiveness may still be included for nonantifungal purposes in formulations, providing that these ingredients are safe at the concentrations used and are in compliance with the Panel's combination policy.

The Panel recommends that the Category II conditions be eliminated from OTC topical antifungal products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

1. Category II Active Ingredients

Camphor
Canbdicidin
Coal tar
Menthol
Phenolates
  Phenol
  Phenolate sodium
Resorcinol
Tannic acid
Thymol
Tolindate

a. *Camphor.* The Panel concludes that camphor is safe but is not effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm at concentrations greater than 0.2 percent. The Panel also concludes that at concentrations less than or equal to 0.2 percent, camphor is an inactive ingredient that can be used in formulations for product identification.

Camphor ($C_{10}H_{16}O$) has the chemical formula of a ketone. Camphor is a solid, translucent, crystalline substance with a characteristic odor and an aromatic, pungent taste. Natural crude camphor is prepared by steam distilling the bark and wood of the camphor tree, *Cinnamomum camphora*, an evergreen of Southeast Asia. Synthetic camphor is produced from pinene, a hydrocarbon obtained from oil of turpentine. Camphor is relatively insoluble in water, but readily soluble in alcohol, chloroform, ether, and volatile oils.

Camphor is physically incompatible with several chemicals including menthol, phenol, thymol, resorcinol, and salicylic acid, forming a liquid or soft mass (eutectic mixture) when mixed with them (Ref. *1*).

(1) *Safety.* Most of the recorded cases of acute toxicity from camphor resulted from accidental poisoning, by taking a preparation called "camphorated oil" instead of the intended castor oil. Absorption through mucous membranes occurs rapidly, and toxic symptoms may begin shortly after ingestion. Camphor is rapidly removed from the blood by the liver, where it is conjugated with glucuronic acid. Early symptoms of poisoning include headache, excitement, nausea, vomiting, and delirium. Death occurs in servere cases as a result of convulsions and respiratory collapse (Ref. *2*).

In mice the LD_{50} intraperitoneally is 3,000 mg/kg. The intraperitoneal minimum lethal does in rats is 900 mg/kg. The toxic dose varies greatly in humans. The oral minimum lethal dose in humans is reported as 50 mg/kg (Ref. *3*). Death has occurred in children from as little as 0.75 g (Refs. *4* and *5*), but an adult has taken 20 g without harm (Ref. *4*). In fact, camphor has been given by injection intramuscularly as a respiratory stimulant in doses of 60 to 200 mg (Ref. *6*).

From the above discussion of the toxicology of camphor, the Panel concludes that camphor poses no serious problem in concentrations for 2 percent or less.

If a person used 2 g of a 2-percent camphor preparation, then the skin would be exposed to a total of 40 mg of camphor. Assuming total rapid absorption of the entire amount (certainly not likely), this would still be less than that given by injection on some occasions. The Panel therefore concludes that camphor would be safe for OTC topical use in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* When camphor is rubbed on the skin, it is a rubefacient (a substance that produces redness of the skin). When gently applied to the skin, camphor may produce a feeling of coolness caused by selective stimulation of cold-sensitive nerve endings. Camphor also has a mild local anesthetic action that may help to relieve itching. Camphor 0.5 percent is still commonly added to topical preparations as an antipruritic (an ingredient that relieves itching) (Ref. *7*). Camphor has also been used as a counterirritant in concentrations of 10 to 22 percent.

Camphor is one of the essential oils which are obtained from natural sources, usually plants. Frequently these oils are combinations of chemical ingredients including hydrocarbons, alcohols, phenols, aldehydes, ketones, acids, and esters in varying mixtures.

The antimicrobial activity of these oils does not necessarily depend on the type or concentration of the major ingredient. Their activities vary widely, making it difficult to predict either antibacterial or antifungal activity. Generally, essential oils high in phenolic compounds are the most active while the ones containing terpene are the least active. Because

most essential oils are effectively insoluble in water, other solvents must be found in order to perform in vitro tests.

Camphor has been classified as a highly active essential oil (Ref. *8*). Camphor is known to have preservative and "germicidal" activity; it may be hypothesized that camphor may well have antibacterial or antifungal activity. Mixtures of essential oils have often been used. Combining resins with these oils resulted in increased and longer lasting preservative activity. Antimicrobial activity has been indicated to be greater when camphor or other oils are not in the colloidal form.

Camphor is weakly antiseptic, but it is a poor fungicide. One in vitro study showed that a 1:1,000 aqueous dilution of camphor killed only 7 percent of various dermatophytes after 24 hours (Ref. *9*).

Further specific in vitro testing with more modern testing procedures is required before any final conclusion can be made on the antibacterial and antifungal activity of camphor.

When camphor is mixed with phenol, "an unexplained chemical reaction takes place" and phenol is converted to a "relatively innocuous material" (Ref. *10*). In 1941 a eutectic mixture containing either equal parts of camphor and phenol or 3 parts phenol and 1 part camphor was introduced for the treatment of athlete's foot (Ref. *11*). This mixture was painted between the toes for the immediate relief of itching and was said to be nonirritating. But users were warned not to apply it to wet skin because the preparation became caustic in contact with water. Although this treatment was widely publicized to cure athlete's foot after 1 week of daily applications (Ref. *12*), there was concern about the unsupervised use of the product because of its potential causticity and resulting localized necrosis. There was also concern about the potential absorption of phenol if the preparation was applied liberally and then bandaged (Ref. *13*).

Experimental studies with rabbits were done to determine the irritation potential of comphor-phenol mixtures. The mixtures were applied twice daily to clipped rabbit skin, which was then covered with gauze to simulate shoes and socks. A 1A:1 camphor-phenol mixture produced slight irritation and redness on dry skin, but severe burns and scabs were produced after the fourth application on moist skin. Application of a 3:1 phenol-camphor mixture produced a severe burn after two treatments on dry skin. This burning was even worse on wet skin. If one part of liquid petroleum was added to the 3:1 mixture, almost no irritation occurred. Warnings were again issued about the potential causticity of the camphor-phenol mixture (Ref. *14*).

In vitro studies using the camphor-phenol mixture on agar plates showed that it effectively inhibited mycelial growth and suppressed sporulation of the pathogenic fungus, *Trichophyton rosaceum (T. rosaceum)* (Ref. *15*). However, clinical trials in the early 1940's came to conflicting conclusions about the effectiveness of the 1:1 camphor-phenol mixture. In 1942, 40 soldiers in Florida with mild to moderately severe athlete's foot were treated with either Whitfield's ointment (benzoic acid-salicylic acid ointment) or the camphor-phenol mixture (Ref. *16*). No KOH preparations or cultures were taken. The results were essentially identical in each of the 20-member groups. "Cures" occurred in about 3 to 5 days with Whitfield's ointment and about 3 to 6 days with camphor-phenol. Patients preferred the camphor-phenol treatment, as it stopped the pain almost immediately, was easy to apply, did not irritate, and did not soil clothing.

In 1943, a study of 85 naval aviation students with clinical athlete's foot compared the use of camphor-phenol on the right foot with an alcoholic solution of iodine 2 percent, benzoic acid 5 percent, and salicylic acid 3 percent on the left foot (Ref. *10*). The treatments were observed to be equally effective in patients who had only scaling and peeling of the toes, with exfoliation and clinical improvement evident after 3 days of treatment. But 1 week after stopping treatment, both groups had positive cultures. The camphor-phenol mixture caused immediate tingling and anesthetizing of the skin for about 4 hours, followed by the reappearance of discomfort. Patients who initially had blistering showed no healing of tissue after 3 days of camphor-phenol treatment, and many blisters had enlarged and spread. The researchers concluded that the camphor-phenol mixture did not cure athlete's foot. Also, patients objected to the unpleasant odor of this mixture.

A controlled study of athlete's foot in 137 British soldiers was also reported (Ref. *17*). Although no cultures were performed, all subjects had positive KOH preparations before treatment. The left foot was painted four times daily with a 1:1 camphor-phenol mixture, then exposed to the air for 1 hour. The right foot was treated twice daily with the control, Whitfield's ointment containing 0.5 percent dithranol (an ingredient used to treat psoriasis). The feet were kept dry. The camphor-phenol mixture was nonirritating except for slight smarting in fissured areas, but irritation developed in many of the controls. The average time to "cure" was 4.5 days with camphor-phenol and 5.5 days with Whitfield's containing dithranol. A case was considered a failure if it did not clear within 9 days. Three failures occured in the camphor-phenol group, compared to 11 failures in the Whitfield's group.

The relapse rate, determined by examining the soldiers weekly for 3 months, was significantly less in soldiers with athlete's foot, jock itch, and ringworm of the underarm treated with camphor-phenol (1.73 percent) than with the control (6.08 percent). It was concluded that camphor-phenol was a specific remedy for dermatophytosis. Again, camphor-phenol was found to be clean and not greasy. It was also nonirritating and was easily applied. The Panel concludes that this study is not adequate proof of effectiveness of the camphor-phenol combination.

The Panel has seen no data on the effectiveness of camphor as a single antifungal ingredient. The only clinical studies are of camphor combined with phenol. The Panel concludes that camphor is not effective for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

(3) *Evaluation.* The Panel concludes that because it has seen no data on the effectiveness of camphor as a single antifungal ingredient, camphor should be placed in Category II for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. The Panel also concludes that camphor in concentrations less than or equal to 0.2 percent is safe and may be used in formulations for product identification purposes.

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b. *Candicidin.* The Panel concludes the candicidin is not generally recognized as safe and effective for the treatment of athlete's foot, jock itch, ringworm, external feminine itching associated with vaginal yeast infection, or superficial skin infections caused by yeast (*Candida*).

The Panel received only one submission on candicidin (Ref. *1*). This submission contained in vitro data but no information on safety or clinical effectiveness for the conditions listed above. Condicidin has been marketed as intravaginal tablets, capsules, and ointment for prescription use only. This ingredient has never been marketed for the treatment of extra-vaginal conditions such as external feminine itching associated with vaginal yeast infection.

The Panel concludes that because candicidin has never been marketed for the conditions discussed in this report and is not generally recognized to be effective in these conditions, it should be classified in Category II.

Reference

(1) OTC Volume 070253.

c. *Coal tar.* The Panel concludes that coal tar is not safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm and that there are insufficient data available on its effectiveness for this use.

Coal tar, a blackish-brown liquid obtained from the destructive distillation of bituminous coal, was first described in 1681 (Ref. *1*). Most coal tars produced in the United States are byproducts from coke ovens and are further refined by fractional distillation in closed retorts. Coal tar varies widely in composition depending on its source, the temperature of distillation, and type of equipment used in its production. It is a hetero-geneous mixture of tar acids and hydrocarbons which polymerize at high temperatures (Ref. *1*), forming about 10,000 different compounds of which only about 400 had been identified as of 1963 (Ref. *2*). Therapeutic coal tar is generally available as either crude coal tar or as liquid carbonis detergens, a 20-percent coal tar solution in alcohol. Coal tar has a characteristic odor similar to naphthalene. It is slightly soluble in water and partly soluble in alchohol, chloroform,, and ether (Ref. *3*).

During the 20th century, coal tar has gradually replaced other types of tar for dermatologic use, including shale tar (ichthyol) and wood tars, such as juniper tar (oil of cade) and pine tar (pix liquida). Coal tar was first used therapeutically by German, French, and English dermatologists around the turn of the century. Other tars known as pitch and asphalt had been used to treat skin diseases since ancient times (Ref. *1*).

(1) *Safety.* Although various coal tar preparations have been used to treat skin conditions for many years, documented safety data are few; for example, one submission (Ref. *4*) gave only an estimated LD_{50} for mice and rats (14.5 ml/kg). Blacow (Ref. *5*) stated that coal tar may cause irritation and acne-like eruptions of the skin. Arena (Ref. *6*) reported that coal and wood tars are photosensitizing compounds.

The composition of coal tar varies, but it generally consists of 2 to 8 percent light oils (benzene, toluene, xylene); 8 to 10 percent middle oils (phenols, cresols, naphthalene); 8 to 10 percent heavy oils (naphthalene and derivatives); 16 to 20 percent anthracene oils; and about 50 percent pitch. In such a mixture, phenol confers the highest acute toxicity potential (Ref. *7*).

Sax (Ref. *8*) classified coal tar as a slight local irritant and allergen and further stated that coal tar may contain carcinogens.

Determining the safety of coal tar is complicated by the myriad of names appearing in the older literature used to described coal tar and its preparations, e.g., coal tar, coal tar oil, tar extract, tar, coal tar distillate, crude coal tar, Brazilian tar, pityrol, and coal tar pitch. Safety assessment was further complicated by loose terminology, such as "coal tar solutions," and by the failure to specify the solvent systems.

One of the major concerns about the use of coal tar is its cancer-inducing potential. Fisher (Ref. *9*) reviewed some of the aspects of tar and its effect on the skin. He reported that tar erythema was a common effect of exposure and is provoked by sunlight acting on skin which has been photosensitized by tar or pitch. Fisher also indicated that except for the scrotum (Chinmey Sweep's cancer), the effect of tar on the skin was limited to exposed parts. He described tar keratoses as patches of rough, dirty, gray keratin with irregular outline. After building up for a few weeks, they drop off and leave white, rough patches where new patches then form.

De Moragas (Ref. *10*) said that the eruption of multiple keratoacanthomas on the exposed areas of a patient with pemphigus foliaceus (a chronic, generalized, vesicular and scaling skin eruption) treated with the Brazilian tar preparation (Jamarsan) attested to the strong carcinogenic properties of the compound. Keratoacanthomas are rapidly growing papular lesions which consist of craters filled with a horny plug. De Moragas indicated that two types of tumors occurred on the light-exposed areas of the skin. Most of the lesions had the clinical appearance of keratoacanthomas, and a few looked like verrucae filiformis (warts with soft, thin, threadlike projections on their surfaces). This report suggests that light may enhance the carcinogenic potential of coal tar.

Greither, Gisbertz, and Ippen (Ref. *11*) found 13 confirmed cases of carcinona in patients who reported using tar over many years. The most frequent use reported was for scrotal eczema. The investigators theorized that the lengthy, uncontrolled self-medication contributed to the cancer. They suggested careful medical supervison, a low tar concentration, and only periodic application of tar as the most appropriate safeguards against the risk of skin carcinoma.

Shabad et al. (Ref. *12*) suggested that the benz(a)pyrene content of a tar can serve as an indicator of the acrcinogenicity of tars and ointments. These workers found that the benz(a)pyrene concentration in wood tars varied from 0 to 338.2 $\mu g/g$, whereas the benz(a)pyrene content in coal tars was about 15 times higher (5,000 $\mu g/g$). A corticosteriod-tar ointment (benz(a)pyrene content 225 $\mu g/g$) was tested by skin application in C57xCBA mice. By the end of the 1-year treatment

period, all surviving animals had malignant skin tumors (carcinomas and sarcomas) which metastasized and were transplantable.

Linnik (Ref. *13*) studied the benz(a)pyrene content of pit coal tar used in a corticosteriod-tar ointment and found that the pit coal tar contained 5 μg/g benz(a)pyrene. The ointment containing this tar was studied in 18 mice hybrids (F, C57xCBA) by rubbing in the ointment five times weekly for 1.5 months, then three times weekly for 10.5 months. The total benz(a)pyrene dose administered in the ointment was 4.3 μg for each animal. Within 4 months, cutaneous papillomas (nonmalignant tumors) developed in two mice. One and one-half years later, 16 of 17 surviving mice had developed cutaneous neoplasms, which are new and abnormal growths of tissue. Linnik concluded that the carcinogenic activity was due to the benz(a)pyrene content of the pit coal tar.

Wallcave et al. (Ref. *14*) evaluated the carcinogenic potential of eight asphalts and two coal tar pitches of known polynuclear aromatic hydrocarbon content applied topically to Swiss mice. Thirty-one epidermal; carcinomas and 22 papillomas (benign tumors) were observed in over 90 percent of the 58 animals treated with coal tar pitch. One carcinoma and five papillomatous growths were observed in 218 mice treated with asphalts. The coal tars contained much larger amounts of polynuclear aromatic hydrocarbons than the asphalts. The investigators also suggested that some aromatic hydrocarbons played a prominent role in carcinogenesis.

Hirohata et al. (Ref. *15*) evaluated the carcinogenicity of a variety of tar-containing skin preparations. Chemical analysis of aromatic hydrocarbons was performed on each product. It was found that carcinogenic activity correlated with the benz(a)pyrene content of the preparation.

These reports dealing with the carcinogenicity of coal tar preparations suggest to the Panel that there is a very real potential for certain coal tars to induce skin cancer. The reviewed literature also appears to strongly substantiate this concern. These specific questions remain to be answered: (1) What specific ingredients are carcinogenic; (2) What period of time is involved; (3) Are other factors involved in the carcinogenic process?

In addition to carcinogenisis, a variety of other skin reactions to coal tar have been reported in the literature from 1965 to the present. Most of these are not life threatening, but can be quite irritating topically. One of the more commonly noted effects of coal tar on the skin is a phototoxic effect. Kaidbey and Kligman (Ref. *16*) and Burckhardt and Schmid (Ref. *17*) are among several who have noted the role of coal tar in photosensitization. The reported reactions range from mild to severe; the reactions, to an extent, are strongly influenced by the vehicle (Ref. *16*).

It has been reported that coal tar preparations may actually cause skin problems, some of them similar to conditions being treated. Hitch (Ref. *18*) has reported an acneform (resembling acne) eruption at the site of contact to oils and tars. Characteristics that distinguish this drug-induced reaction from acne include age of patient, sites of eruption, and history of exposure to oils and tars. Kaidbey and Kligman (Ref. *19*) also reported a dose-related acnegenic effect of crude coal tar or distilled coal tar. These investigators noted lesions of the inflammatory papulopstular type appearing in whites, while in blacks, small open comedones (blackheads) appeared. Stankler (Ref. *20*) noted that tar preparations are messy and can cause irritation, folliculitis, and dermatitis. In a patient with psoriasis tar preparations may also precipitate generalized pustular psoriasis.

Several other investigators have attested to the varying degrees of severity of dermal irritation produced by coal tar use.

Stone (Ref. *21*) noted that 5 percent crude coal tar produced a 45.9-percent delay in wound healing in animals. He suggested that this delay may have resulted from the direct effect of the tar on the wound or because tar increases the severity of infections.

The Panel has carefully reviewed the recorded toxicity of industrial and medicinal coal tar. In view of the reported scrotal cancers (Ref. *9*), the animal carcinogenicity of coal tar, and the potential for long-term use in athlete's foot, jock itch, and ringworm, the Panel concludes that coal tar is not a safe OTC topical antifungal drug for these indications.

(2) *Effectiveness.* The antibacterial activity of a large class of coal tar disinfectants depends on phenol homologues, with a variety of substituted groups added onto the phenol. Certain kinds of soap solubilize the components in these coal tar disinfectants, thus increasing their activity. No in vitro data were submitted for coal tar, but it could be expected that a large portion of the coal tar component may be neutral oils. As the proportion of neutral oils incrases, the antibacterial activity decreases. Lacking other data, one would have to assume minimal, if any, antibacterial or antifungal activity for these compounds.

Coal tar is generally used in concentrations of 0.5 to 5.0 percent in ointments, creams, and shampoos. In the dilute concentration of 0.1 percent, it is astringent (Ref. *22*). At 2 to 4 percent concentraions it is antipruritic, and in concentrations of 6 to 20 percent, it is keratoplastic, causing thickening of the upper layers of the skin (Ref. *23*). Coal tar is rarely used in concentrations above 10 percent because of frequent irritation of hair follicles resulting in folliculitis.

At present, coal tar is commonly used to treat skin conditions such as psoriasis, seborrhea, and atopic dermatitis, while it is rarely prescribed for treatment of fungal skin infections. In 1956, however, crude coal tar (2 to 50 percent) in a base of lanolin and petrolatum was still listed in a major dermatology textbook (Ref. *24*) as one of several possible treatments for unresponsive tinea, being described as "messy but effectively antiparasitic, rarely irritating."

The earliest use of coal tar for fungus infections is uncertain, but in the late 1800's unspecified types of tar were mentioned as being useful in the treatment of ringworm (Ref. *25*) and jock itch (Ref. *26*). In 1917, a coal tar paint composed of equal parts of tar, acetone, and flexible collodion was reported to be successful in treating a case of jock itch, diagnosed with positive skin scrapings. The authors reported that itching was relieved within 1 hour and skin lesions leared in 2 days, although they recurred after 10 days (Ref. *27*). However, no culture was reported. A similar coal tar paint (or varnish), which was applied thickly to the skin with a cotton swab then dusted with talcum powder, was still used in 1942 for the treatment of chronic dermatophytosis of the hands and feet (Ref. *28*).

The first major experience with crude coal tar in the United States was reported by White (Ref. *29*) in 1921. White treated several skin diseases with a 5-percent concentration of coal tar in an ointment base of petrolatum, cornstarch, and zinc oxide. This coal tar ointment was reported to be of "distinctive benefit" in treating two phases of epidermophtosis: (1) moist eczematoid conditions with uncomfortable, raw, red areas (not specified as to feet or groin), and (2) chronically itchy and thickened scaly patches on the upper thighs (jock itch). The author recognized that the coal tar was mainly soothing and palliative and recommended it be followed by

treatment that would more effectively destroy the fungus.

The same coal tar formula used by White (Ref. *29*) was cited in textbooks appearing in 1925 (Ref. *23*) and 1942 (Ref. *28*) as being useful. Additional ingredients used in combination with coal tar included phenol (purported to make the product more soothing) (Ref. *23*) and an alkali, such as potassium subcarbonate (included to soften and remove the outer horny layer of skin) (Ref. *30*).

In contrast to White's advice (Ref. *29*), several authors have cautioned against using coal tar on the irritated, weeping skin lesions that sometimes occur in dermatophyte infections of the feet and groin (Refs. *1* and *28*). These investigators felt that coal tar may unduly irritate skin which is already inflamed, although no evidence was presented to substantiate this concern.

Evidence that tar will irritate skin infected with bacteria was supplied by Stone and Willis (Ref. *31*). A 5-percent crude coal tar ointment in a base containing 94 percent petrolatum and 6 percent cholesterol esters applied to the skin of rabbits which had previously been injected with bacteria (*Micrococcus*) caused induration (redness and thickening) of the skin. After 24 hours, skin induration measured 12.7 mm at the tar-treated sites, compared with 4.3 mm at sites treated with the base alone.

The Panel concludes that the inclusion of coal tar in antifungal medications is mainly of historic interest. To the Panel's knowledge, there are no controlled studies demonstrating the clinical effectiveness of coal tar for treating either athlete's foot, jock itch, or ringworm.

(3) *Evaluation.* The Panel concludes that coal tar should be placed in Category II for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

In view of the abundant data demonstrating a carcinogenic potential of crude coal tar or preparations from crude coal tar containing aromatic hydrocarbons, and a lack of data supporting antifungal effectiveness, the Panel concludes that the small benefit and serious risk incurred from coal tar does not justify its use in the treatment of athlete's foot, jock itch, and ringworm.

Also, there are no double-blind, controlled clinical studies supporting the effectiveness of coal tar for the treatment of athlete's foot, jock itch, or ringworm. It appears that the inclusion of coal tar in antifungal medications is mainly of historic interest.

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d. *Menthol.* The Panel concludes that menthol is not effective and that there are insufficient data available to determine its safety at concentrations greater than 0.2 percent for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. The Panel also concludes that at concentrations less than or equal to 0.2 percent, menthol is an inactive ingredient that can be safely used in formulations for product identification.

Menthol (peppermint camphor) is an alcohol which is either extracted from peppermint or other mint oils or prepared synthetically. It consists of colorless, hexagonal needlelike crystals with a pleasant, minty odor and cool taste. Menthol is only slightly soluble in water, but is very soluble in alcohol, either, and chloroform. Chemically incompatible with camphor, phenol, thymol, resorcinol, and other substances, menthol forms a liquid or soft mass when mixed with them (Ref. *1*). In currently marketed products, menthol is present in a concentration of 0.1 to about 125 percent.

(1) *Safety.* In rats the oral LD_{50} is 3,180 mg/kg, and the lowest lethal dose

subcutaneously is 2,000 mg/kg. In humans, the lowest lethal oral dose is reported to be 50 mg/kg (Ref. *2*).

Toxic effects in humans from excessive ingestion of mentholated products can include nausea, vomiting, abdominal pain, flushed face, and symptoms of central nervous system depression, such as dizziness, staggering gait, sleepiness, slow respiration, and coma (Ref. *3*). The fatal dose of menthol in humans is approximately 2 g (Ref. *4*).

Menthol may cause hypersensitivity reactions including contact dermatitis in certian individuals. Symptoms include hives, erythema, and other cutaneous lesions. However, the sensitization index is low. Nasal drops containing menthol may cause spasm of the glottis in young children. Cases of dangerous asphyxia from menthol have been reported in infants following such local application (Ref. *4*).

The Panel considers the following data necessary to establish the safety of menthol: (1) absorption from small areas of application to broken and intact skin; (2) local effects on wound healing; and (3) potential for hypersensitivity or idiosyncratic reactions.

The Panel concludes that more data are needed to determine the safety of menthol in concentrations greater than 0.2 percent for OTC topical application in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* Menthol in concentrations of 0.1 to 2 percent is usually added to topical medications to produce a counterirritant effect on the skin, with resulting antipruritic and mild analgesic actions (Ref. *1*.). Menthol stimulates nerve endings, thus inducing a feeling of refreshing coolness on the skin. This feeling may temporarily bring great comfort, but is often later replaced by sensations of heat, tingling, and slight pain, resembling the reestablishment of circulation after a limb has been "asleep". Menthol 2 percent was added to dusting powders recommended in the past for the treatment of fungal infections (Ref. *5*).

Menthol is a poor fungicide. At a 1:1,000 dilution, menthol killed no dermatophytes after a 60-minute exposure and only 21 percent of dermatophyte cultures after a 24-hour exposure (Ref. *6*). Dermatophytes were also not inhibited in vitro by a powder containing 2 percent menthol in talc (Ref. *7*). However, a 1:250 dilution of menthol (in a base containing alcohol, glycerin, ethylene glycol, soap, and water) was bactericidal to *Staphylococcus albus* (*S. albus*) and *Bacterium typhosus* (*B. typhosus*) in 2.5 minutes. A similar 1:750 dilution of menthol was bactericidal to the same organisms in 15 minutes (Ref. *8*). From these results the phenol coefficent for menthol was calculated to be 5.1.

Although menthol may be useful in providing symptomatic relief of fungal infections through its antipruritic action, the Panel concludes that it is not an effective antifungal ingredient.

(3) *Evaluation.* The Panel has placed methol in concentrations greater than 0.2 percent in Category II because no controlled, clinical trials have been performed on this ingredient to determine its effectiveness in the treatment of athlete's foot, jock itch, and ringworm. Also, the limited in vitro data available show menthol to be a poor fungicide. The Panel concludes that menthol in concentrations less than or equal to 0.2 percent is safe and may be used in formulations for product identification purposes.

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e. *Phenolates (phenol and phenolate sodium).* The Panel concludes that the phenolates (phenol and phenolate sodium) are not effective and that there are insufficient data available on their safety in concentrations less than or equal to 1.5 percent for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Phenol is hydroxybenzene and was discovered in coal tar in 1834 by Ringe who named it "carbolic acid." It was also once called phenic acid. Originally produced through the dry distillation of hardwoods and coal, it is now produced synthetically from benzene (Ref. *1*). In 1865 Lister began to use carbolic acid for the prevention and treatment of sepsis. He sprayed it in operating rooms, cleansed the skin with it before surgery, and applied it in wound dressings (Ref. *2*). Phenol soon gained wide acceptance as a disinfectant for sanitary, medical, and surgical purposes, and was adopted as a standard for comparison of disinfectant power. The phenol coefficient expresses the ratio of killing effectiveness of a disinfectant as compared to phenol under standard test conditions against the same bacteria (Ref. *1*). Today phenol has been largely replaced by more effective and less toxic compounds (Ref. *3*).

Phenol consists of colorless to light pink, needle-shaped crystals which gradually darken on exposure to light and air. It has a distinctive aromatic odor. Phenol contains not less than 98 percent C_6H_5OH, while liquefied phenol USP contains 10 percent water (1 g of phenol dissolves in 15 g of water). Phenol is very soluble in alcohol, ether, glycerin, and volatile and fixed oils (Refs. *1* and *3*). When combined with camphor, menthol, resorcinol, or thymol, it forms a liquid or soft mass (Ref. *1*). Since the pka of phenol is 10.0 at 25° C (Ref. *4*), the phenolate ion will predominate only at extremely alkaline pH. Therefore, for the purpose of the present discussion, only un-ionized phenol need be considered.

Pheonlate sodium (C_6H_5ONa), also known as sodium phenoxide, sodium carbolate, and sodium phenate, is the sodium salt of phenol. It is a white to reddish deliquescent substance composed of rods or granules. It is soluble in water and alcohol. Aqueous solutions are strongly alkaline and caustic (Ref. *4*).

The Panel considers phenol and phenolate sodium to be a single ingredient when both are contained in a product formulation. The total level of phenol and phenolate sodium is expressed as percent phenol.

(1) *Safety.* The toxicology of phenol has been extensively reviewed in the literature (Ref. *5*). The potential toxicity of phenol in concentrations greater than 1.5 percent was described by the Advisor Review Panel on OTC Antimicrobial I Drug Products in the Federal Register published September 13, 1974 (39 FR 33121). The Advisory Review Panel on OTC Antimicrobial II Drug Products agrees that phenol is toxic in aqueous or alcoholic solutions in concentrations greater than 1.5 percent.

In rats the oral LD_{50} of phenol is 414 mg/kg; the topical LD_{50} (by skin absorption) is 669 mg/kg. In humans the minimum lethal oral dose is 140 mg/kg (Ref. *6*).

According to Goodman and Gilman (Ref. *7*), "Phenol is absorbed by all

routes of administration and can reach the circulation even when applied to the intact skin." Ingestion of even small amounts may cause nausea, vomiting, circulatory collapse, tachypnea, (excessively rapid respiration), paralysis, convulsions, coma, greenish or smoky-colored urine, necrosis of the oral tissue and gastrointestinal tract, jaundice, and death (Ref. *4*). In fatal cases, death usually occurs in less than 2 hours as a result of respiratory failure, although occasionally cardiac arrest is the cause (Ref. *3*).

Concentrated solutions are toxic and cause death if ingested. Phenol has been used for suicide and is a common cause of accidental poisoning. The symptoms of toxicity usually develop rapidly and death has occurred within 2 or 3 minutes after ingestion. The average fatal dose of phenol is 15 g, but death has been reported following the ingestion of as little as 1.5 g. Conversely, recovery has followed the ingestion of as much as 30 g (Ref. *3*).

Systemic absorption causes central nervous system effects seen as a momentary stimulation followed by a depression of the central nervous system. The blood pressure falls, partly because of central vasomotor depression out mainly because the myocardium and the smaller blood vessels are affected by a direct toxic action of phenol (Ref. *7*).

Mild to severe signs of systemic poisoning have been reported following application of 2 or 3 percent aqueous solutions of phenol to open wounds. In mice, aqueous solutions of phenol too dilute to cause local irritation were absorbed through the skin in a quantity sufficient to cause systemic poisoning (Ref. *5*). Absorption through the skin depends on the area exposed rather than on the concentration applied (Ref. *3*).

When phenol is applied derectly to the skin, it forms a white film of precipitated protein. This turns red and eventually sloughs. Phenol that remains in contact with the skin penetrates deeply and may cause extensive necrosis. Phenol exerts a local anesthetic action. A 5-percent solution produces almost complete local anesthesia, but is irritating to exposed tissue and may also cause necrosis (Ref. *7* and *8*).

Even though dilute solutions of phenol (up to 3 or 4 percent) are only mildly irritating (Ref. *3*), even lower concentrations have not been shown to be totally safe. A 1-day-old baby died 11 hours after application of a 2-percent solution on an umbilical bandage. Another baby, aged 6 days, was treated for a skin ulcer with phenol-camphor complex (strength not given) and developed cirulatory failure, cerebral intoxication, and methemoglobinemia which required exchange blood transfusion (Ref. *9*). This author suggested that even greatly diluted phenol was a dangerous material to apply to the skin.

Gosselin et al, (Ref. *2*) reported that "much evidence exists to suggest that in man phenol may be considerably less toxic by mouth than by absorption from wounds, body cavities, or even intact unbroken skin. The safest viewpoint is to regard any amount of phenol as dangerous." The major hazard of phenol poisoning is its systemic effects. Gosselin et al. also stated that severe or fatal phenol poisonings have occurred after topical exposure, suggesting a hypersensitivity or idiosyncratic reaction. They cite two cases of collapse from 5 percent carbolic acid compresses. Although phenol poisoning begins very abruptly, the intoxication's dangerous phase is usually complete in 24 hours.

Deichmann (Ref. *5*) reviewed the literature on phenol toxicity before 1948 and gave an excellent summary of the toxicity potential of dilute aqueous preparations of phenol. Dilute solutions of from 1 to 5 percent phenol when used as wet compresses over a period of time have caused gangrene of the extremities, as well as systemic toxicity when applied to open wounds or large body areas.

The Panel is not aware of any more recent research on the use of dilute solutions of phenol. Therefore, there is still an open question on the safety of dilute aqueous or alcoholic solutions when applied to small body surfaces once or twice daily. But there is no doubt that such dilute solutions are absorbed and have a local effect. Deichmann says of Freystadtl's findings, "five minutes of contact of 2 percent aqueous phenol with the human skin affected the sensations of cold, touch, pain, and heat." From this one can conclude that sufficient phenol was absorbed to affect local nerve endings.

The Panel received no data on the effect of dilute solutions of phenol on broken skin, such as might be the case with athlete's foot, jock itch, or ringworm. In most reports of toxicity from dilute solutions of phenol, bandaging the application was necessary to produce severe local changes (Ref. *5*). Using phenol in athlete's foot, jock itch, and ringworm would be similar to using it under a bandage because the affected areas would be covered by clothing.

Based on the above review, the Panel concludes that there are insufficient data on the safety of aqueous or alcoholic solutions of phenol in concentrations less then or equal to 1.5 percent. Specifically lacking are controlled studies evaluating (1) the absorption from small areas of application to either broken or intact skin, (2) the local effects on wound healing, and (3) the potential for hypersensitivity or idiosyncratic reaction.

(2) *Effectiveness.* Phenol, in concentrations of 1 to 2 percent, has frequently been added to aqueous solutions, ointments, and creams for its antipruritic effects (Ref. *1*), although 0.5 to 1.0 percent phenol is now more commonly used (Ref. *10*). In 3 to 4 percent solutions, phenol is mildly irritating but actively anesthetic to skin (Ref. *3*). A 15-percent phenol solution in alcohol has marked irritant and anesthetic action on skin, inducing local redness and edema after 10 minutes of contact (Ref. *5*). Liquified phenol (80 percent phenol in water) is widely used as a superficial skin caustic (Ref. *10*).

In products submitted to the Panel, phenol was incorporated in aqueous, ointment, and powder vehicles. The vehicle is crucial to phenol's activity. For instance, an in vitro study in 1933 showed that 2 percent phenol ointment, also called carbolic acid ointment and "antiseptic ointment," was not bactericidal against *Staphyococcus aureus (S. aureus)* using agar plate tests (Ref. *11*) The ointment base consisted of petrolatum or a combination of petrolatum and anhydrous wool fat (lanolin). In contrast, 2 percent phenol in water-miscible bases, such as vanishing cream, did show zones of inhibition against *S. aureus* in agar plate tests (Ref. *12*). In aqueous and alcoholic solutions, phenol is bacteriostatic in concentrations of 1:800 (Ref. *3*). In another source, phenol was reported to be bacteriostatic in a 1-percent strength (Ref. *10*). It is absorbed by bacterial cells and combines and denatures the cell proteins Ref. *13*).

Reports of in vitro studies vary widely in describing fungicidal concentrations of phenol. Rook, Wilkinson, and Ebling (Ref. *10*) reported phenol to be fungicidal in a concentration of 1.3 percent. Golden and Oster (Ref. *14*) determined the minimal fungicidal concentration of phenol dissolved in 95 percent alcohol against cultures of *T. mentagrophytes* to be 9 percent against 5-day cultures, 15 percent against 10-day cultures, and greater than 15 percent against 15-day and 20-day cultures. In another study, concentrations of 0.7 to 1.0 percent phenol were fungicidal for several dermatophyte fungi (Ref. *15*).

Other, much older studies found fungicidal dilutions of phenol to be 1:25 for *T. rosaceum* and 1:100 for *M. audouinii* (Ref. *16*). Another source listed 1:70 for *T. rosaceum* (Ref. *17*). O'Brien and Bonisteel (Ref. *18*) reported that phenol 2 percent in a petrolatum ointment base had little or no activity against *T. interdigitale*. Riley and Flower (Ref. *19*) reported that phenol 5 percent also has antifungal activity after 48 hours against *C. albicans* in a 1:25 dilution, but not a 1:50 dilution. O'Brien and Bonisteel further reported that phenol 2 percent in petrolatum ointment did not inhibit *M. albicans*, whereas in cold cream or vanishing cream it was slightly fungistatic against *M. albicans* (Ref. *18*).

Phenol has not been widely used as an antifungal agent to treat dermatophytic fungal infections. Carbolic acid mixed with equal parts of glycerin was mentioned in 1881 as a treatment for ringworm of the scalp, but was thought to be to irritating and toxic (Ref. *20*). In the 1940's, equal parts of phenol and camphor were popularized as an athlete's foot remedy. (See part III, paragraph B.1.a. above—Camphor.) Despite warnings about potential toxicity from this mixture, at least one death resulted from its application. An 18-year-old man died of acute pulmonary congestion within a few minutes of applying a mixture of 1:4 camphor-phenol to a 60-square inch area of raw, inflamed ringworm on the trunk (Ref. *21*). The inflamed skin was believed to have helped induce the rapid absorption of phenol, which led to acute phenol poisoning.

In 1946, Hopkins et al. (Ref. *22*) tested various fungicides including DN phenol (2,4, dinitro-ortho-cyclohexyl-phenol) and trichlorophenol in soldiers at Fort Benning who had athlete's foot verified by positive KOH preparations. The fungicides were used in various concentrations and vehicles. In these studies no control subjects using the vehicle alone were included. No cultures were performed after treatment, and no lag period following treatment was included. Table 8 shows the results for DN phenol and trichlorophenol:

TABLE 8.—DN PHENOL AND TRICHLOROPHENOL AS FUNGICIDES

	Time period		
	1 to 2 weeks	3 to 4 weeks	4-plus weeks
Trichlorophenol			
Clinically cleared	27 (18%)	34 (47%)	22 (51%)
KOH negative	90 (59%)	53 (73%)	34 (79%)
Total number of cases	152	72	43

TABLE 8.—DN PHENOL AND TRICHLOROPHENOL AS FUNGICIDES—Continued

	Time period		
	1 to 2 weeks	3 to 4 weeks	4-plus weeks
DN phenol			
Clinically cleared	73 (18%)	116 (49%)	92 (72%)
KOH negative	235 (58%)	192 (81%)	114 (89%)
Total number of cases	405	237	128

The best results were seen with a 10-percent DN phenol solution in alcohol and propylene glycol, although 5 to 20 percent concentrations were also tested. Irritation was noted in 13 percent of the soldiers treated with DN phenol. Fifteen percent of those treated with trichlorophenol showed irritation; 1 percent had severe irritation. Trichlorophenol was concluded to be rapidly fungistatic, but often too irritating, particularly in concentrations greater than 1.0 percent.

(3) *Evaluation.* The Panel concludes that phenol and phenolate sodium should be placed in Category II for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. It agrees with the "United States Dispensatory" (Ref. *3*) which says: "Phenol has had some use as a fungistatic agent, but other agents are considered more effective and less toxic." The Panel also agrees with Reddish's (Ref. *23*) assessment which states that "other derivatives of phenol have been suggested for the treatment of dermatiphytosis. Most of them, however, have been abandoned or were very short-lived, because of either insufficient activity or excessive skin irritation." The Panel concludes that the use of phenol for athlete's foot, jock itch, and ringworm is outdated, irrational, and potentially dangerous. The in vitro concentrations required for effective antifungal action often exceed a 1.5-percent concentration of phenol. In fact, one study (Ref. *14*) demonstrated that a phenol concentration of 15 percent or greater was necessary to kill cultures of *T. mentagrophytes*, a fungus frequently seen on the feet and in the groin. The Panel further concludes that the symptomatic antipruritic relief which would be offered by the inclusion of phenol does not justify the potential risks of skin irritation or systemic toxicity that may result from the topical application of phenol.

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f. *Resorcinol.* The Panel concludes that resorcinol is not safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm and that there are insufficient data available on its effectiveness for this use.

The chemical name of resorcinol is 1,3-benzenediol. Resorcinol is a white powder and belongs to the phenolic group of chemicals. It was disovered in 1863, synthesized in 1868, and used dermatologically in 1884. Soluble in water, alcohol, ether, and fats, resorcinol is a strong reducing agent in alkaline solution (Ref. *1*). Resorcinol forms a liquid or softens when mixed with camphor, menthol, or phenol. Upon exposure to the air, resorcinol turns pink and may discolor skin or light-colored hair (Ref. *2*).

(1) *Safety.* Resorcinol, like phenol, is a protein precipitant. The compound resembles phenol in its systemic actions except that resorcinol causes more prominent central stimulation (Ref. *3*). The Panel received only one product submission containing resorcinol in the rather high concentration of 10 percent. Overall, the data available on the toxicity of resorcinol are scarce and of poor quality. One source reports the acute oral LD_{50} of resorcinol in the rat to be 980 mg/kg (Ref. *4*). Another source listed 301 mg/kg as the acute oral LD_{50} in the rat (Ref. *5*). This source also listed the following lowest published lethal doses of resorcinol given subcutaneously: 340 mg/kg in the mouse; 400 mg/kg in the rat and guinea pig; but only 110 mg/kg in the cat.

Gosselin et al. (Ref. *6*) reported that resorcinol has a toxicity rating similar to phenol but that convulsions are more prominent with resorcinol. Deichmann and Gerarde (Ref. *7*) suggested that if percutaneous absorption of resorcinol should occur, the resulting effects may include edema, necrosis, methemoglobinemia, respiratory difficulty, convulsions, and even death. These investigators reported the probable lethal adult oral dose of resorcinol to be about 2g.

Blacow (Ref. *8*) reported that resorcinol may be absorbed through the skin or from ulcerated surfaces and that prolonged use may lead to myxedema (severe hypothyroidism) due to the antithyroid action of the drug. He suggested that resorcinol could be a dangerous drug when applied over large surfaces of skin, especially when used in high concentrations.

Stenback and Shubik (Ref. *9*) reported on a study dealing with the toxicity and carcinogenicity of a number of topically applied chemicals, including resorcinol. Fifty 7-week-old female mice were used for each tested concentration of the chemicals. The chemicals were dissolved in acetone, and 0.02 mL was dropped on shaved skin between the animals' flanks twice weekly for the life of the animals. The mice were examined weekly for lesions and tumors. Complete autopsies were performed and grossly observed tumors studied histologically. Animals treated with 50 percent, 25 percent, and 5 percent concentrations of resorcinol developed skin lesions with ulceration, inflammation, and hypeplasia. Two skin tumors and one subcutaneous fibrosarcoma were noted. These results were not statistically significant when compared to the control group.

Even though Blacow (Ref. *8*) reported that resorcinol may be absorbed through the skin or ulcerated surfaces, no data were presented. The Panel therefore cannot determine the degree of absorption. Certainly it woud be expected that some resorcinol would be consumed in its role as a protein precipitant and that this precipitated protein may even then prevent further absorption. Without data, however, this is pure speculation.

In view of the lack of data on the absorption characteristics of resorcinol, the Panel is concerned about the relatively high concentration currently marketed (10 percent) and the total amount that might reach systemic circulation, where it may have even more prominent effects than phenol. The Panel believes that the minimal antifungal benefits of resorcinol do not warrant the potentially high risk of using it in a 10-percent concentration to treat athlete's foot. A lower concentration may prove to be entirely safe, but no data were presented to allow the Panel to estimate a safe level.

(2) *Effectiveness.* Resorcinol is used topically for its antibacterial, antifungal, and local irritant effects on skin (Ref. *2*). In vitro studies (Refs. *10* and *11*) have shown resorcinol to be a rather weak fungistatic and fungicidal agent. When a 1:25 dilution of 5 percent resorcinol was tested against *C. albicans*, slight growth was observed, but a 1:50 dilution allowed abundant growth after 48 hours (Ref. *10*). Resorcinol was found to be fungistatic but not fungicidal against dermatophytic fungi at dilutions of 1:200, 1:300, and 1:1,600 tested against *T. rosaceum, M. audouinii*, and *Achoriin schoenleinii* (*A. schoenleinii*), respectively (Ref. *11*).

The pharmacologic action of resorcinol varies markedly with its concentration. Resorcinol is antipruritic in 0.5 to 3 percent solutions and in ointments containing up to a 5-percent concentration (Ref. *12*). Resorcinol is also keratoplastic in 1 to 3 percent concentrations (Ref. *1*) and keratolytic in 10 to 50 percent concentrations (Ref. *12*). The keratolytic action of resorcinol in 10 percent and 15 percent concentrations in various ointment bases is identical, implying that resorcinol is mildly caustic (Ref. *1*). Resorcinol is usually used in concentrations of 5 percent in ointments, pastes, gels, and lotions, although concentrations from 1 to 20 percent are also used (Ref. *2*) Compound Resorcinol Ointment NF XIII contains 6 percent resorcinol (Ref. *13*).

Several old dermatology textbooks mention the use of resorcinol for dermatophytic fungal infections. In 1907, Whitfield recommended 10 percent resorcinol in alcohol or water for the treatment of ringworm of the groin (Ref. *14*). He described this concoction as very irritating, but "prompt, cleanly, and effective." A later book listed a similar but less concentrated solution of 3 to 6 percent resorcinol in water for the treatment of jock itch (Ref. *15*). A 1932 textbook mentioned resorcinol ointment or lotion in concentrations of 2 to 5 percent for the treatment of ringworm of the palms and soles (Ref. *16*).

In the early 1940's resorcinol 0.25 to 2 percent was used as a wet dressing for treating the acute blistering an oozing states of dermatomycoses. In the concentration of 1:1,000 it was used as a daily footbath for "obstinate" cases of athlete's foot (Ref. *17*). Another book listed resorcinol ointment 2 to 10 percent as a keratolytic for use about the face, but it was not specifically recommended for use in fungus infections (Ref. *18*). Resorcinol 10 percent was still being listed in 1975 for treating athlete's foot, probably because of its mildly keratolytic action (Ref. *2*).

The Panel knows of no clinical studies demonstrating the effectiveness of resorcinol as an antifungal ingredient. It therefore concludes that resorcinol is of questionable effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

(3) *Evaluation.* The Panel has seen no data on the percutaneous absorption of resorcinol. The literature has proven vague on whether systemic toxicity has ever been observed from the topical application of resorcinol on intact or broken skin. The Panel is concerned that the 10-percent concentration of resorcinol in the currently marketed product may far exceed the concentration actually needed to produce the desired therapeutic effect. At a lower concentration resorcinol could possibly be safe and effective in the treatment of athlete's foot, jock itch, and ringworm. However, without data this is pure speculation.

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g. *Tannic acid.* The Panel concludes that tannic acid is safe but is not effective for OTC antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Tannic acid, also known as tannin, occurs in the bark and fruit of many plants, especially in the bark of oak trees. It is also a naturally extractable material from tea and coffee. It is prepared commercially by extraction from nutgalls.

Tannic acid appears as yellowish-white to light brown, amorphous, bulky powder or flakes with a faint characteristic odor and astringent taste. It is very soluble in water, alcohol, and acetone and pratically insoluble in organic solvents such as chloroform, ether, and benzene (Ref. *1*).

(*1*) *Safety.* Tannic acid has been widely formulated as a component of topical ointments, gargles, irrigation solutions, lotions, lozenges, and mouthwashes. Tannic acid precipitates proteins and forms insoluble complexes with some alkaloids and glycosides. It is because of the latter property that tannic acid gained use orally as an antidote for ingested alkaloids and glycosides (Ref. *2*).

Tannic acid has little action on intact skin. When applied to abraded tissue, however, it precipitates protein to form a protective film on the surface of the wound. This is why tannic acid was formerly used extensively in burn treatment (Ref. *3*).

The oral LD_{50} of tannic acid in rabbits is 5,000 mg/kg (Ref. *4*). In veterinary medicine, the drug is used topically as a hemostatic astringent (Ref. *5*).

Systemically, tannic acid causes liver toxicity; tannic acid in barium enemas reportedly has the potential to induce liver damage and even death (Ref. *2*). The lowest published oral lethal dose of tannic acid in humans is 500 mg/kg (Ref. *4*).

The Panel is mindful of the potentially hepatotoxic effect of tannic acid. Nevertheless, it concludes that topically used tannic acid is more likely to interact with surface proteins so extensively that even when used on the fissured areas of athlete's foot, percutaneous absorption of tannic acid is unlikely. The Panel therefore concludes that tannic acid is safe when used topically in the treatment of athlete's foot, jock itch, or ringworm.

(2) *Effectiveness.* As a vegetable astringent, tannic acid has little action on intact skin, but, as stated above, precipitates proteins locally on the surface of abraded skin to form a mechanically protective tannate film (Ref. *3*). Tannic acid has been used as a styptic and astringent in concentrations of 1 to 20 percent (Ref. *6*).

The Panel found no in vitro data on tannic acid.

The only references known to the Panel on the use of tannic acid in fungal infections are dermatology textbooks from the early 1940's. During this period, tannic acid was used to treat hyperhidrosis, sometimes associated with athlete's foot (Refs. *7* and *8*). Five percent tannic acid was used along with zinc peroxide, boric acid, bentonite, and talc in a foot powder. Tannic acid was also combined with menthol, phenol, glycerin, and alcohol and used as a tincture to relieve itching (Ref. *7*).

A 2-percent tannic acid aqueous soak was used to help "hasten epithelialization" in the subacute phase of dermatophytosis of the hands and feet (Ref. *8*). A 5-percent aqueous solution was used to treat athlete's foot associated with a "great deal of weeping and oozing" until the acute manifestations subsided (Ref. *9*). After the acute skin lesions were largely healed, markedly hyperhidrotic cases of athlete's Foot were sometimes treated once daily with a dusting powder containing equal parts of tannic acid, zinc oxide, and boric acid. The powder was to act as an antiperspirant and astringent (Ref. *8*).

Based on the above review, the Panel concludes that the inclusion of tannic acid in antifungal medications is largely of historical interest. The Panel knows of no studies demonstrating either antifungal activity in vitro or clinical effectiveness of tannic acid as an antifungal agent in the treatment of athlete's foot, jock itch, or ringworm. The Panel therefore concludes that tannic acid is not effective for the treatment of these conditions.

(3) *Evaluation.* The Panel concludes that because it has found no in vitro or clinical data on the effectiveness of tannic acid, this ingredient should be placed in Category II for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

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h. *Thymol.* The Panel concludes that thymol at concentrations greater than 0.2 percent is not effective and that there are insufficient data available to determine its safety for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. The Panel also concludes that at concentrations less than or equal to 0.2 percent, thymol is an inactive ingredient and can be safely used in formulations for product identification.

The chemical formula of thymol is $C_{10}H_{14}O$; its chemical name is 5-methyl-2-(1-methylethyl) phenol. Thymol is also known as thyme camphor. It is obtained by fractional distillation from the volatile oil of *Thymus vulgaris, Monarda punctata* (horsemint), and other related plants. It may also be prepared synthetically from *p*-cymene or *m*-cresol. It occurs as large colorless crystals or white crystalline powder with an aromatic odor similar to thyme and pungent taste. Thymol is practically insoluble in water (1 g in 1,000 mL), but is soluble in alcohol and ether. Because it is affected by exposure to light, it must be stored in light-resistant containers. When thymol is triturated with an equal weight of either camphor, menthol, chloral hydrate, or some other substances, a liquefied mixture results (Ref. *1*).

Thymol was originally introduced as a disinfectant with uses similar to those of phenol. Thymol has a more agreeable odor than phenol and is also a more powerful bactericide, although its activity is greatly reduced in the presence of organic matter and protein. Thymol is used in concentrations of 1 percent in alcohol and 2 percent in dusting powder as an antiseptic and antifungal agent (Ref. *2*). Thymol occurs in concentrations of 0.125 to 1.25 percent in the antifungal products submitted for review.

Safety. Thymol is physically and structurally related to phenol; hence, its toxicology is similar to that of phenol. (See part III. Paragraph B.1.e. above—Phenolates (phenol and phenolate sodium).) However, toxic signs and symptoms for thymol are much less severe than for phenol in equal concentrations.

The oral LD_{50} of thymol in mice is 1.8 g/kg (Ref. *3*). The intravenous LD_{50} in mice was reported as 74 mg/kg (Ref. *4*). Jenner (Ref. *5*) studied the acute oral toxicity of thymol by intubation in the rat and guinea pig. The LD_{50} for the rat was found to be 980 mg/kg, and for the guinea pig, 880 mg/kg.

In humans, ingested thymol can cause nausea, vomiting, albuminuria (albumin in the urine), headache, tinnitus (ringing in the ears), dizziness, muscular weakness, thready pulse, slow respiration, and lowered body temperature. "Therapeutic" doses depress the heart (Ref. *2*). Ingestion of 1 g thymol does not usually cause adverse symptoms other than a feeling of warmth in the stomach. Doses larger than 1 g have resulted in toxic symptoms. Fats and alcohols increase the absorption of thymol and aggravate the toxic symptoms (Ref. *6*).

Worm infestations were treated in the past with thymol, especially in the Far East. In 1922, Barnes (Ref. *7*) estimated that over the years nearly 1½ million doses of thymol had been administered for hookworm and tapeworm. The usual oral dose was 1.3 g. Barnes noted that fewer than 20 fatalities resulting from the use of thymol are reported in the literature.

Samitz and Shmunes (Ref. *8*) noted that dentists and dental technicians found thymol one of the less frequent sensitizers in occupational dermatoses. However, rashes are not uncommon. A recent textbook noted that thymol 0.5 percent in lotions was irritating (Ref. *9*). Also, because of its strong irritancy potential thymol has had little value as a bactericide for wounds or mucous membranes. It is better tolerated on intact skin (Ref. *2*). Safety data are not available on the absorption of thymol from small areas of application to broken skin and intact skin. Data on the local effects of thymol on wound healing and thymol's irritation potential are also needed. The Panel concludes that more information is needed to determine the safety of thymol at concentrations greater than 0.2 percent in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* In the past, thymol was called a "strong fungicide" based on in vitro tests with dermatophytes. A 1:1,000 aqueous solution of thymol was fungicidal to 100 percent of the dermatophytic organisms tested for a 30-minute exposure time, whereas a 1:7,500 aqueous solution of thymol was fungistatic to dermatophytic cultures after 4 to 6 weeks of exposure (Ref. *10*). Thymol was found to have a phenol coefficient of 26 against *T. gypseum* (Ref. *11*). In another in vitro study with *T. mentagrophytes,* the minimal fungicidal concentration of thymol in 95 percent ethyl alcohol was found to be 1.5 percent at 5 days, 2.0 percent at 10 and 15 day, 3.0 percent at 20 days (Ref. *12*).

Thymol was felt to have potential value as an antifungal therapeutic agent when all the fungi in human scales infected with dermatophytes were killed after 30-minute exposures to 3 percent thymol in 50 percent alcohol or 5 percent thymol in 95 percent alcohol (Ref. *13*). *T. interdigitale* was completely inhibited by 5 percent thymol in an ointment base of petrolatum, wool fat, and yellow wax (Ref. *14*). A 1-percent concentration of thymol in talc completely prevented culture growth of *T. inguinale* and caused a 2.8-cm zone of inhibition in the growth of *T. interdigitale* (Ref. *15*). Thymol 10 percent in chloroform has been used to preserve fungus cultures. Application of a few drops of the mixture to the culture tube's cotton stopper promptly stops fungal growth (Ref. *16*). If the culture is then sealed in wax, it will last up to 6 years.

Thymol is also fungicidal against *M. albicans,* and a phenol coefficient of 17 has been reported (Ref. *11*). A saturated aqueous solution of thymol killed 10 species of yeasts obtained from human isolates after 1-minute exposure times. The minimal effective fungicidal concentrations for three different yeasts were 7, 8, and 10 percent thymol in water (Ref. *17*).

A 5-percent thymol ointment (petrolatum, wool fat, and yellow wax) was fungistatic to *Candida* in vitro. The most effective base tested for releasing 5 percent thymol in cultures of *M. albicans* was vanishing cream, which resulted in a 20-mm zone of inhibition. Bases containing either cold cream or petrolatum with yellow wax and wool fat were less effective in releasing 5 percent thymol, with zones of inhibition of 16 mm and 12 mm, respectively (Ref. *14*).

Against *Candida tropicalis*, a 1:1,500 dilution of thymol was fungicidal after a 1-minute exposure, and a 1:2,000 dilution was fungicidal after 30-minute and 60-minute exposures (Ref. *18*). Thymol has in vitro antibacterial activity similar to that of phenol. (See part III. paragraph B.1.e. above—Phenolates (phenol and phenolate sodium).)

Thymol 0.044 percent was bactericidal to *S. albus* and *B. typhosus* after 2.5 minutes of exposure; thymol 0.033 percent was bactericidal to the same bacteria after 15 minutes of exposure. The solvent in this study contained alcohol, glycerin, ethylene glycol, soap, and water, and was not, itself, bactericidal in the dilutions used in testing (Ref. *19*).

In a study performed in 1925, a mixture containing 5 percent thymol and 2 percent cinnamon in alcohol was painted on areas of candidiasis in fruit handlers working in a canning plant (Ref. *19*). The mixture brought "speedy relief." "Prompt relief" resulted when the same mixture was painted between the toes and on the soles of persons with *Epidermophyton* infections (Ref. *20*). In another study, 10 to 20 percent thymol in olive oil was applied to skin lesions of actinomycosis, along with the oral administration of thymol 1 to 2 g daily, with good results (Ref. *21*).

Clinical trials using thymol 2.5 percent and oil of cinnamon 1 percent in cold cream or vanishing cream base were recommended in 1941 on the basis of in vitro fungistatic activity against both dermatophytes and *M. albicans* (Ref. *14*).

Thymol 10 percent in chloroform was applied twice daily to the scalp to treat favus caused by the dermatophyte fungus *A. schoenleinii* (Ref. *22*). Thymol treatment resulted in less scale and less irritation within 2 weeks. After 3 months it was alternated with 4 percent chrysarobin in chloroform, acting as an irritant to the scalp. Treatment was stopped after 1 year except for thymol applications twice weekly. Hair regrowth was then normal and all fungal cultures were negative.

A clinical trial was performed at Fort Benning, Georgia (Ref. *23*). Sixty-nine cases of KOH-positive athlete's foot were treated initially with thymol (concentration not given), and 34 percent experienced mild-to-moderate irritation. After 1 to 2 weeks, itching had been relieved in 37 percent of 52 cases, but only 17 percent were clinically clear. After 2 to 4 weeks of treatment, examination of 30 patients revealed that only 40 percent were clinically clear. It was concluded that thymol was not very effective and was often irritating.

Some years later, 2 to 4 percent thymol in chloroform was reported to control chronic *Candida* infections in and around the nails, with chloroform acting as a useful drying agent (Ref. *24*).

Although thymol has been regarded as an active antiseptic and fungicidal agent in the past, there have been no controlled studies demonstrating its effectiveness when applied to skin for the treatment of athlete's foot, jock itch, or ringworm. Indeed, the only clinical trial performed with thymol on athlete's foot (Ref. *23*) suggested that thymol was very irritating in many cases and not very effective in clearing athlete's foot.

The Panel concludes that thymol is not an effective antifungal ingredient for the treatment of athlete's foot, jock itch, and ringworm.

(3) *Evaluation.* The Panel has placed thymol at concentrations greater than 0.2 percent in Category II because the only clinical trial that evaluated this ingredient showed it to be ineffective in clearing athlete's foot. The Panel concludes that thymol at concentrations less than or equal to 0.2 percent is safe and may be used in formulations for product identification.

References

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(*15*) Fredell, W., V. Burlingame, and G. Reddish, "Antiseptic Powders," *Drug Standards*, 22:107–112, 1954.

(*16*) Morris, G., "Use of Thymol as a Preservative for Fungi," *Archives of Dermatology and Syphilology*, 67:514, 1953.

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(*23*) Hopkins, J., et al., "Fungistatic Agents for Treatment of Dermatophytosis," *Journal of Investigative Dermatology*, 7:239–253, 1946.

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1. *Tolindate.* The Panel concludes that tolindate is not generally recognized as safe and effective for the treatment of athlete's foot, jock itch, and ringworm. There are no reports in the medical or pharmaceutical literature that address its use, safety, or effectiveness in these diseases. It is not contained in any marketed OTC antifungal product, but data on this ingredient were submitted to the Panel (Refs. *1* and *2*).

The Panel is aware that an active investigational new drug exemption (IND) exists for tolindate; however, because tolindate now has no clinical use it cannot be generally recognized as appropriate for OTC use.

The Panel questioned whether tolindate was chemically similar enough to tolnaftate (a Category I ingredient) to warrant including it in the review of the

safety and effectiveness of OTC drugs. The Panel concluded that although tolindate's antifungal action could possibly by predicted on the basis of structural similarity to the tolnaftate molecule, there was no way to scientifically assess its activity without complete antifungal testing. Also, the solubility and stability of these two drugs could be totally unrelated (Ref. *3*).

The Panel therefore determined that because of (1) the lack of any scientific publications dealing with tolindate, (2) the lack of safety data in the public domain, and (3) the lack of effectiveness data in the public domain, tolindate should be classified in Category II.

References

(*1*) OTC Volume 070170.
(*2*) OTC Volume 070171.
(*3*) Summary Minutes of the 26th Meeting of the OTC Antimicrobial II Panel, May 20, 1977, as incorporated in OTC Volume 07A PA2.

2. *Category II labeling.* The Panel concludes that certain labeling claims related to safety or effectiveness of an ingredient are unsupported by scientific data or, in some instances, by sound theoretical reasoning. The Panel therefore concludes that such labeling should be removed from the market.

Many claims from current labels have been placed in Category II either because they are vague, too broad, incomplete, or modified incorrectly, or because they do not specifically indicate that the product effectively treats or prevents athlete's foot, jock itch, or ringworm. Such labels mislead the lay person.

Many claims would appear to be acceptable; however, certain modifying words can make these claims unclear or even imprecise. For this reason, modifiers such as "most" or "fast" are not allowed. Other examples of vague modifiers are "scientific" as in "scientific treatment"; "persistent" as in "Persistent cases."

The Panel considers the following labeling claims to be unacceptable:

"Athlete's foot," "ringworm," "jock itch" (when these words are used alone).
"Antifungal" (when used alone).
"Adjunctive treatment."
"Promotes healing."
"Helps heal."
"Kills most athlete's foot fungi."
"Kills athlete's foot on contact."
"Kills athlete's foot fungi on contact."
"Kills jock itch fungi on contact."
"Kills athlete's foot fungi fast."
"Kills jock itch fungi fast."
"For the treatment of athlete's foot and ringworm of the skin, exclusive of bodyfold areas."
" 'Scientific treatment' for athlete's foot."
"Kills fungus spores."
"Temporary relief of ringworm."
"Temporary relief of itching and discomfort due to athlete's foot."
"Helps restore normal skin even in severe or persistent cases."
"Proven fungicide for athlete's foot, jock itch, and body ringworm fungi."
"Fungicidal against athlete's foot, jock itch, and ringworm fungi."
"The broadest proven dermatophyte spectrum."
"Speeds healing of athlete's foot."
"Speeds healing of jock itch."
"Broad spectrum antifungal (for treatment of athlete's foot and jock itch)."
"For fast relief of itching and burning of athlete's foot and jock itch."
"Penetrating action goes under crust and skin surface to kill athlete's foot fungi."
"Kills all known athlete's foot and jock itch fungi."
"Kills all major types of athlete's foot fungi."
"Kills all major types of jock itch fungi."
"Prevention and control of minor skin infections including athlete's foot."
"Minor fungus skin infections."
"Minor skin irritations associated with fungus."
"Other skin fungus infections."
"For the treatment of inflamed conditions of the skin, such as eczema, athlete's foot, and other fungal infections."
"Combats and controls infection-causing fungi."
"For irritations caused by fungus infections."
"Controls bacteria and fungi."
"For fungus infections of hands, groin, or body."
"For superficial fungal infections of the skin."
"Helps prevent fungal infections."
"Guards against fungus growth."
"Inhibits the growth of fungi and bacteria."
"Helps prevent germ and fungus infection."

Because the following labeling claims do not specifically indicate that the product effectively treats or prevents athlete's foot, jock itch, or ringworm, the Panel considers them misleading to the lay person:

"First-aid."
"Aids in drying up excessive secretions."
"As an antiseptic."
"An inhibitory antiseptic."
"Protects broken skin from infection."
"Invisible shield."
"Fungicidal."
"Fungistatic."
"Bactericide."
"Germicide."

Any claims that contain a "percent cured" rate have been placed in Category II because the percentages could change, depending on when and how the test is run.

Examples of this kind of labeling are as follows:

"Clinical studies show that it cured 78 percent of athlete's foot cases."
"Clinical improvement was obtained in 88 percent of the athlete's foot cases."

C. *Category III Conditions for Which the Available Data Are Insufficient To Permit Final Classification at This Time.*

The safety and efficacy of the following ingredients were classified on the basis of activity and use as antifungal agents. Ingredients for which no antifungal claim is made, including ingredients that have been reviewed by the Panel and placed in Category III for antifungal effectiveness, may still be included in formulations for nonantifungal purposes providing they are safe at the concentrations used and are in compliance with the Panel's combination policy.

Furthermore, the Panel believes that antifungal ingredients placed in Category I for the treatment of athlete's foot, jock itch, and ringworm may also be effective in the prevention of athlete's foot. At present, however, prophylaxis data on most of these ingredients are insufficient to support such a labeling claim. Before the prevention of athlete's foot may be included on labeling, a clinical trial should be conducted as detailed elsewhere in this document (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

1. Category III Active Ingredients

Aluminum salts
  Alcloxa
  Aluminum sulfate
  Potassium alum
Basic fuchsin
Benzethonium chloride
Benzoic acid
Borates
  Boric acid
  Sodium borate
Caprylates
  Sodium caprylate
  Zinc caprylate
Chlorothymol
Chloroxylenol
Cresols
  m-Cresol
  Secondary amyltricresols
Dichlorophen
Oxyquinolines
  Benzoxiquine
  Oxyquinoline

Oxyquinoline sulfate
Parabens
Methylparaben
Propylparaben
Phenyl salicylate
Povidone-iodine
Propionic acid and its salts
Sodium propionate
Zinc propionate
Salicylic acid
Sulfur
Triacetin

a. *Aluminum salts (alcloxa, aluminum sulfate, and potassium alum).* The Panel concludes that aluminum salts (alcloxa, aluminum sulfate, and potassium alum) are safe but that there are insufficient data available to permit final classification of their effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Alcloxa, also known as aluminum chlorhydroxy allantoinate, is a white powder. Its chemical formula is $Al_2(OH)_4ClC_4H_5N_4O_5$. It is soluble in 55 parts water and 200 parts alcohol. A saturated solution of alcloxa has a pH of about 4.7 (Ref. *1*).

Aluminum sulfate, $Al_2(SO_4)_3 \cdot H_2O$, is a white, crystalline, odorless powder. It is also known as cake alum and patent alum. It is very soluble in water, 1 g dissolving in about 1 mL water, but is insoluble in alcohol. The aqueous solution of aluminum sulfate is acidic (Ref. *2*).

Potassium alum, also known as aluminum potassium sulfate, has a chemical formula of $AlK(SO_4)_2 \cdot 12H_2O$. It has been known since ancient times when it was used as a styptic and as a mordant (a) substance used to fix coloring matter in textiles or other materials) in dyes. Potassium alum is a white or colorless crystalline powder prepared from the mineral bauxite and sulfuric acid, with potassium sulfate added. One g potassium alum is soluble in about 7.5 mL water, but is insoluble in alcohol. When potassium alum is dispensed in powders containing phenol, salicylates, or tannic acid, a green or gray color may develop because of traces of iron found in the potassium alum (Ref. *2*).

The aluminum salts have been submitted to the Panel in powder formulations in the following concentrations: alcloxa, 0.25 percent; aluminum sulfate, 1.5 percent; and potassium alum, 15 to 21 percent.

(1) *Safety.* Dreisbach (Ref. *3*) reported that salts of metals are used as "astringents, deodorants, and antiseptics." When applied to the skin, aluminum salts are not usually absorbed, but may act by precipitating protein which forms a superficial protective layer on mucous membranes or damaged skin (Ref. *4*).

Sax (Ref. *5*) reported that aluminum compounds have little or no toxicity. It has also been suggested that chronic poisoning does not occur and that fatalities from aluminum salts have not been cited in recent years (Ref. *3*). Nevertheless, it is known that certain aluminum salts, namely chloride and sulfate, do tend to hydrolyze and produce the corresponding acid, which in turn is irritating.

Various aluminum salts have long been used as astringents and antiperspirants. Standard references (Refs. *3* and *5*) report an absence of toxicity, and the Panel recognizes the safety of these salts when topically applied. For these reasons the Panel concludes that aluminum salts are safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* Leyden and Kligman (Ref. *6*) tested various aluminum salts (chloride, chlorohydrate, acetate, and diacetate) for antibacterial, antifungal, and astringent properties. They found that a mere 1-percent concentration of aluminum chlorohydrate was needed to completely inhibit all organisms but *T. mentagrophytes* when tested in vitro. Test organisms included *S. aureus, Pseudomonas,* and *C. albicans.* Concentrations of 10 percent aluminum acetate and 30 percent aluminum chloride, however, were necessary to completely inhibit the microorganisms (*S. aureus, Pseudomonas, C. albicans,* and *T. mentagrophytes*) in vitro.

In vitro results did not correlate with in vivo results in patients with athlete's foot. Although least effective on agar plate tests, aluminum chloride in a concentration of 30 percent was clinically far superior to the other compounds. Leyden and Kligman believed that astringency was mainly responsible for these results and noted that aluminum chloride was the most effective astringent in the group of compounds tested. It is important to note that these investigators did not specifically define athlete's foot. They used any patient with a symptomatic, macerated intertrigo of the toewebs.

In view of the lack of well-designed, controlled, clinical studies, the Panel concludes that aluminum salts are of questionable effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. The Panel proposes that an upper limit of 10 percent is a sufficient concentration for antifungal activity to be demonstrated. Higher concentrations would be present for their drying effect.

(3) *Proposed dosage*—(i) *Concentration.* Aluminum salts (a) alcloxa 0.25 to 10.0 percent (b) aluminum sulfate 1.5 to 10.0 percent; (c) potassium alum 1.5 to 10.0 percent.

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

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

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

References

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b. *Basic fuchsin.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of basic fuchsin for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Basic fuchsin, a red dye used as a stain in histology and bacteriology, is composed of a mixture of rosaniline and pararosaniline hydrochlorides. It is a dark green, crystalline powder that is soluble in water and alcohol but insoluble in ether (Ref. *1*). Basic fuchsin was submitted to the Panel in a concentration of 0.3 percent.

(1) *Safety.* Basic fuchsin is one of several triphenylmethane (rosaniline) derivatives that are active against certain fungi and gram-positive microorganisms. Some of the methylrosaniline dyes have been used orally as anthelmintics (agents that

destroy worms). For direct application to tissues, these dyes are generally used in concentrations of 1:5,000 to 1:1,000. For instillation into closed cavities the concentration is reduced to 1:10,000 (Ref. *2*).

Little is known about the acute or chronic toxicity of basic fuchsin. the only report dealing with the specific toxicity of basic fuchsin gave the following information: The lowest published lethal dose was 150 mg/kg when given orally to rabbits. The lowest published toxic dose was 2,500 mg/kg when given orally to mice (Ref. *3*). Obviously, this is not precise toxicity data and supports Sax's observation that the details of the safety of basic fuchsin are unknown (Ref. *4*).

Plunkett (Ref. *5*) reported that no threshold limit for gentian violet, another triphenylmethane dye, had been established. Occupational exposure to this compound came from its use in typewriter ribbons, carbon paper, and othe such items where it might cause eczema, acne-like eruptions, papillary growth, or, occasionally, epitheliomata (a tumor derived from epithelium). On ingestion, gentian violet may produce inflammation of the lips, headache, nausea and vomiting, diarrhea, and weakness. (No specific dose was associated with these symptoms.)

Blacow (Ref. *6*) reported that basic fuchsin is a controlled substance in Great Britain under the Carcinogenic Substance Regulations of 1967, which require all those engaged in manufacturing this compound to undergo 6-month medical examinations. Blacow observed that "this was good reason for considering its (basic fuchsin) disuse in the treatment of fungous skin lesions."

Although the Panel found no further information on the carcinogenic potential of basic fuchsin, it considers this to be its most serious toxicity potential.

(2) *Effectiveness.* The triphenylmethane dyes were used shortly before World War I as antiseptics for wounds, burns, and skin infections. They were usually used at concentrations of 0.1 to 0.5 percent in aqueous solutions. They are most active against gram-positive bacteria, inhibiting gram-positive cocci at concentrations between 1:750,000 and 1:100,000, but up to 10 times those concentrations were required to inhibit gram-negative bacteria (Ref. *7*). The presence of serum greatly decreased their antibacterial activity (Ref. *8*).

The dyes are most active in the basic than the acidic form, forming a liposoluble pseudo-base that can penetrate the cell membranes of microorganisms (Ref. *9*). The basic dyes apparently bind to the acid groups within bacterial cells, including nucleic acids (Ref. *10*). Because the antimicrobial activity of the dyes generally increases with the degree of alkyl substitution in the molecule, basic fuchsin with only one methyl group is much less active than some of the other triphenylmethane dyes with more methyl groups, particularly crystal violet and malachite green (Ref. *11*).

The in vitro antifungal activity of basic fuchsin has not been widely investigated; the Panel is aware of only a few reports which include such in vitro activity. In one report, the highest dilutions of basic fuchsin (in distilled water) that were fungistatic were 1:200 for *T. rosaceum*, 1:100 for *M. audouinii*, and 1:20 for *A. schoenleinii (Ref. 12)*. A later report stated that basic fuchsin did not show any significant fungicidal or fungistatic activity against *T. interdigitale or Epidermophytom rubrum (E. rubrum) (Ref. 13)*.

Basic fuchsin was first used as an antifungal agent by Castellani (Ref. *14*), who reported its use in the 1920's in the form of carbol-fuchsin. This was a mixture of a saturated alcoholic solution of basic fuchsin and 5 percent aqueous carbolic acid. He wrote that "the simple carbol-fuchsin gives good results," but he did not provide supportive data or advocate the use of basic fuchsin as a single ingredient. Instead, he combined it with boric acid, acetone, and resorcinol to increase its action and make it more penetrating. The resulting carbol-fuchsin paint became commonly known as Castellani's Paint or Magenta Paint B.P.C. (British Pharmaceutical Codex).

Basic fuchsin was one of several antibacterial chemicals and formulations tested in 1974 to examine the innibition of growth of microorganisms on human skin (Ref. *15*). In an occlusion test, a 1-percent aqueous solution of basic fuchsin was painted on the skin, allowed to dry, and then covered with plastic film for 48 hours. Under the increased heat and moisture, basic fuchsin had an impressive antibacterial effect against gram-positive bacteria. In an expanded flora test, basic fuchsin also showed "high activity" against gram-positive organisms but did not prevent the growth of gram-negative bacteria when the flora expanded. (This test evaluates the antibacterial effect of substances on greatly increased bacterial flora with both gram-positive and gram-negative organisms after they have multiplied under occlusion with plastic wrap for 48 hours.) In both the occlusion tests and the expanded flora tests, basic fuchsin was less effective than Castellani's Paint.

The Panel is not aware of any clinical studies using basic fuchsin alone as an antifungal agent. All reports involve the use of carbol-fuchsin paint which combines several ingredients which are potentially antifungal (phenol, boric acid, resorcinol, alcohol, and acetone) with basic fuchsin. (See part III. paragraph D. below—Combination Products Used in the Treatment of Athlete's Foot, Jock Itch, and Ringworm.)

Because of the lack of clinical effectiveness data using basic fuchsin as a single active antifungal ingredient, the Panel concludes that this ingredient is of questionable effectiveness in the treatment of athlete's foot, jock itch, and ringworm.

(3) *Proposed dosage*—(i) *Concentration.* Basic fuchsin 0.3 percent.

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

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

(5) *Evaluation.* The Panel recommends complete safety testing of basic fuchsin. The Panel also recommends in vitro testing and one double-blind, placebo-controlled clinical trial to determine the effectiveness of basic fuchsin in the treatment of athlete's foot, jock itch, and ringworm. Data to demonstrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

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(15) Marples, R. R., and A. M. Kligman, "Methods for Evaluating Topical Antibacterial Agents on Human Skin," *Antimicrobial Agents and Chemotherapy*, 5: 323–329, 1974.

c. *Benzethonium chloride.* The Panel concludes that there are insufficient data available to permit final classification of the safety or effectiveness of benzethonium chloride for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Benzethonium chloride is a cationic, surface-active agent with a quaternary amine structure. It is very soluble in water and soluble in alcohol and acetone. Benzethonium chloride is incompatible with many commonly encountered substances. For example, it loses its activity in the presence of soap, tissue constituents, and pus. Acid and salt solutions may also precipitate it (Ref. *1*).

(1) *Safety.* The Advisory Review Panel on OTC Antimicrobial I Drug Products reviewed benzethonium chloride for indications other than antifungal and placed it in Category III for safety. (See **Federal Register** of September 13, 1974 (39 FR 33131).) In reviewing benzethonium chloride for antifungal use, the Advisory Review Panel on OTC Antimicrobial II Drug Products concurs in the Category III safety classification.

Studies dealing with fertility, reproduction, and teratology have been done in rats and rabbits (Ref. *2*). Oral doses of benzethonium chloride ranging from 1.125 to 35.576 mg/kg were administered to the test animals. Except for the highest dose level, little or no toxic effects were observed. However, a reduction in average body weight gain was noted in test rats receiving 35.576 mg/kg in both subchronic and chronic exposures.

To determine the blood levels of C^{14}-benzethonium chloride, the drug was given once daily at dose levels of 1.125 and 3.558 mg/kg to pregnant rats. Maximum blood levels of 1.5 nanograms per gram (ng/g) of C^{14}-benzethonium chloride were obtained after cumulative dosing to day 15. No adverse effects on the rats were observed at these blood levels.

If one assumes that as much as 5 g of a foot powder containing 0.13 percent benzethonium chloride were applied to broken skin, a total of 6.5 mg benzethonium would be available for absorption. Further assuming complete, rapid absorption into the blood, the 6.5 mg would be distributed into 7 L of blood, resulting in a blood concentration of about 1.0 μg/mL. Of course, it is highly unlikely that complete absorption would occur. However, a potential for toxicity does exist. At the oral dose level of 35.576 mg/kg, there was a reduction in weight gain in rats. Assuming that at an oral dose 10 times the level mentioned in the C^{14} study (35.58 mg/kg), and assuming a blood concentration 10 times higher (15 ng/g), then one can see that if absorption from broken skin is significant (and this is unknown), a potential toxicity problem may exist. The Panel therefore recommends that studies be done to determine the degree of absorption from broken skin (as evidenced by blood levels) and the relationship between these blood levels and the blood concentration that produced no adverse effect in animals.

(2) *Effectiveness.* In vitro activity of benzethonium chloride, a quaternary ammonium compound, was described by the Advisory Review Panel on OTC Antimicrobial I Drug Products. (See **Federal Register** of September 13, 1974 (39 FR 33131).) Quaternary ammonium compounds are generally more active against gram-positive organisms than gram-negative organisms. Their activity is decreased in the presence of organic materials, anionic compounds, soaps, certain metallic ions, and hard water.

The data on the in vitro antifungal activity of benzethonium chloride are limited. Studies reviewed by the Panel included use-dilution tests and phenol coefficients (Ref. *3*). Details of the testing procedures were not given. The Panel concludes that further in vitro work needs to be done on this ingredient.

Benzethonium chloride is contained in only one product submission under review by the Panel (Ref. *3*). In this product it appears in a 0.13-percent concentration in combination with at least one other active ingredient. The studies in this submission also evaluate a multi-ingredient product. Although the product appears to demonstrate in vivo effectiveness, the Panel has placed benzethonium chloride in Category III because of insufficient data on its antifungal effectiveness as a single active ingredient.

(3) *Proposed dosage*—(i) *Concentration.* Benzethonium chloride 0.13 percent.

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

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

(5) *Evaluation.* The Panel recommends that safety studies be done to determine the degree of absorption of benzethonium chloride from broken skin, as evidenced by blood levels, and the relationship between these blood levels and the blood levels that produced no adverse effects in pregnant rats (1.5 ng/g). The Panel also recommends in vitro testing and one double-blind, placebo-controlled clinical trial to determine the effectiveness of benzethonium chloride in the treatment of athelete's foot, jock itch, and ringworm. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

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(2) OTC Volume 130115 (submitted to the Advisory Review Panel on OTC Oral Cavity Drug Products).

(3) OTC Volume 070190.

d. *Benzoic acid.* The Panel concludes that benzoic acid is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Benzoic acid (C_6H_5COOH) is also known as phenylformic acid, flowers of benzoin, and flowers of Benjamin. It is a colorless, tasteless, crystalline

substance readily soluble in organic solvents and soluble up to 0.37 percent in water. Benzoic acid occurs in both the free and esterified state in various plants, the balsams and resins obtained from the plants, and in coal tar. It also occurs as a hippuric acid (benzoylglycine) in the urine of most vertebrates. Benzoic acid may be synthesized from a variety of compounds, such as toluene, benzaldehyde, and benzotrichloride (Refs. *1* and *2*).

(1) *Safety.* Although none of the data submitted to the Panel for review gave direct toxicological data on benzoic acid, the Panel recognizes that general consensus exists on the safety of benzoic acid confirmed by its long history as a food preservative.

Goodman and Gilman (Ref. *2*) report that a daily intake of 4 to 6 g benzoic acid does not cause toxic symptoms other than slight gastric irritation; large doses of benzoic acid produce systemic effects similar to those produced by the salicylates. Blacow (Ref. *3*) has estimated that an acceptable daily benzoic acid intake for humans could be up to 5 mg/kg. According to Sax (Ref. *4*), benzoic acid causes only slight local or systemic toxicity.

The Panel concludes that benzoic acid is safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* Benzoic acid has been widely used in a concentration of 0.1 percent as a food preservative, preventing bacterial growth when added to a slightly acidic medium. It is much less effective at an alkaline pH because benzoate salts are formed (Ref. *2*).

The submissions reviewed by the Panel include cream, liquid, powder, and ointment formulations of benzoic acid in concentrations ranging from 0.75 to 12 percent.

Benzoic acid applied to the skin in high concentrations has been used as a keratolytic (Ref. *2*). In an in vitro test to determine the antimicrobial activity of more than 100 antiseptic powders, benzoic acid, at concentrations of 1 percent and 2.5 percent, showed mild antifungal activity against *T. interdigitale* (Ref. *5*).

A study by Oster and Golden (Ref. *6*), based on in vitro results, concluded that a 0.91-percent solution of benzoic acid compared favorably in activity to a 1-percent solution of undecyclenic acid.

Agar-cup testing showed benzoic acid to have very small zones of inhibition against *C. albicans, T. mentagrophytes,* and *T. purpureum.* The minimal fungicidal levels were not accurately determined but appeared high (Ref. *7*). The Panel concludes that further in vitro testing should be done on benzoic acid using current techniques.

In a 3-year study involving over 7,500 voluntary patients, Hopkins et al. (Ref. *8*) studied many antifungal agents, including benzoic acid, in the treatment of dermatophytosis. Cultures were done before treatment, and KOH preparations were done at each following visit. Results were given for patients with positive KOH preparations. At the end of more than 4 weeks of treatment (exact time not given), 60 percent (55/92) of the patients treated with benzoic acid were clinically clear; 68 percent (63/92) were "fungus negative." Of the patients treated with undecylenic acid, 70 percent (204/292) were clinically clear; 79 percent (231/292) were "fungus negative." The researchers reported that benzoic acid compared favorably with undecylenic acid. Shortcomings in the study design include failure to obtain cultures at that end of the investigation, to list the causative organism, and to present data and study results clearly and coincisely.

Because there is no well-designed, clinical study showing the effectiveness of benzoic acid in the treatment of athlete's foot, jock itch, and ringworm, the Panel recommends this ingredient be placed in Category III.

(3) *Proposed dosage*—(i) *Concentration.* Benzoic acid 0.075 to 12 percent.

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

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

(5) *Evaluation.* The Panel recommends in vitro testing and one double-blind, placebo-controlled clinical trial to demonstrate the effectiveness of benzoic acid in the treatment of athlete's foot, jock itch, and ringworm. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

References

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e. *Borates (boric acid and sodium borate).* The Panel concludes that borates (boric acid and sodium borate) are safe in concentrations of 5 percent or less but are not safe in concentrations exceeding 5 percent. The Panel also concludes that there are insufficient data available to permit final classification of their effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Boric acid, H_3BO_3, occurs as colorless or white crystals or powder. It is obtained from sodium borate and other borates by displacement with a stronger acid. One g boric acid dissolves in 18 mL water, 18 mL alcohol, and 4 mL glycerin.

Sodium borate, $Na_2B_4O_7$, also known as borax, is an odorless, colorless or white crystalline powder. It is found in several lake waters and brines and also in minerals. One g dissolves in about 16 mL water and about 1 mL glycerin. Sodium borate is insoluble in alcohol (Ref. *1*).

(1) *Safety.* Borate compounds (boric acid and sodium borate) are used in concentrations ranging form about 0.5 percent to 12 percent.

Sodium borate has been used as a cleansing agent since ancient times. Its use as an internal cleanser was first recorded in the Middle East in 875 (Ref. *2*). Since that time, many extensive reviews and articles have been written on the use of borated compounds. One of these reviews lists the LD_{50} of subcutaneously administered boric acid in animals as follows: 2.0 g/kg in mice; 1.2 g/kg in guinea pigs; 1.0 g/kg in dogs (Ref. *3*). The oral LD_{50} for dogs was reported to be about twice that of the subcutaneous dose.

Toxicity data in humans appear to be unpredictable (Ref. *3*). For example, a 70-year-old woman died after ingesting 7.5 g boric acid powder, but a 42-year-

old woman reportedly survived an intravenous dose of 15 g boric acid. Locksley and Farr (Ref. *4*) reported administering 20 g borax (sodium borate) intravenoulsy to human subjects over a period of 75 seconds. No deaths resulted. However, six infants died after receiving 3 to 6 g of this drug orally (Ref. *5*).

Fisher et al. (Ref. *6*) investigated the absorption of boron from borated talc. They reported that when a 10-percent ointment is applied to extensively denuded areas, up to 2 g boric acid may be excreted by a patient within 24 hours following the application. These investigators then used a preparation of 5 percent boric acid in talc to study its absorption in infants. The powder was applied freely to diapered areas, with each infant receiving about 168 g of powder (8.4 g boric acid) per month over a 12-month period. Blood samples taken every 2 months failed to show any significant increase in blood concentration of boron even when the infants had minor skin irritations. The investigators concluded that "the circumstances recounted in the literature under which true boric acid poisoning has been encountered appear to be largely, if not entirely, limited to the striking misuse of boric acid, in that it was applied repeatedly in copious quantities as pure or essentially full strength powder to extensive areas of denuded or macerated skin of a small infant.".

In reviewing some cases of known intoxication, these same researchers (Ref. *6*) found that the blood concentration of boric acid ranged from 52 to 296 mg/100 mL in those cases that were "unmistakably intoxication by boric acid." They concluded from their investigations that "there are few reliable data in the literature regarding the concentration of boric acid in the blood that is accompanied by evidence of toxic condition in the patient."

Kingma (Ref. *3*) surveyed the literature from 1882 to 1957 and found 37 cases of alleged boric acid poisoning from topical application. In 26 of these cases it appeared that pure boric acid was applied to raw surfaces. In three cases a 5-percent boric acid solution was used in large quantities or applied to large surfaces. In two of the cases, boric acid ointment was used. Based on his review, Kingma recommended that pure boric acid should never be used on raw surfaces and that a 3-percent concentration limitation for solutions and ointments would greatly increase the safety margin of the drug. He further pointed out that experiments with 5-percent borated talcum had documented the safety of this preparation. Kingma's conclusions were substantiated by two other review articles (Refs. *6* and *7*).

Pfeiffer and Jenney (Ref. *2*), in discussing the passage of boric acid through skin, mucous membranes, and serous surfaces, reported that when the torsos of two subjects were anointed with a 10-percent boric acid ointment, no detectable boric acid was found in the urine. These investigators concluded that boric acid is only negligibly absorbed through intact skin. Granulating wounds or surfaces, however, are rich in blood supply and permit the rapid absorption of boric acid applied in solution, as a powder, or as an ointment. Pfeiffer and Jenney suggested that the very young rank first and the very old rank second in susceptibility to boric acid or sodium borate poisoning.

Goldbloom and Goldbloom (Ref. *8*) gave clinical histories of four infants poisoned from the topical application of various boric acid preparations. One of the four died, but the cause of death could not be pinpointed as the boric acid poisoning. They also surveyed the various routes of intoxication with mortalities for each group. There were 28 recorded cases of boric acid poisoning following the topical application of boric acid to wounds, burns, and skin eruptions. Nineteen of these cases were fatal. Based on this review, it appears that boric acid (or sodium borate) can be absorbed through broken skin to such a degree that toxic effects and even death may result. Most deaths from the topical application of boric acid occurred with pure boric acid powder or saturated solutions over large areas of skin. The risk factors for potential toxic absorption appear to be concentration of boric acid or sodium borate in a product, age of the patient, skin condition, and duration of exposure.

A review of the literature (Ref. *9*) containing 81 references summarized the current status of boric acid poisoning. This review fairly well substantiated that preparations containing 5 percent or less of boric acid presented no great toxicity problem when applied to intact skin. When skin is inflamed or broken, concentrated forms of boric acid should never be used. Concentrations up to 5 percent when used on relatively small areas, such as jock itch or ringworm, should be safe. If one assumes that 1 g of a 5-percent preparation was applied to the skin and all of the boric acid was rapidly absorbed, a total of 50 mg would be absorbed and distributed into 7,000 mL of blood. This, of course, is far below the blood levels achieved by Locksley and Farr (Ref. *4*), who reported no deaths occurring from a 20-g intravenous dose of sodium tetraborate.

Based on the submitted data and a review of the pertinent literature, the Panel concludes that no great hazard exists from the topical application of borate preparations containing a concentration of 5 percent or less.

(2) *Effectiveness.* Boric acid has historically been used as a treatment for superficial fungal infections. It has also been used to treat oral candidal infections. In vitro data were not submitted for this ingredient nor are they available in the recent medical literature.

Boric acid is one of the more common components of OTC topical antifungal drugs. However, none of the literature submitted and reviewed met the Panel's definition of a well-designed clinical study. All studies lacked KOH microscopic examinations and cultures. The therapeutic trials were not blinded or controlled.

Only in a study by Weidman and Glass (Ref.*10*) was boric acid tested as a single active ingredient. This study used a 5-percent boric acid in talc preparation and compared the treatment and prophylactic effects of this drug to various other topical agents. The authors stated that they made no attempt to discriminate between mycotic and bacterial toeweb infections. There were no control subjects. Of the 20 patients originally treated, six were "cured," three "nearly cured," one "improved," seven remained "stationary," and three "worsened."

The Panel is not aware of any other studies evaluating the effectiveness of boric acid as a single ingredient in the treatment of fungal diseases. Therefore, because of the lack of data evaluating the topical use of boric acid as an antifungal agent, the Panel recommends Category III for effectiveness.

(3) *Proposed dosage*—(i) *Concentration.* Boric acid and sodium borate may be used alone or in combination to equal a total borate recommended concentration of 0.5 to 5 percent.

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

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

(5) *Evaluation.* The Panel recommends in vitro testing and one double-blind, placebo-controlled clinical trial to determine the effectiveness of borates in

the treatment of athlete's foot, jock itch, and ringworm. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III. paragraph E. below—Guidelines for safety and Effectiveness Studies.)

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(9) OTC Volume 070221.

(10) Weidman, F. D., and F. A. Glass, "Dermatophytosis and Other Forms of Intertriginous Dermatitis of the Feet. A Comparison of Therapeutic Methods," *Archives of Dermatology and Syphilology*, 53:213–225, 1946.

f. *Caprylates (sodium caprylate and zinc caprylate).* The Panel concludes that the caprylates (sodium caprylate and zinc caprylate) are safe but that there are insufficient data available to permit final classification of their effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Caprylic acid (normal octylic acid) is a long-chain saturated fatty acid with eight carbon atoms. It is one of several fatty acids occurring naturally in human sweat and sebum and has antifungal properties. As the pH shifts from acid to alkaline on the surface of the skin, caprylic acid is converted to its less active salt form, known as caprylate (Ref. *1*). In the products reviewed by the Panel, sodium caprylate occurs in concentrations of 1 to 26 percent; zinc caprylate is present in a 5-percent concentration.

At the Pasteur Institute in 1913, Kiesel investigated the ability of fatty acids to retard the germination of molds (Ref. *2*). He demonstrated that the length of the carbon chain in the fatty acid determined the antifungal activity of the fatty acid. This antifungal activity increased up to 11 carbon atoms, provided that the carbon chain was unbranched and not substituted with hydroxyl groups (Ref. *3*).

In 1938, Peck and Rosenfeld (Ref. *4*) showed by in vitro testing that fatty acids could inhibit growth and be fungicidal to dermatophytes and various other pathogenic fungi. They further demonstrated in vitro that human sweat was fundicidal and fungistatic because of its fatty acid content. In clinical studies Peck et al. (Ref. *5*) showed that sodium propionate, one of the fatty acid components of sweat, could be successfully used to treat jock itch and athelete's foot.

The clinical use of fatty acids in the form of caprylates, propionates, and nundercylenates as antifungal agents became common during the 1940's and has continued up to the present. Interestingly, it was during this same period that the fatty acids were commonly incorporated into bread as antimicrobial agents, following confirmation in 1939 by Hoffman et al. (Ref. *6*) that the fatty acids had remarkable fungistatic activity against common bread molds.

(1) *Safety.* The oral LD_{50} of caprylates in rats is reported to be 1,410 mg/kg. An intravenous LD_{50} in mice is reported to be 600 mg/kg (Ref. *7*). One report indicated a topical LD_{50} in rabbits to be 710 mg/kg, which appears to be unexpectedly low compared to the previously mentioned LD_{50}'s (Ref. *7*). The Panel concludes that either the rabbit is especially sensitive to the topically administered caprylates, or the reported figure may be incorrect.

Dreisbach (Ref. *8*) indicated that the caprylates are nonirritating and that a toxic oral dose would be more than 2 g/kg. Sax (Ref. *9*) suggested that many of the details of the toxicology of the caprylates are unknown. In humans, however, sodium caprylate has been used to treat various dermatophytoses without significant toxicity or irritation. A 10-percent sodium caprylate ointment was used in 46 patients without irritation or sensitization even where the epithelium had been denuded (Ref. *10*). However, when a 10-percent jelly and poweder were used to treat vaginitis, both preparations produced some irritation (Ref. *11*). Cohen (Ref. *12*) gave intravenous doses up to 8 g in humans with no ill effects. Daily intravenous doses of 3 g for 3 months were also tolerated.

Considering Cohen's work (Ref. *12*) and the lack of toxicity known to occur from the caprylates, the Panel concludes that the caprylates are safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* The caprylates have in vitro antimicrobial activity against dermatophytes, *C. albicans*, and bacteria. The antimicrobial activity varies significantly with the pH of the in vitro test system. Antimicrobial activity is greater at acid pH than at alkaline ph (Ref. *3*).

The caprylates can be either fungistatic or rungicidal against dermatophytes, depending on the concentration of the caprylates, the pH of the environment, and the exposure time to the drug. In vitro, caprylic acid was found to be fungistatic at concentrations of 0.009 percent and 0.015 percent against *Trichophyton purpureum (T. purpureum)* and *T. interdigitale*, respectively. As the pH of the environment increased from 4.5 to 7.5, the concentration of caprylic acid required for fungistatic action against *T. interdigitale* increased tenfold from 0.003 to 0.03 percent. In the same study, at pH 6.5 the in vitro fungicial concentration of caprylic acid against *T. interdigitale* was 0.45 percent (Ref. *3*).

In another in vitro study carried out at a test system pH of 7.5, the concentrations of sodium caprylate necessary to completely inhibit fungal growth for 3 weeks were 0.1 percent for *T. rubrum, E. floccosum*, and *M. audouinii*, and 1.0 percent for *T. mentagrophytes* (Ref. *13*). The same concentrations were also fungicidal to these same test organisms, and no growth occurred within 3 weeks after the fungal mats were removed from the culture tubes and replanted on dextrose agar slants.

The investigators also used the Burlingame-Reddish technique to determine the shortest time at pH 7.4 needed to kill fungi exposed to 0.1, 1, and 10 percent concentrations of sodium caprylate. A concentration of 0.1 percent was not fungicidal to any of the dermatophytes, whereas a 1-percent concentration of sodium caprylate was fungicidal after 5 minutes for *T. rubrum* and *T. mentagrophytes*. For *M. audouinii*, however, a 1-percent concentration was fungicidal only after 15 minutes, but a 10-percent concentration sodium caprylate killed *M. audouinii* after a 5-minute exposure time. Spores of *T. mentagrophytes* were not killed by 1 : 5 dilutions of sodium

caprylate after exposures of 5, 10, and 15 minutes (Ref. *13*).

Lyons and Livingood (Ref. *14*) performed a test procedure similar to the one described above but with 20 percent caprylic acid in an aerosol containing isopropyl alcohol and propylene glycol. These investigator showed that a 5-minute exposure was required to kill *T. purpureum*. In contrast to earlier studies by Golden and Oster (Ref. *15*), these investigators found that a 1-minute contact with 5, 10, or 20 percent caprylic acid did not kill *T. purpureum* (Ref. *14*).

Sing and Verhagen (Ref. *16*) used 10 percent caprylic acid in an ointment base at pH 6.7 and found a 2.7-cm zone of inhibition after 96 hours in a culture of *T. mentagrophytes*. They observed that the fungus developed resistance to the caprylic acid over exposure periods of 1 to 3 months, and the zones of inhibition of the cultures gradually became smaller over a 4-week period. This observation raised the possibility that fungi living on the skin might develop a certain degree of resistance against caprylic acid and other fatty acids found naturally in sweat.

Vicher et al. (Ref. *17*) found that in a subfungistatic concentration of 0.01 percent, sodium caprylate inhibited the metabolism and growth of *T. rubrum* as shown by decreased mycelial dry weight, decreased pigment formation, and altered fatty acid composition of the *T. rubrum*.

The effects of sodium caprylate on *C. albicans* have been extensively studied. In 1962, Watt et al. (Ref. *18*) found that the inclusion of 2.5×10^{-3} molar (M) sodium caprylate in Sabouraud's dextrose agar was the maximum concentration of caprylate tolerated for slight growth of *C. albicans*. At this concentration the caprylate inhibited the separation of buds from the parent cells of *C. albicans*, changed the affinity of the yeast cells for staining, and caused enlargement of the nuclei of the cells and buds (Ref. *18*). Sodium caprylate was bound to the cells within 5 minutes and began to inhibit them within that time. As the concentration of sodium caprylate was increased from 0.0025 to 0.1 M, the cellular integrity of *C. albicans* was progressively lost, with disorganization and collapse of the cells, leakage of important cellular constituents, and ultrastructural changes in cytoplasmic organelles (Ref. *19*).

Tsukahara (Ref. *20*) suggested that the adsorption of caprylic acid to the yeast cells must be extremely strong and specific because once the cells of *C. albicans* are exposed to caprylic acid, even rapid washing with distilled water does not affect its fungicidal activity. He also found the minimal fungistatic and fungicidal concentrations of caprylic acid at pH 5.6 to be 1/1,600 M and 1/400 M, respectively. Tsukahara also showed that *C. albicans* cells were completely killed by treatment with 10^{-3} M caprylic acid for 10 minutes in a phosphate buffer solution at pH 5.91. However, he noted a sharp drop in fungicidal activity between pH 6.24 and 6.64 after 10 to 60 minutes of treatment with caprylic acid. Caprylic acid did not show fungicidal activity above pH 6.98 during a 1-hour exposure. After 24 hours of exposure, however, complete suppression was noted. Tsukahara concluded that caprylic acid should be used in an acid buffered solution at a pH below 6.24. It is interesting to note that Keeney, Ajello, and Lankford (Ref. *13*) reported that at pH 7.4 the fungistatic and fungicidal concentrations of sodium caprylate against *C. albicans* were 0.1 and 1 percent, respectively.

In 1941, Cowles (Ref. *21*) discovered that the fatty acids including sodium caprylate, were bactericidal at low pH values. This activity increased with increasing chain length of the fatty acids. In a later study, the concentration of caprylic acid necessary to inhibit the growth of *S. aureus* at pH 6.5 was reported to be 0.06 percent (compared with concentrations of 0.015 and 0.009 percent required to inhibit the growth of *T. interdigitale* and *T. purpureum*, respectively) (Ref. *3*).

The Panel is aware of only two clinical studies in which caprylates were used as a single active ingredient to treat dermatophytic fungal infections (Refs. *10* and *22*). In 1945, Keeney et al. (Ref. *10*) used a 10-percent sodium caprylate ointment (carbowax base) in a controlled study to treat 91 midshipmen with athlete's foot at the U.S. Naval Academy. Forty-six men used the caprylate ointment; the other 45 used the ointment base alone. Athlete's foot was diagnosed by a positive KOH preparation and clinical signs and symptoms before beginning the study. Two cultures were also taken from each participant before beginning treatment. Of the 91 men, 57.3 percent (52/91) eventually had positive cultures, 5.8 percent (5/91) of which were positive for *C. albicans*.

The men were told to apply the ointment to the feet every evening and remove it in the morning. Followup examinations with KOH preparations were performed once weekly for 6 weeks. After the first 2 weeks, 43 percent (17/40) of the caprylate-treated group were clinically clear; only 27.5 percent (11/40) of this group still had positive KOH preparations. In contrast, only 2 percent of the control group had cleared, and 74.3 percent (29/39) still had positive KOH preparations.

The best results in this study were seen after 4 weeks of treatment in the caprylate-treated group: 64 percent (25/39) of the men were symptomatically clear, and only 9.3 percent (4/43) had positive KOH evidence of fungi. These results contrasted with the 4-week results of the control group where only 8 percent (3/37) of the men were clinically clear and 56.7 percent (19/33) had positive KOH preparation. Interestingly, after the 4-week period the participants apparently became indifferent to following instructions and treatment became erratic. This resulted in a relapse of clinical symptoms in 76 percent (25/33) of the treated group in the fifth week of treatment, although only 14.2 percent (6/42) had positive KOH preparations at this time.

After the sixth week of treatment, 50 percent (19/38) of the treated group were again clear. This success contrasts sharply with the control group in which only 13 percent (5/39) of the men were clear after 6 weeks. No irritation or sensitization was reported even when the caprylate ointment was applied to denuded skin. Itching was also relieved soon after application of the sodium caprylate ointment. Although the results obtained with the caprylate ointment appear to be significantly better than those obtained with the ointment base, they must be viewed in light of the following inadequacies in study design: (1) No double-blinding, (2) no lag period after treatment stopped, and (3) no followup cultures.

In 1946, Hopkins et al. (Ref. *22*) reported the use of a 5-percent sodium caprylate ointment in infantry soldiers at Fort Benning, Georgia, in hot, humid weather. This report was part of a large, uncontrolled study using 7,500 volunteers to test over 70 fungicides. The criteria for cure were strictly clinical and included the disappearance of itching, scales, and vesicles. A KOH preparation was performed at each visit to determine whether the patient was "fungus negative." A fungal culture was obtained before beginning teatment, but the results were not reported.

Among 44 men treated with 5 percent sodium caprylate ointment for 1 to 2 weeks, 27 percent (12/44) became clinically clear, 45 percent (20/44) were fungus negative, and itching was relieved in 58 percent (26/44). Half of these subjects remained in the study 3 to 4 weeks later. Of these 22 soldiers, 36 percent (8/22) were clinically clear and 83 percent (18/22) were fungus negative. Skin irritation developed in 2 percent (1/

44) of all participants, but was not severe.

As another part of the Fort Benning study, 26 men were treated for jock itch for 1 week only. Of these, 39 percent (10/26) were clinically clear and 46 percent (12/26) were fungus negative. Another subgroup of 15 patients was treated for 2 weeks only. Of these patients, 27 percent (4/15) were clear while 40 percent (6/15) were fungus negative. Hopkins et al. (Ref. *22*) concluded that the results obtained from sodium caprylate ointment were similar to those from undecylenic acid.

Keeney (Ref. *23*) reported that a 20-percent solution of sodium caprylate adjusted to pH 7.4 was effective in treating *C. albicans* lesions in the mouth when applied three to four times daily. He also reported that a 10-percent caprylate jelly appeared promising in the treatment of vaginal *C. albicans* infections.

In 1946, Keeney (Ref. *11*) presented two detailed case reports in which caprylates were used successfully to treat candidiasis: A 20-percent aqueous solution of sodium caprylate completely cleared oral cadidiasis of 6 months' duration in a 2-year-old child after 20 days of treatment. Similar results were noted in five other children with similar oral lesions. In addition, a 47-year-old woman with extensive candidiasis of the mouth, vagina, neck, arms, hands, thighs, and buttocks was treated with various dosage forms of 10 percent sodium caprylate. She was completely cleared in about 2 months.

Reich et al. (Ref. *24*) reported the results of the treatment of 93 women with vaginitis caused by *C. albicans*. Each patient was seen twice weekly and treated intravaginally with 20 percent aqueous sodium caprylate and a cream and powder containing 10 percent sodium caprylate and 5 percent zinc caprylate. In addition, each patient douched nightly with dilute caprylate solution and inserted caprylate cream intravaginally. Fungal cultures were repeated weekly, and the patients were instructed not to douche within 24 hours before culture. A "cure" required three consecutive negative cultures. Culture results were negative in 62.3 percent (58/93) after 1 week, 70 percent (65/93) after 2 weeks, 76.4 percent (71/93) after 3 weeks, and 86.2 percent (80/93) after 5 weeks. Cultures of over half of the patients became negative after 7 days and remained negative throughout the following weeks. The treatment failed in 14 percent (13/93) of the patients. Reich et al. concluded that caprylic acid was a very effective agent for the treatment of vaginal candidiasis and noted the following advantages of caprylic acid: "marked fungistatic and fungicidal action, ready penetration of epithelial layers, and considerable bacteriostatic effect on *Staphylococcus aureus* and beta-hemolytic streptococcus."

In 1954, Neuhauser (Ref. *25*) administered a caprylic acid-resin complex in capsule form to treat intestinal candidiasis in two patients with severe diarrhea. One patient received a dose of 115 mg caprylic acid four times a days, and the other patient received a dose of 121 mg caprylic acid four times a day. Both patients improved dramatically within 1 week. Treatment was continued for about 1 month, at which time stool cultures were negative for *C. albicans*. No undesirable drug-related side effects were observed.

The Panel concludes that sodium and zinc caprylate should be placed in Category III for clinical effectiveness in the OTC treatment of athlete's foot, jock itch, and ringworm. The Panel notes that the controlled study by Keeney et al. (Ref. *10*) in 1945, although it does not meet all of the criteria suggested elsewhere in this document for clinical testing of antifungal products, represented a well-designed study for its time. Nonetheless, further evidence of effectiveness is needed to fully assess the caprylates.

(3) *Proposed dosage*—(i) *Concentration.* Sodium caprylate and zinc caprylate may be used alone or in combination to equal a total caprylate concentration of 10 to 20 percent.

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

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

(5) *Evaluation.* The Panel recommends one double-blind, placebo-controlled clinical trial to determine the effectiveness of the caprylates in the treatment of athlete's foot, jock itch, and ringworm. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

In addition, the Panel concludes that the caprylates have the added desirable attribute of significant in vitro activity against *C. albicans*, which is often present in jock itch but less commonly found in athlete's foot. The Panel knows of no double-blind, controlled studies in which caprylates are compared to an inactive control, such as the ointment base, in the treatment of *C. albicans* infections. Consequently, the Panel would require such a study before a product containing caprylates could be labeled as effective against *C. albicans* infections of the skin.

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g. *Chlorothymol.* The panel concludes that there are insufficient data available to permit final classification of the safety an effectiveness of chlorothymol for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Chlorothymol ($C_{10}H_{13}C10$) is a white, crystalline, granular powder with an aromatic pungent taste and characteristic odor. It becomes yellowish-brown with age and exposure to light. Chlorothymol is almost insoluble in water, but soluble in alcohol, ether, benzene, and chloroform (Ref. *1*). In marketed products, chlorothymol is present in concentrations of 0.2 to 1.0 percent.

(1) *Safety.* Chlorothymol is structurally and physically related to phenol; hence its toxicology is similar to that of phenol. (See part III. paragraph B.1.e. above—Phenolates (phenol and phenolate sodium).) In equal concentrations, however, toxic signs and symptoms for chlorothymol are much less severe than for phenol.

Chlorothymol is apparently strongly irritating to the skin (Ref. *2*). Aqueous solutions are so intensely irritating to mucous membranes (Ref. *3*) that by themselves they are almost impossible to use in the mouth in a high enough concentration to be practical (Ref. *4*).

The systemic effects of chlorothymol are presumably like those of thymol and phenol. However, it is probably less toxic than either of these two agents (Ref. *3*).

(2) *Effectiveness.* Chlorothymol is a much stronger antifungal agent than thymol, a characteristic which is indicative of the general principle that substitution of halogen atoms on a phenol ring increases the fungicidal power of the chemical (Ref. *5*). In vitro tests with *T. mentagrophytes* indicated that the minimal fungicidal concentration of chlorothymol dissolved in 95 percent ethyl alcohol is 0.1 percent for 5-day cultures and 0.5 percent for 10-day, 15-day, and 20-day cultures. In vitro testing of 10 antifungal agents (including thymol, phenol, salicylic acid, and undecylenic acid) found chlorothymol to be the most powerful (Ref. *2*). Using *monilia tropicalis (M. tropicalis)* as a test organism, chlorothymol was found to inhibit growth at an aqueous solution concentration of 1:9,000. It did not, however, inhibit growth at a concentration of 1:5,000 if protein from vesicle fluid or blood serum was present. Fungicidal dilutions of chlorothymol were found to be 1:7,000 at 1 minute and 1:8,000 at 30 minutes and 60 minutes (Ref. *5*). In another in vitro test of chlorothymol, guinea pig scales infected with *T. mentagrophytes* were immersed in various antifungal agents. After exposures of 5 to 60 minutes, 5 percent *p*-chlorothymol in propylene glycol did not inhibit fungal growth (Ref. *6*).

Chlorothymol has phenol coefficients of 63.3 against the typhoid bacillus and 158 against staphylococci. In the presence of organic matter, these phenol coefficient values were reduced to 21.7 and 57.3, respectively (Ref. *7*). Chlorothymol 0.005 percent (0.5 g in 1,000 mL solution), in combination with thymol, thyme oil, boric acid, eucalyptol, menthol, and methyl salicylate, was once an important antibacterial ingredient of NF antiseptic solution (Ref. *7*). The solution was used chiefly as a mouthwash for halitosis.

The Panel is not aware of any clinical studies using chlorothymol as the sole antifungal ingredient.

(3) *Proposed dosage*—(i) *Concentration.* Chlorothymol 0.02 to 1 percent.

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

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

(5) *Evaluation.* The Panel recommends complete safety testing of chlorothymol. The Panel also recommends one double-blind, placebo-controlled clinical trial to determine the effectiveness of chlorothymol in the treatment of athlete's foot, jock itch, and ringworm. Data to demostrate safety and effectiveness will be required in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

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h. *Chloroxylenol.* The Panel concludes that chloroxylenol is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Chloroxylenol is a halogen-substituted phenolic compound developed in Germany in 1927. Chloroxylenol (4-chloro-3,5-dimethyl-phenol) is also known as parachlorometaxylenol or PCMX. It is a white, crystalline powder with a melting point around 115.5° C. One g chloroxylenol dissolves in 3 L of water at 20° C; in hot water it is more soluble. Chloroxylenol is also soluble in 95 percent alcohol, ether, benzene, terpenes, fixed oils, and in solutions of alkali hydsroxides (Ref. *1*).

In submission reviewed by the Panel, chloroxylenol occurs in concentration of 0.5 to 3.75 percent.

(1) *Safety.* The oral LD_{50} of chloroxylenol in rats is 5 g/kg and in mice, 3.6 g/k. The oral minimal lethal dose is 2.8 g/kg in the rat and 1.5 g/kg in the mouse. Rats can tolerate 10 consecutive daily oral doses of 20 to 30 mg/kg. The topical minimal lethal dose in the rabbit is 4 g/kg (5 to 7 daily doses). Rabbits can tolerate topical application of 2 g/kg daily for 10 days without adverse effects (Ref. *2*).

In high concentrations (30 percent chloroxylenol in propylene glycol) this drug may be damaging to the rabbit eye (Ref. *3*). But in concentrations normally used in topical antifungal preparations, chloroxylenol may be only a moderate irritant to the eye (Ref. *4*).

Several studies have been conducted to assess the safety of chloroxylenol when applied to the skin. Unfortunately, most of these studies have been on the final formulation, which makes assessment of chloroxylenol a little more difficult.

A 30-day topical study was conducted at three dose levels of chloroxylenol (112.5, 360, and 1,200 mg/kg) in rabbits. The low dose was achieved by application of 1.5 mL of 3.75 percent chloroxylenol. Females in the low-dose group lost 0.65 percent body weight, while males gained 10.54 percent. (Control males also gained weight.) The females in the two higher-dose groups did not show this weight loss; rather, they gained 6 percent. No other adverse effects were noted in the group receiving 3.75 percent chloroxylenol (Ref. *2*).

Dogs have also been treated topically with solutions of 3.75 percent chloroxylenol (0.5 mL/kg) for 1 year. Interim data after 8 months reveal no evidence of toxicity at this level (Ref. *2*).

Rabbits were dosed topically with 1.8 percent and 18 percent solutions of chloroxylenol in propylene glycol at a rate of 1.0 mL/kg/day/. Fifteen applications were made of abraded skin, 65 applications on intact skin, No gross signs of systemic toxicity were noted in any test animals. The 18-percent chloroxylenol solution caused moderate to extreme skin irritation, the 1.0-percent chloroxylenol caused only minimal skin irritation characterized by mild erythema and desquamation. These same signs were also noted in control animals receiving only propylene glycol vehicle. Representative tissue samples at autopsy showed no pathologic changes attributable to chloroxylenol treatment. (Ref. *5*).

A patch test using 163 randomly assigned subjects (71 females, 92 males) showed that pure chloroxylenol did not irritate or sensitize under the test conditions (Ref. *3*). In a repeated insult patch test involving 64 subjects, a 2-percent solution of chloroxylenol in propylene glycol proved too irritating for continued application. One to three applications produced irritation resembling a chemical burn. In this same test, a 0.2-percent solution of chloroxylenol in propylene glycol irritated the skin no more than the vehicle (Ref. *3*).

From these studies, it appears that high concentrations of chloroxylenol in a vehicle in which it is soluble can severely irritate the skin. In 2 percent concentrations, chloroxylenol apparently also retains some irritation potential, though considerably lessened, but a 1.8-percent solution in propylene glycol is no more irritating than the vehicle. It may therefore be concluded that in the concentrations used in athlete's foot preparations, chloroxylenol would not be irritating to the point of precluding its use.

In an inhalation study (Ref. *3*) of aerosol chloroxylenol, rats were exposed to either 205 mg/L or 988 mg/L of aerosol formulation for 1 hour. (This would be 0.1 mg/L and 5 mg/L of chloroxylenol. Stated differently, if a rat inhales at the rate of 100 times per minute with a tidal volume of approximately 1.5 mL, then the lung exposure to chloroxylenol would be 3.6 mg/kg/h and 180 mg/kg/h, respectively.) The low dose resulted in no deaths. The high dose resulted in 6 deaths out of 10 animals during the exposure period and one death among the survivors during a 14-day observation period. The vehicle for the aerosol was ethanol, and the aerosolizer was a mixture of fluorinated hydrocarbons. The Panel recognizes that the vehicle may affect the final results of this study. Because deaths did not occur in the low-dose group at the same rate as the high-dose group, this was considerded not to be the case.

It has recently been reported that chloroxylenol in doses in the general use range is rapidly and completely absorbed into systemic circulation from the oral, topical, or subcutaneous routes of administration (Ref. *6*). A study was conducted comparing the oral and topical absorption, distribution, excretion, and biotransformation of C^{14}-chloroxylenol in rats (Ref. *6*). A 48-mg/kg dose of C^{14}-chloroxylenol was applied to the shaved and abraded backs of the rats. The chloroxylenol was in a commercial product solution which was diluted to 25 percent. The solution was applied to a 25-cm^2 pad backed by aluminum foil and was allowed to stay in place for 6 hours. The orally dosed rats were given the same 25-percent solution (48 mg/kg chloroxylenol).

At the apopropriate times after administration, the rats were killed. Blood samples were taken, and urine and feces were collected for excretion analysis. Orally administered chloroxylenol was absorbed faster and more completely than the topically administered dose. About one-half of the topically applied chloroxylenol was absorbed in 6 hours with peak blood levels attained 2 hours after application. Peak plasma levels from oral doses occurred after 30 minutes and were about five times higher than those obtained from dermal application. Plasma half-life from the oral chloroxylenol was 60 minutes. Of the total urinary metabolites, 75 percent was chloroxylenol glucuronide, 13 percent was chloroxylenol sulfate, 10 percent was hydroxy-chloroxylenol glucuronide, and 2 percent was hydroxy-chloroxylenol sulfate (Ref. *6*). The Panel considers this a well-conducted experiment that demonstrates the rather rapid detoxification of absorbed chloroxylenol when administered in relatively low doses on a single, acute dosing basis.

In a 90-day oral study in rats (Ref. *2*), chloroxylenol was tested at dose levels of 8-mg/kg, 24 mg/kg, and 75 mg/kg. Propylene glycol was administered to the vehicle control group. Animals in the 8-mg/kg and control groups showed no effect from treatment. Groups receiving 24 or 75 mg/kg chloroxylenol showed treatment effects which included slight hemoconcentration, leucocytosis, monocytosis, and a few cases of nasal or ocular discharge.

Chloroxylenol was given orally in chronic studies in rats. Rabbits and dogs were treated topically. In these studies the most obvious signs of toxicity were decreased weight gain, gastrointestinal distress, sedation, liver degeneration and thickened, exudative skin (Ref. *2*).

A diluted commercial solution of chloroxylenol was used in subchronic and chronic studies in dogs (Ref. *7*). Doses of 120 mg/kg, 60 mg/kg, and 1.2 mg/kg chloroxylenol were administered orally to beagles for 13 weeks. The only dose-related effect observed was an increase in liver weight. Occasional vomiting was observed in the two higher-dose groups, but this could have been vehicle induced. Although this study is inconclusive because of the possible influence of the vehicle, it appears to the Panel that relatively low doses of chloroxylenol can be systemically tolerated, at least over a 13-week period. The Panel is concerned about the effect of chronic administration on the liver, but does not consider that topical application of chloroxylenol to small areas of the skin

over short periods of time would result in liver damage.

Zondek (Ref. *8*) studied the use of chloroxylenol in humans, using the oral, percutaneous, and intramuscular routes of administration. He administered up to 94 g chloroxylenol over a 7-day period in an attempt to treat urogenital infections. Zondek noted that no toxic effects were seen in any of the cases he treated with chloroxylenol.

Zondek and Finkelstein (Ref. *9*) studied the absorption, metabolism, and excretion of chloroxylenol administered percutaneously to 11 humans. The chloroxylenol was disolved in an alcohol-oil mixture and was applied as a 40-percent solution of chloroxylenol. The area or size of application was not specified. Five g chloroxylenol was necessary to produce detectable blood levels, while 8 g applied topically resulted in blood levels of 10 μg/mL after 3 hours and 40 μg/mL after 24 hours. A 20-g dose resulted in 40 μg/mL in 30 minutes and 10 μg/mL remained 72 hours after dosing. The researchers stated that percutaneous administration of up to 30 g daily could be given without toxic effects.

Ten g chloroxylenol dissolved in olive oil was administered orally to one patient. Blood levels were found to be 20 μg/mL after 1 hour, 14 μg/mL after 24 hours, and 0 μg/mL after 48 hours (Ref. *9*).

Twelve patients were injected intramuscularly with a 10-percent solution of chloroxylenol in olive oil containing 2 percent anesthesin (benzocaine). The blood was analyzed two to six times over a 48-hour period. Blood concentrations varied according to dose (either 1 or 2 g chloroxylenol), but blood levels never exceeded 40 μg/mL, which occurred in a patient with hepatitis. When 2 g chloroxylenol was given intramuscularly, blood concentrations of 12 to 30 μg/mL were observed 1 to 2 hours after injection. Forty-eight hours after injection, no chloroxylenol was present in the blood (Ref. *9*). Zondek (Ref. *8*) reported that following intramuscular injection, 10 percent was excreted in the urine as free chloroxylenol, 14 percent as chloroxylenol glucuronide, and 17 percent as chloroxylenol sulfate.

These studies in humans are rather old (early 1940's), and the mode of treating urinary infections described in these reports is no longer used. Nevertheless, these studies demonstrate that blood levels of chloroxylenol possibly attained from topical application to athlete's foot, jock itch, or ringworm would not be toxic. Human patients have been given doses of chloroxylenol by the oral, parenteral, or percutaneous routes that are larger than would be used in antifungal products. Some of these large doses were administered over periods of at least 1 week, and no toxic effects were observed. Even though some cases of minor irritation have been reported, the Panel concludes that chloroxylenol in concentrations of 3.75 percent or less is safe for OTC antifungal use in treatment of athlete's foot, jock itch, or ringworm.

(2) *Effectiveness.* Chloroxylenol has been shown to be active in vitro against fungi and gram-positive and gram-negative bacteria. It was tested in a propylene glycol vehicle in tenfold serial dilutions from 8 mg/mL to 8×10^{-9} mg/mL. Chloroxylenol killed *C. Albicans* at 8×10^{-1} mg/mL, but growth was seen at 8×10^{-2} mg/mL. Against *T. Mentagrophytes*, chloroxylenol inhibited growth only at the highest concentration (8 mg/mL). The minimal inhibitory concentration of chloroxylenol in propylene glycol is reported as 0.125 mg/mL against *C. Albicans* and 1.0 mg/mL against *T. mentagrophytes* Ref. *10*).

The Panel reviewed in vitro data on 4.8 percent chloroxylenol in a pine oil-soap vehicle (Refs. *6* and *7*). The submissions noted that studies on chloroxylenol alone are difficult to do because of the very low solubility of this ingredient in water. In vitro data included studies that had used the modified A.O.A.C. (Association of Official Agricultural Chemists) phenol coefficient test and determination of killing dilutions for a variety of species of fungi and bacteria. The comparative phenol coefficient test is appropriate because chloroxylenol is a substituted phenol. Spore suspensions of dermatophytic fungi were used in these tests.

Chloroxylenol is usually included in products for its antibacterial activity. The results of the studies mentioned above show that chloroxylenol has much greater activity against gram-positive organisms than gram-negative organisms. The most resistant strain was *P. aeruginosa.*

The killing dilution (defined as the extent to which the product may be diluted and still kill the test organism within 10, but not 5, minutes) was determined after velvet transfer of the organism from the skin. The results showed killing dilutions of 1:300 for *T. rubrum*, 1:160 for *T. mentagrophytes*, 1:200 for *E. floccosum*, and 1:125 for *C. albicans*. Using the modified A.O.A.C. testing procedure, the following killing dilutions were obtained: 1:130 for *C. albicans*, 1:150 for *M. canis*, *T. mentagrophytes*, and *T. interdigitale*, and 1:300 for *T. rubrum*. *C. albicans* was the most resistant organism, but *Candida* species as a whole were more susceptible to chloroxylenol than dermatophyte spores. The minimal inhibitory concentrations are as follows: *C. albicans* 16,000 μg/mL, *T. rubrum* 48,000 μg/mL, *M. canis* 48,000 μg/mL, and *T. interdigitale*, 48,000 μg/mL (Ref. *7*).

The effect of organic material (serum) on the antifungal activity of chloroxylenol was determined. Dilutions of chloroxylenol in distilled water, 5 percent serum in distilled water, and in some cases 20 percent serum in distilled water were tested. The results expressed in μg/mL in distilled water, 5 percent serum, and 20 percent serum, respectively, are as follows: *T. interdigitale*—3,125, 3,125, and 2,400; *C. albicans*—2,700, 4,000, and 1,040; *M. canis*—3,125 and 2,500; *T. mentagrophytes*—3,125 and <800; *T. rubrum*—6,250 and 4,800. As expected, the activity of chloroxylenol decreased in the presence of organic material (Ref. *7*).

The Panel concludes that the susceptibility of the dermatophites to chloroxylenol is not great. Because of the very high minimal inhibitory concentration values obtained, very high concentrations of chloroxylenol would have to be used in formulations to obtain any antifungal effect.

The Panel was able to locate only one published study (Ref. *11*) examining the effectiveness of chloroxylenol in the treatment of athlete's foot. In this study by Walker, 128 patients with clinically diagnosed athlete's foot were treated with a 0.5-percent chloroxylenol solution containing various other ingredients (thymol, menthol, acetone, and wormwood). Diagnosis was confirmed by positive KOH preparation or positive culture in 112 patients. Shortcomings of the study design include the lack of controls and double-blinding and the failure to collect adequate followup data after therapy was discontinued. Patients were treated for varying lengths of time, ranging from 1 to 9 weeks. The author reported that "92 percent had symptoms cleared and improvement shown; 8 percent had poor results." But he gave no specific data on clinical appearance, KOH, and culture growths.

The Panel concludes that the effectiveness of chloroxylenol is questionable because of the lack of a controlled clinical trial.

(3) *Proposed dosage*—(i) *Concentration.* Chloroxylenol 0.5 to 3.75 percent.

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

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

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

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1. *Cresols (m-cresol and secondary amyltricresols).* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of cresols (*m*-cresol and secondary amyltricresols) for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Cresols are methyl derivatives of phenol. Derived from coal tar, cresols are separated from phenol by fractional distillation (Ref. *1*). They are soluble in organic solvents and fixed alkali hydroxides, but are relatively insoluble in water (Ref. *2*).

Cresol is also known as cresylic acid and tricresol, as it contains a mixture of three chemical isomers of cresol. Cresol NF contains not more than 5.0 percent phenol. It is a colorless or yellowish-brown liquid which turns brown with aging and exposure to light and must be preserved in light-resistant containers (Ref. *3*).

(1) *Safety.* Cresol is structurally and pharmacologically related to phenol and is just as toxic. (See part III. paragraph B.1.e. above—Phenolates (phenol and phenolate sodium).) The symptoms and treatment of cresol poisoning are also similar to those of phenol (Refs. *2* and *4*).

For *m*-cresol the oral LD_{50} in rats is 242 mg/kg and the LD_{50} via skin absorption is 620 mg/kg (Ref. *5*).

Cresol is a general protoplasmic poison and associates with protein (Ref. *6*). Many cases of cresol poisoning have been reported. In humans the oral ingestion of 8 g or more produces rapid circulatory failure and death. After ingestion, there is a severe burning sensation in the mouth and upper abdomen, difficulty in swallowing, vomiting, and diarrhea. White spots are seen on the mucous membranes. Unconsciousness and circulatory collapse then follow. If the patient survives, jaundice, reduced excretion of urine, and uremia may develop (Ref. *2*). Chronic poisoning from oral or percutaneous absorption may produce digestive disturbances, neurological disorders, vertigo, and skin eruptions (Ref. *6*).

Cresol is also a skin irritant and may cause erythema, a burning sensation, or numbness (Ref. *2*).

One of the submissions to the Panel (Ref. *7*) was for a product composed of camphorated *m*-cresol. It was stated that an inter-molecular complex was formed between camphor (66 percent) and *m*-cresol (22 percent). According to Francis (Ref. *8*) such a complex is possible. Francis devised techniques to determine the amount of free cresol in such a complex and stated that "a mixture containing 20% total *m*-cresol by weight (26 mole percent) seems to contain about 1½% free *m*-cresol." He further stated that the low content of free cresol probably accounted for the high tolerance which wounds and tissues showed to these mixtures. The Panel believes that conclusive evidence that a complex forms between *m*-cresol and camphor is lacking.

It appears to the Panel that the real significance concerning the safety of camphor-cresol combinations is summed up in the following conclusion to Francis' paper: "The fact that these are equilibrium mixtures means that they will liberate free phenol or cresol as fast as that originally present is consumed and this may explain their known antiseptic and surface anesthetic effects."

Therefore the Panel concludes that in the combination of 66 percent camphor and 22 percent *m*-cresol all of the cresol would be available for absorption and thus has a significant toxicity potential. (For the Panel's discussion of camphor, see part III. paragraph B.1.a. above—Camphor.)

The Panel concludes that more data are needed to determine the safety of cresols for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. In marketed products, secondary amyltricresols are present in a concentration of 0.1 percent and *m*-cresol, 22 percent. However, the Panel concludes that not enough safety data are available to justify a 22-percent concentration and proposes an upper limit for cresols of 2.2 percent.

(2) *Effectiveness.* Cresol is more active against bacteria than phenol and has a phenol coefficient of 2 to 3. The three chemical isomers of cresol (*m*-cresol, *o*-cresol, *p*-cresol) vary little in bactericidal properties (Ref. *1*). Although cresol is a fairly effective antibacterial against common pathogenic bacilli, it is less active agent against cocci (Ref. *4*). Bacterial spores are killed only after long exposure to high concentrations of cresol (Ref. *1*).

Because cresol is relatively insoluble in water, it is usually marketed as saponated cresol solution (compound cresol solution). This consists of 50 percent cresol in saponified linseed oil or other vegetable oils (Ref. *4*). This solution mixes readily with water to produce a milky mixture, containing 3 to 5 percent concentrations of cresol and is used for disinfecting inanimate objects, such as hospital floors, dishes, and instruments (Refs. *3* and *4*). Saponated cresol solution has also been used as a handwash at 2 percent concentration (1 percent cresol), as a vaginal douche at 0.2 percent concentration (0.1 percent cresol), and on wounds at 1.0 percent concentration (0.5 percent cresol). Cresol has also been used in concentrations of 0.25 to 0.5 percent as a bacteriostatic agent in parenteral solutions (Ref. *2*).

The local irritant action of *m*-cresol has been much reduced by esterification with acetic acid to produce *m*-cresylacetate, a colorless, oily liquid with characteristic ordor. In the 1940's and 1950's, *m*-cresylacetate served as a local antispetic and mild analgesic when applied to mucous membrances of the upper respiratory tract (Ref. *1*). It was specifically used to treat infections of the nose and ear, including fungal infections of the external auditory canal (Refs. *9* and *10*). It was also used to treat infected root canals and tooth sockets. Athlete's foot was also treated with *m*-cresylacetate (Ref. *9*). It was relatively nontoxic and caused little irritation to skin or mucous membranes, even in full strength (Ref. *1*).

The cresols have been regarded as good disinfectant agents against vegetative fungi as well as against

bacteria, although they are ineffective against spores (Ref. *3*). In 1933, phenol coefficients for cresol were determined to be 1 for *T. gypseum* and 3 for *Monilia albicans (M. albicans)* (Ref. *11*). Later, the fungicidal dilutions of cresol against *M. tropicalis* were determined to be 1:180, 1:200, and 1:300 after exposures of 1, 30, and 60 minutes, respectively (Ref. *12*). In 1955, cresol disinfectant 0.25 to 5 percent was found highly effective in inhibiting the growth of *T. interdigitale* on matchstick fragments contaminated through direct contact with cultures. The exposure times ranged from 5 minutes to 24 hours, and cultures were performed both with and without a 1-minute washing in water (Ref. *13*). In a later study, the skin of guinea pigs was artifically infected with *T. mentagrophytes*. The resulting scales which formed on the skin were used in the in vitro testing of a 1-percent cresol solution. This solution prevented the growth of *T. mentagrophytes* on infected guinea pig scales after immersion periods of 30 and 60 minutes, but not after 5- and 15-minute immersions (Ref. *14*).

Cresol has not been widely used as an antifungal agent on skin. It has been used in prophylactic footbaths for athlete's foot (Ref. *15*). The Panel is aware of only two clinical studies, neither one controlled, in which cresols were used to treat athlete's foot.

At Fort Benning, Georgia, tetrabromcresol in unstated concentrations was used to treat 41 soldiers with athlete's foot (Ref. *16*). After 1 to 2 weeks, itching had been relieved in 45 percent of 36 cases; 8 percent were clinically clear and 36 percent had negative KOH examinations. After 3 to 4 weeks of treatment, only 5 percent of 21 cases examined were clinically clear although 57 percent were KOH negative. Severe irritation occurred in 2 percent of the cases. Tetrabromcresol seemed to give a low percentage of satisfactory results, but too few cases were studied to be conclusive.

The other study was done in a penitentiary (Ref. *17*) where 69 cases of athlete's foot were treated with an unstated concentration of *m*-cresylacetate. Of these cases, 16 were cured, 7 were nearly cured, 28 improved, 16 remained stationary, and 2 were worse. Overall, *m*-cresylacetate was concluded to make an "excellent showing" with improvement or cure in 73.7 percent of the cases. Skin irritation occurred in only one case, and patients did not complain of the odor of *m*-cresylacetate. Although fungal cultures were done before treatment began, culture results were not correlated with treatment results. No KOH examinations were performed, and no double-blind controls were included. However, *m*-cresylacetate was considered superior to both boric acid powder and Whitfield's ointment.

The Panel concludes that the effectiveness of the cresols is questionable because of the lack of a controlled clinical trial.

(3) *Proposed dosage*—(i) *Concentration.* *m*-Cresol and secondary amyltricresols may be used alone or in combination to equal a total cresol concentration of 0.1 to 2.2 percent.

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

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

(5) *Evaluation.* The Panel recommends the following toxicity studies for cresols: (1) Absorption from small areas of application to broken and intact skin; (2) local effects on wound healing; (3) irritation potential; and (4) potential for hypersensitivity. The Panel also recommends one double-blinded, placebo-controlled clinical trial to determine the effectiveness of cresols in the treatment of athlete's foot, jock itch, and ringworm. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

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j. *Dichlorophen.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of dicholorphen for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Dichlorophen, commonly known as G–4, is a halogenated bis-phenol consisting of two phenolic rings attached by a methylene (CH_2) linkage.

Dichlorophen was first prepared in 1929 (Ref. *1*). A light tan, free-flowing powder with a weak phenolic odor, dichlorophen darkens on exposure to bright light. Like other halogenated 2,2'-bis-phenols, including hexachlorophene, dichlorophen is practically insoluble in petrolatum solvents and has very low solubility in water (0.003 g in 100 mL at 25° C). However, dichlorophen is readily soluble in alcohols, glycols, ketones, esters, and ethers (Ref. *2*).

(1) *Safety.* Dichlorophen has been formulated for topical veterinary use as a shampoo, a component in flea powders, and for use in ear, eye, and wound medicaments in concentrations of 0.1 to 2.0 percent. It is used orally in veterinary medicine for tapeworms.

Dichlorophen overdosage may cause tremors, depression, and loss of appetite (Ref. *3*). The oral LD_{50} of dichlorophen has been reported to be 1.24 g/kg for

guinea pigs, 2.0 g/kg for dogs, and 1.58 g/kg for mice (Ref. *4*).

Dichlorophen was used in over 50 cases of tapeworm in dogs at an oral dose level of 0.18 g/kg body weight. Even though data on absorption from the gastointestinal tract were not presented, the report stated that dichlorophen appeared to be well tolerated (Ref. *5*). In another study (Ref. *6*), 133 dogs were given 0.22 g dichlorophen and 0.22 mL toluene per kg body weight as an anthelmintic. No toxicity was observed from repeated doses (frequency or total number of doses were not reported). In a third study, the regimen just described was given to cats. Toxicity was minimal or absent in most animals (Ref. *7*).

More recently, Kimbrough (Ref. *8*) found an oral LD_{50} of dichlorophen in peanut oil to be 1,660 mg/kg in female adult rats and 1,500 mg/kg in male adult rats. Signs of toxicity included diarrhea and central nervous system depression. The intravenous LD_{50} of dichlorophen suspended in saline lecithin administered to adult male rats was reported to be 16.8 mg/kg.

In a two-generation rat reproduction study (Ref. *8*), a dietary level as high as 1,000 parts per million (ppm) (50 mg/kg/day) dichlorophen produced no effect. Gross and microscopic examination of the various organs, including the brains of the parents as well as the offspring, showed no morphologic alterations attributable to dichlorophen. The marked disparity between the oral and intravenous LD_{50} suggested either poor absorption from the gut or rapid breakdown.

The above data tend to suggest no high degree of toxicity from dichlorophen. Nevertheless, the Panel is still concerned that oral studies may not adequately reflect the true toxicity potential of this chemical when administered by other routes.

Dichlorophen has been used as a taeniacide (an agent that destroys tapeworms) in veterinary medicine for years, but is not marketed for oral use in humans in the United States. It is, however, listed in the British Pharmacopeia. In Europe, adult oral doses of 2 to 3 g every 8 hours for three doses have been used for tapeworm; 1 to 2 g have been used in children. Because dichlorophen exerts a laxative effect, purgatives are not needed afterward. An appreciable number of patients treated with dichlorophen have colic, diarrhea, and nausea lasting 4 to 6 hours. Lassitude is another common symptom (Ref. *9*). Dichlorophen sometimes causes hives (route of administration not given). Jaundice and even death have followed very large doses of dichlorophen (Ref. *10*). The use of dichlorophen in dentifrices has "in exceptional cases" been followed by inflammation of the mucous tissue of the mouth and inflammation of the tongue and lips. Dermatitis around the mouth may also occur (Ref. *11*).

Patch tests of 4 and 12 percent dichlorophen in petrolatum showed no irritation on human skin (Ref. *4*). Gosselin et al. report no irritation at concentrations of 1 percent and little irritation at 4 percent (Ref. *12*).

There are two reports of allergic contact sensitization caused by dichlorophen-containing ointments and powders used to treat athlete's foot in the United States (Ref. *13*) and Germany (Ref. *14*). Contact allergy to dichlorophen has also been reported from its use as a preservative in cosmetics (Ref. *15*), dentifrices (Ref. *16* and *17*), and medicated bandages applied to the lower legs for the treatment of dermatitis associated with varicose veins (Ref. *18*). In one study, 48-hour patch testing with 4 percent dichlorophen in petrolatum in 194 humans gave three positive reactions (Ref. *2*).

The Panel could not find any studies on the use of dichlorophen on broken skin, such as on athlete's foot or jock itch. Dichlorophen is structurally related to hexachlorophene and certain aspects of toxicity observed in dichlorophen suggest the possibility that dichlorophen, like hexachlorophene, may possibly affect the central nervous system. For example, dichlorophen in large oral doses has caused tremors, depression, loss of appetite, and lassitude in animals. All of these reactions possibly indicate central nervous system activity.

Hanig, Yoder, and Krop (Ref. *19*) studied dichlorophen in rats to determine any effect this chemical might have on cerebrospinal fluid pressure as an indicator of possible central nervous system effects. These workers found no correlation between actions resulting in cerebrospinal fluid pressure changes and the degree of chemical similarity to hexachlorophene. They did not specify the dose of dichlorophen and the route of administration, though it may be assumed that hexachlorophene and dichlorophen were treated similarly. This evidence also suggests differences between hexachlorophene and dichlorophen, though it does not answer the question of effect of route of administration on toxicity potential.

The Panel is concerned that potentially toxic amounts of dichlorophen may be absorbed into the bloodstream from topical application for the following reasons: (1) Preparations for athlete's foot, jock itch, and ringworm may be used for an extended period of time; (2) these areas of application (diseased skin) may afford a significant route for absorption; and (3) occlusion of these areas of application by clothing or shoes may enhance absorption. Therefore, the Panel recommends Category III for safety pending a full assessment of the absorption characteristics of dichlorophen and its toxicity potential from extended use.

(2) *Effectiveness.* The linkage of two phenolic rings greatly increases bactericidal and bacteriostatic potency and generally decreases toxicity and irritancy compared to the corresponding monophenols (Ref. *1*). Maximum antibacterial and antifungal activity of a bis-phenol occurs when hydroxyl groups are linked in the ortho positions of each phenolic group, and chlorine is attached in the para position to the hydroxyl groups in each phenolic group (Ref. *20*). The presence of chlorine generally increases activity against gram-positive bacteria, but the chlorine must be in the 4-position of each phenolic ring for maximum activity against gram-negative bacteria and fungi (Ref. *1*).

Years ago, dichlorophen was found to have special merit as a mildew-proofing agent for fabrics (Ref. *1*). Other antifungal uses of dichlorophen have included slime control in paper mills, mold control in meats, and mildew prevention in paper, boards, felt, and rope (Ref. *2*).

Dichlorophen is fungicidal and fungistatic against several types of fungi. Fabric has been impregnated with dichlorophen is concentrations of 0.2 to 0.5 percent of fabric weight. This treatment was highly effective against cellulose-decomposing fungi. Dichlorophen is less active against protein decomposers, requiring 1 to 3 percent levels on the basis of material weight to give full mildew protection (Ref. *1*).

Less information is available about the antidermatophytic properties of dichlorophen. Shoe dubbing and shoe leather impregnated with dichlorophen 5 percent failed to inhibit growth of either *T. interdigitale* or *E. floccosum* (Ref. *21*). In vitro studies indicated that 1 percent dichlorophen in talc was fungistatic against three dermatophytes, with zones of inhibition of 1.1 cm for *T. rubrum*, 0.9 cm for *T. gypseum*, and 1.2 cm for *Trichopyton inguinale* (*T. inguinale*) (Ref. *22*). A dilution of 1:2,000 of dichlorophen killed *T. interdigitale* in 10 minutes but not in 5 minutes (Ref. *2*). The minimal inhibitory concentration of

dichlorophen against *T. mentagrophytes* was reported to be 6.25 μg/mL (Ref. *23*).

The halogenated bis-phenols are generally much more active against gram-positive than gram-negative bacteria. They are markedly bacteriostatic but slow acting, requiring a contact time of several hours to provide reasonable germicidal action. Because phenol coefficients are based on end points of 100 percent kill after a maximum of 15 minutes' contact time, single numerical values cannot be determined for dichlorophen. However, phenol coefficients ranging from 20 to 40 at 20° C and 45 to 62 at 37° C have been determined for dichlorophen. The bacteriostatic dilution of dichlorophen was 1:750,000 against *S. aureus* and 1:25,000 against *Escherichia coli* (Ref. *1*). Although a concentration of 1:2,500 of dichlorophen did not kill *S. aureus* in 5 minutes, it did kill *S. aureus* in 10 minutes (Ref. *2*). The minimal inhibitory concentration of dichlorophen against *S. aureus* has been reported to be 3.12 μg/mL (Ref. *23*). There in no evidence of development of bacterial resistance to dichlorophen. Formulated in soap solutions, dichlorophen has antimicrobial powers equivalent to other phenolic compounds, such as cresol.

The antimicrobial activity of bis-phenols is decreased by the presence of organic matter, although much of the loss is probably overcome through prolonged contact time. The antibacterial and antifungal activity of dichlorophen is also decreased by the presence of nonionic emulsifying agents (Ref *1*). For instance, the growth of *S. aureus* is inhibited by one part of dichlorophen in 2 to 5 million parts of plain broth, but only by 1:1,000 dilutions of dichlorophen if a nonionic detergent is present in the broth (Ref *2*). The antimicrobial activity of dichlorophen in cosmetic and drug formulations containing nonionic detergents must therefore be carefully considered.

Dichlorophen ointment has been used to treat ringworm infections in animals. In 1947, 2 percent dichlorophen in a petrolatum base was used to successfully treat 50 cases of ringworm in cattel (Ref. *24*) and was judged superior to topical medications containing iodine, mercury, or sulfur in arresting the spread of *Trichophyton album* infections in cattle (Ref. *25*). Later, 2 percent dichlorophen in vanishing cream base or petrolatum was used successfully to treat fungus infections in dogs and cats (Ref. *26*). Two percent dichlorophen was reported not to be effective against *Trichophyton verrucosum* infections in cattle (Ref. *27*). But in 1964, 10 percent dichlorophen in diacetone alcohol was used in Australia to successfully treat contagious foot rot in sheep, a disease with mixed bacterial causes (Ref. *28*).

In 1955, 2 percent dichlorophen in polyethylene glycol ointment USP was one of several antifungal ointments screened for effectiveness against *T. mentagrophytes* in a guinea pig animal model system (Ref. *29*). In this study, dichlorophen ointment was no better than the ointment base alone, since neither could prevent the establishment of *T. mentagrophytes* infection within 12 to 14 days following spore inoculation. In contrast, tests using the same ointments and spore concentrations with agar cup plate method and wet filter paper test demonstrated dichlorophen to be highly active in vitro (Ref. *29*).

Dichlorophen is included in many topical proprietary preparations as a preservative. A concentration of 0.5 percent dichlorophen in aqueous solution (prepared by combining it with the salts of aliphatic amines which contain an alkyl group with 12 to 18 carbon atoms) showed bacteriostatic and fungistatic activity (Ref. *2*). Cosmetics and topical medications frequently contain lower concentrations of dichlorophen, with 0.05 percent and 0.25 percent listed as preservative levels in one report (Ref. *18*). In the antifungal products submitted to the Panel, dichlorophen was always combined with other agents used against fungi, including undecylenates, chlorothymol, salicylic acid, or boric acid.

Dichlorophen has not been widely used as an antifungal agent to treat dermatophyte fungal infections in humans. No clinical trials, controlled or uncontrolled, using dichlorophen as a single antifungal ingredient have been submitted to the Panel. In fact, the Panel is aware of only a few anecdotal and poorly documented cases in the literature in which dichlorophen was used to treat fungal infections in humans (Refs. *25* and *26*).

Based on the above review of available data on dichlorophen's effectiveness, the Panel concludes that dichlorophen, in concentrations less than or equal to 0.5 percent, should be classified as a preservative rather than an active antifungal agent. The Panel further concludes that dichlorophen in concentrations above 0.5 percent should be Category III for clinical effectiveness, as the Panel knows of no data on the use of dichlorophen as a single active ingredient in the treatment of athlete's foot, jock itch, or ringworm.

(3) *Proposed dosage*—(i) *Concentration.* Dichlorophen 0.5 to 5.0 percent.

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

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

(5) *Evaluation.* The Panel requires a full toxicological assessment of dichlorophen, including blood concentrations that cause toxic effects, definition of target organs, metabolic rate, and possible blood levels obtainable from applications to broken skin. The Panel also recommends one double-blind, placebo-controlled clinical trial to determine the effectiveness of dichlorophen in the treatment of athlete's foot, jock itch, and ringworm. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

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k. *Oxyquinolines (benzoxiquine, oxyquinoline, and oxyquinoline sulfate).* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of oxyquinolines (benzoxiquine, oxyquinoline, and oxyquinoline sulfate) for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Oxyquinoline, also as 8-hydroxyquinoline and 8-quinolinol, is a white or faintly yellow crystalline powder with a pleasant characteristic odor. Its chemical formula is C_9H_7NO. One g oxyquinoline dissolves in 1,500 mL water. It is freely soluble in alcohol, acetone, chloroform, benzene, and mineral acids. Oxyquinoline is obtained by heating *o*-aminophenol with *o*-nitrophenol, glycerol, and sulfuric acid. It has bacteriostatic, fungistatic, deodorant, and keratolytic properties (Refs. *1* and *2*).

Benzoxiquine is the benzoate ester of oxyquinoline and is also known as 8-hydroxquinoline benzoate and 8-quinolinol benzoate. It is practically insoluble in water, but soluble in alcohol and ether.

Oxyquinoline sulfate, the sulfuric acid salt of oxyquinoline, is also referred to as 8-hydroxyquinoline sulfate and 8-quinolinol sulfate. It is a pale yellow, crystalline powder with a slight saffron odor and burning taste. It is freely soluble in water, slightly soluble in alcohol, and insoluble in ether (Ref. *1*). Pharmacologically, the sulfate and benzoate salts are similar in action to oxyquinoline.

The oxyquinolines are contained in currently marketed products in concentrations of 0.06 to 2.5 percent.

(1) *Safety.* Acute toxicity studies in mice showed oxyquinoline to be more toxic to female than to male mice at every concentration tested. The salt forms of oxyquinoline, however, were found to be less toxic than the parent compound. The intraperitoneal LD_{50} in mice was reported as 48 mg/kg (Ref. *3*). The oral LD_{50} in guinea pigs was 1,200 mg/kg (Ref. *4*) and the oral LD_{50} in rats was 1,200 mg/kg (Ref. *5*). An intramuscular injection of 30 mg/kg oxyquinoline was lethal to mice. Rabbits have tolerated single oral doses of 3.7 g/kg (Ref. *6*).

Humans have been given oral doses of 3 g in solution four times daily without apparent ill effect. When infected in animals, oxyquinoline is "distinctly toxic and causes marked stimulation of the central nervous system" (Ref. *6*).

The Panel is concerned about Hueper's report (Ref. *7*) that oxyquinoline may be a carcinogen. In this study, 20 percent oxyquinoline in a gelatin solution vehicle was administered to rats twice weekly intravaginally or intrarectally for a maximum of 2 years. Of the 30 rats that received the drug intravaginally, the author reported:

> In seven rats, which received intravaginal instillations of oxyquinoline, there was a marked glandular and sometimes papillary hyperplasia of the endometrium. This condition was in most cases associated with a purulent endometritis. The vaginal epithelial lining was markedly hyperplastic in three rats. In two instances, there existed in the mucosa of the cervical canal beneath a single layer of mucous-producing cylindrical cells, a stratified squamous-cell epithelial lining. The uterine cancers occuring in this series were adenocarcinomas of squamous-cell carcinomas.

These observations additionally supported the thesis that oxyquinoline is a carcinogen. Hueper advised that this chemical should be used with definite caution in humans until such time that epidemiologic studies on population groups show it to be innocuous to humans.

A recent report (Ref. *8*) summarized the studies which attempted to evaluate the carcinogenic potential of oxyquinoline. The summary included tests on mice and rats by the oral, subcutaneous, and intravaginal routes of administration. Most of the studies were reported as being either inadequately controlled or involving too few animals. The authors concluded that the carcinogenicity of oxyquinoline could not be evaluated on the basis of available data in animals. However, a mutagenicity study at a dose of 20 to 40 μg per plate noted point mutations in *Salmonella typhimurium (S. typhimurium)* TA100 in the presence of rat liver homogenate (Ref. *9*).

To assess oxyquinoline's potential for toxicity the following "worse case" is presented: If it is assumed that an average application of a 2.5-percent preparation of oxyquinoline is 1 g and that rapid complete absorption of the drug occurs, it is conceivable that the total absorbed dose could be 25 mg. This would be equivalent to an absorbed dose of 0.35 mg/kg in an adult. The Panel is concerned about this potential absorbed dose because it is known that the lethal intramuscular dose in mice is 30 mg/kg. Also, the metabolic rates of oxyquinoline are unknown. If three or four applications of the drug are made and if amounts larger than 1 g are applied (not an unusual occurrence), then oxyquinoline levels in the blood may be reached that could manifest toxic symptoms.

(2) *Effectiveness.* Oxyquinoline is reported as active only in the presence of divalent metal ions, such as iron and copper. The activity of the divalent metal-chelate complex is antagonized by

cobalt ions (Ref. *10*). Oxyquinoline is active under these circumstances against gram-positive and acid-fast organisms and fungi (Ref. *11*). Dolan et al. (Ref. *12*) conducted an in vitro study using epidermal scales taken from guinea pigs infected with *T. mentagrophytes*. The scales were suspended in test tubes of normal saline and a different antifungal agent was added to each tube. The *T. mentagrophytes* organisms were removed from the antifungal agent and tested for viability. Table 9 presents the results expressed as the time it took to kill the organisms in the presence of the antifungal agent:

TABLE 9.—FUNGICIDAL EFFECTS OF THREE ANTIFUNGAL AGENTS

Antifungal agent	Immersion time (minutes)			
	5	15	30	60
5% Undecylenic acid	+	0	0	0
10% Oxyquinoline	+	+	0	0
6% Salicylic acid, 12% benzoic acid	+	0	0	0

+ = Still viable.

The Panel notes that the 10-percent concentration of oxyquinoline is about four times the concentration present in the products on the market. Even at this high concentration, oxyquinoline was less effective than undecylenic acid or Whitfield's ointment.

In vitro data (antifungal and antibacterial) on oxyquinolines have been submitted to the Panel (Refs. *13, 14,* and *15*), but the details of the testing procedures were not given. The Panel recommends in vitro studies using current methods.

A number of poorly designed in vivo studies have evaluated the effectiveness of oxyquinoline (Refs. *15, 16,* and *17*). Two unpublished studies (Ref. *15*) were uncontrolled and lacked double-blinding. Because they were done with 2.5 percent oxyquinoline combined with several other ingredients (benzoic acid, salicylic acid, thymol, menthol, proplyparaben, methylparaben), it is difficult to assess the effect of oxyquinoline.

Oster and Golden (Ref. *16*) evaluated the effectiveness of a 2.5-percent solution of oxyquinoline in 50 percent ethanol on 40 cases of athlete's foot. Diagnosis was based on clinical appearance. KOH preparations were not used, and the study was not blinded or controlled. Of the 40 cases, only 11 had positive cultures for dermatophytes (*T. gypseum* and *E. floccosum*). Patients with mild cases of athlete's foot were clinically cleared in 1 to 2 weeks. After 3 months of treatment all patients were reported as cleared.

Seldowitz (Ref. *17*) studied the therapeutic effectiveness of a rubber insole impregnated with unknown concentrations of oxyquinoline, chloroxylenol, and chlorothymol. The investigator treated only those patients with athlete's foot whose diagnosis had been documented by a KOH preparation and a culture. A total of 44 patients were included in the study; 27 patients were given the medicated insole therapy, and 17 patients were not treated. Of the 27 treated patients, 19 (70.4 percent) cleared clinically and had negative cultures after a varying period of treatment (1 to 9 months with an average of 4 months). The disease course of the untreated patients was either unchanged or had deteriorated. Thirteen of the untreated patients were then given the medicated insole therapy. The results of all 40 treated patients showed that 29 were clinically and mycologically cleared after an average treatment time of 4 months.

The Panel concludes that the effectiveness of 2.5 percent oxyquinoline in various vehicles has not been demonstrated in a well-designed clinical trial.

(3) *Proposed dosage*—(i) *Concentration.* Benzoxiquine, oxyquinoline, and oxyquinoline sulfate may be used alone or in combination to equal a total oxyquinoline concentration of 0.06 to 2.5 percent.

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

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

(5) *Evaluation.* The Panel recommends that adequate studies be undertaken to show (1) the minimal blood levels of oxyquinoline that cause toxic symptoms in animals; (2) the highest "no-effect" blood levels in animals; and (3) metabolic rates of oxyquinoline in humans, including time for total elimination of the drug from the body. A complete assessment of the carcinogenic potential from topically applied oxyquinoline to broken skin is also needed.

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

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1. *Parabens (methylparaben and propylparaben).* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of parabens (methylparaben and propylparaben) for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and

ringworm. The Panel also concludes that at a total concentration of less than 0.4 percent, parabens may be safely used in antifungal formulations as preservatives.

Paraben is an abbreviation used in the United States by the pharmaceutical profession to denote esters of parahydroxybenzoic acid. The methylparabens and propylparabens are the esters most commonly used. Methylparaben occurs as white crystals with a melting point of 131° C and is slightly soluble in water, soluble in oil, and freely soluble in alcohol. Propylparaben is less soluble in water and more soluble in oil because of its longer chain of carbon atoms. Propylparaben occurs as a white crystalline powder with a melting point of 96 to 97° C (Ref. *1*).

(1) *Safety.* Methylparaben and propylparaben are widely used as preservatives in a variety of pharmaceutical preparations in concentrations up to 0.3 percent (Ref. *2*). The parabens in concentrations exceeding 0.3 percent have shown in vitro activity against fungi.

At these concentrations, parabens are reported to be devoid of systemic toxicity (Ref. *2*). Gosselin et al. (Ref. *3*) assigned propylparaben a toxicity rating of 3, indicating moderate toxicity, i.e., where the probable oral lethal dose in humans may be from 0.5 to 5 g/kg. These investigators also stated that propylparaben is less toxic than benzoic or salicylic acid. Dogs injected with propylparaben showed no pathological changes in liver or kidneys (no dose specified).

Goodman and Gilman (Ref. *2*) report that as a component of dermatological and proprietary preparations the parabens are recognized "causes of severe and intractable contact dermatitis." Sax, however, described the parabens as being "slight" allergens (Ref. *4*).

Fisher's original paper on contact dermatitis noted that 3 percent of the patients sensitive to vehicles were sensitive to parabens (Ref. *5*). There has been controversy, however, over this sensitization rate because it is well known that only small quantities of parabens are used as preservatives in skin medications.

Schorr and Mohajerin (Ref. *6*) and Hjorth (Ref. *7*) have indicated that repeated topical applications of low concentrations of these agents can sensitize an individual. This is particularly true when the medications are applied to areas of easy absorption. Although allegic hypersensitization to parabens has been reported in this country, the number of sensitized persons is quite small, considering the wide use of these ingredients.

There are no sensitization data on parabens at antifungal concentrations (greater than 0.4 percent). The Panel concludes that these data are needed to determine the safety of methylparaben and propylparaben for OTC topical application in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* Parabens have gained widespread use as preservatives in cosmetics, foods, and pharmaceuticals. Their antibacterial and antifungal properties were first reported in 1924 in Europe; their commercial production began in the early 1930's in the United States (Ref. *8*).

Parabens in low concentrations are effective against a variety of microorganisms in acid, neutral, and alkaline solutions (Refs. *8* and *9*). The methyl, ethyl, propyl, and butyl esters of paraben are most commonly used as preservatives. Methylparaben 0.1 to 0.2 percent and propylparaben 0.05 percent (approaching the concentration of aqueous saturation) are commonly used preservative concentrations (Ref. *9*). The antifungal products now under review contain either propylparaben 1.75 percent or the combination of methylparaben 1.35 percent and propylparaben 0.45 percent (total parabens 1.80 percent). In these products, parabens are found in combination with other antifungal agents, particularly benzoic and salicylic acid. Parabens have also been combined with oxyquinoline, thymol, chlorothymol, and boric acid.

These *p*-hydroxy benzoate compounds are desirable preservatives because they are essentially colorless, odorless, and stable. Activity among the esters increases with increasing chain length, while water solubility decreases. Mixtures of the esters have been used in preference to a single ester, with claims for their use varying from being simply additive to synergistic. The hexyl and heptyl esters have the greatest antifungal activity (Refs. *8* and *10*).

The parabens have limited solubility in water, but by dissolving them in alcohols, oils, propylene glycol, or sodium hydroxide, the parabens may be incorporated into aqueous products (Ref. *8*). As the chain length of the paraben increases, its lipid solubility also increases. By combining methylparaben and propylparaben in pharmaceutical preparations, manufacturers take advantage of the different solubilities of these two ingredients, permitting an additive preservative effect by having parabens present in both the aqueous and lipid phases of the product. Preservatives must suppress the multiplication of microorganisms in the aqueous phase of the product and also have a high affinity for their microbial hydrophobic lipid cell membranes (Ref. *11*).

In emulsion base creams, nonionic surfactants may bind the parabens, removing them from the aqueous phase and thereby reducing their effective concentration as free preservatives. This reaction can be compensated for during formulating by adding higher concentrations of parabens. Parabens do not interact significantly with other additives likely to be found in emulsion base creams, including methyl cellulose, carboxymethylcellulose, tragacanth, polyethylene glycol, gelatin, or polyvinylpyrrolidone (Ref. *11*).

The parabens are bacteriostatic against gram-positive bacteria and fungistatic as well. Their activity is only slightly decreased in the presence of human serum (Ref. *12*). Studies (Ref. *8*) show that the percentages of methylparaben and propylparaben required to inhibit *S. aureus* were 0.4 percent and 0.05 percent, respectively. In the same study, gram-negative bacteria (*E. coli, Proteus vulgaris,* and *Aerobacter aerogenes*) were also inhibited by methylparaben and propylparaben at concentrations of 0.2 percent and 0.05 to 0.1 percent, respectively. Summaries of the inhibitory concentrations of the parabens from tests made in nutrient media with results read in 24 hours at 37° C, showed the following: 0.1 to 0.4 percent methylparaben and 0.0125 to 0.05 percent propylparaben inhibited gram-positive types of bacteria; 0.2 percent methylparaben and 0.05 to 0.1 percent propylparaben inhibited gram-negative types of bacteria (Ref. *13*).

The parabens are also fungistatic, being mainly active against dermatophytes, *C. albicans,* and common fungi frequently found in the environment. In one study, inhibition concentrations for *T. mentagrophytes* and *T. rubrum* were found to be 0.016 percent for methylparaben and 0.004 percent for propylparaben (Refs. *8*). Another study showed that a concentration of 0.004 percent propylparaben and concentrations greater than 0.008 percent methylparaben were required to inhibit *T. interdigitale* (Ref. *14*). Against *T. mentagrophytes,* the lowest effective concentrations of methylparaben, propylparaben, and butylparaben for growth inhibition varied from 0.01 to 0.1 percent. When 0.2 percent concentrations of propylparaben and butylparaben were combined in a petrolatum and silicone oil base, they

effectively inhibited growth of *T. mentagrophytes* suspended in melted agar (Ref. *15*). In another study in which parabens were suspended in Sabouraud's agar, 200 μg/mL of methylparaben and 50 μg/mL of propylparaben, were the lowest concentrations to completely inhibit *T. rubrum* and *T. mentagrophytes* (Ref. *16*).

The effective inhibitory concentrations of parabens against *C. albicans* were reported to be 0.1 percent for methylparaben and 0.0125 percent for propylparaben (Refs. *8* and *13*). Another report showed similar inhibition of *C. albicans* at 350 μg/mL for methylparaben and 100 μg/mL for propylparaben (Ref. *16*). Methylparaben and propylparaben at concentrations of 1,000 to 2,500 μg/mL in Sabouraud's medium delayed the yeast growth of four strains of *Candida* to 96 hours, in contrast to the normal growth present at 24 hours (Ref. *17*). Another study used cup plate tests with methylparaben and propylparaben dissolved in 25 to 33 percent ethyl alcohol. This study found that most yeasts *(Candida, Saccharomyces,* and *Geotrichum)* were sensitive to as little as 1.0 mg of the esters, but were inhibited more markedly by 5 mg and 10 mg of the esters, with methylparaben the most active ester (Ref. *18*).

The activity of parabens against *C. albicans* in vitro led to several clinical studies on the effects of parabens against candidiasis developing secondary to antibiotic treatment (Refs. *17* through *22*). In one study, 186 patients were treated with either parabens alone, aureomycin alone, or aureomycin with parabens administered by the oral, vaginal, or rectal routes (Ref. *17*). Among patients treated with oral aureomycin alone, 50 percent developed *C. albicans* in the stool. In contrast, 13 percent of the patients treated orally with aureomycin with parabens developed yeast in the stool. It was concluded that parabens "are of value" in preventing overgrowth of *Candida* during aureomycin treatment.

In 1953, 0.2 g parabens was given orally four times daily to a man with widespread candidal infection following antibiotic use (Ref. *19*). After 3 days of parabens treatment, fungal elements were gone from the sputum and feces. In vivo studies were conducted with 17 hospitalized patients who were given daily oral doses of 3 g chlortetracycline and 1.35 g methylparaben and propylparaben (Ref. *18*). Daily stool counts for total yeast content showed that parabens caused anti-yeast activity in some but not all patients. In vitro studies suggested that certain antibiotics (aureomycin, neomycin, and bacitracin) stimulated the growth of *Candida* in broth cultures greater than the growth in control cultures (Ref. *20*). This growth stimulation could be eliminated by the addition of methylparaben and propylparaben, but the total growth of the cultures remained similar to the growth of control cultures.

Two European reports described the oral use of parabens in cases of systemic candidiasis caused by antibiotic treatment. In one report, two of four patients with positive blood smears for *C. albicans* survived (Ref. *21*). In the other study, seven children survived after treatment with 600 mg parabeans daily (Ref. *22*).

The clinical use of parabens against dermatophyte fungal infections has not been extensive. According to one report, parabens were successfully used to treat fungus infections and were found to be colorless, odorless, agreeable, and easy to use (Ref. *23*). Another report discussed the use of 5 percent methylparaben to treat athlete's foot caused mainly by *Epidermophyton interdigitale* (Ref. *24*). Preparations containing parabens and salicylic acid were used, including a tincture, ointment, and power, all applied twice daily. Rapid healing occurred in many cases, but the exact number of cases treated was not reported. No KOH preparations, fungal cultures, or controls were included.

Another investigator reported the use of 5 percent ethylparaben ointment to treat athlete's foot (Ref. *25*). In this partially controlled study, all patients with athlete's foot seen in a dermatology clinic for about 6 months were treated with an ointment containing 5 percent ethyl paraoxybenzoate (paraben). The ointment given to alternate patients contained 3 percent salicylic acid in addition to the 5 percent ethylparaben. Every patient in the study had clinical findings of fungal infection and positive KOH preparations or cultures or both before beginning treatment. Reexamination with KOH preparations and cultures was performed weekly. After the fungi had disappeared, at least two additional examinations for fungus were done at intervals of 1 to 2 weeks.

Among 23 patients treated with the ointment containing ethylparaben alone, 18 (78 percent) were cured, with the disappearance of fungi documented after 6 to 34 days of treatment (average 22 days). The treatment length averaged 37 days. Of 23 patients treated with the ethylparaben-salicylic acid ointment, 17 (74 percent) were cured, with fungi disappearing after 8 to 63 days (average 26 days). The average duration of treatment was 49 days. Eleven (24 percent) of 46 patients who did not respond used one of the two ointments for periods ranging from 28 to 137 days. It was concluded that both ointments had the same therapeutic effect, regardless of the presence or absence of salicylic acid, and that clinical effectiveness was due to the presence of ethylparaben.

Although this study met many of the study design criteria proposed by the Panel, neither it nor any of the other reviewed studies included a treatment group using the ointment base alone, or a lag period between treatment and final examination for fungi. The study design also lacked double blinding.

The Panel is aware of only three other brief reports of clinical trials using parabens to treat dermatophyte fungal infections. In 1935, epidermophytosis of the feet and hands was treated successfully with a salve containing 5 percent propylparaben (Ref. *26*). Later, a 5-percen methylparaben solution in 70 percent alcohol and 5 percent mathylparaben ointment were used to successfully treat fungus infection of the scalp (Ref. *27*). After 5 months the infection did not recur. In the late 1940's, numerous cases of tinea of the hands and feet were treated with paraben ointments and solutions (Ref. *28*). Favorable results occurred with a 6-percent solution of butyl ester in peanut oil, a 10-percent mixture of paraben esters in ointment, and a 20-percent mixture of paraben esters in alcohol solution. The solution form, in either alcohol or propylene glycol, was the most effective.

The Panel is not aware of any controlled studies using either methylparaben or propylparaben for the treatment of athlete's foot, jock itch, or ringworm. Despite promising results obtained with 5 percent methylparaben in the treatment of athlete's foot reported in 1944 (Ref. *25*), no recent studies have confirmed the earlier results. Also, no clinical studies have been submitted to the Panel showing that concentrations of parabens less than 5.0 percent are effective antifungal agents in vivo. While all clinical studies reviewed by the Panel used parabens in concentration of at least 5.0 percent, the total paraben concentration in currently marketed antifungal products is only 1.75 to 1.80 percent. This concentration greatly exceeds the 0.1 to 0.4 percent concentrations usually required for the preservative effects of parabens.

The Panel concludes that parabens in total concentrations of less than 0.4 percent should be classified as preservatives rather than as active

antifungal ingredients. Parabens in concentrations equal to or greater than 0.4 percent may have antifungal activity, but this has yet to be verified in a well-designed, controlled clinical trial.

(3) *Proposed dosage*—(i) *Concentration.* Methylparaben and propylparaben may be used alone or in combination to equal a total parabens concentration of 0.4 to 5.0 percent.

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

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

(5) *Evaluation.* The Panel recommends that the sensitization potential of parabens in concentrations greater than 0.4 percent be determined. The Panel also recommends one doubie-blind, placebo-controlled clinical trial to determine the effectiveness of parabens in the treatment of athlete's foot, jock itch, and ringworm. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

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m. *Phenyl salicylate.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of phenyl salicylate for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Phenyl salicylate, also known as salol, is the salicylic acid ester of phenol. Phenyl salicylate was introduced into medical practice in 1886, but is no longer official in the "United States Pharmacopeia." It is a white, crystalline powder with a melting point between 41° and 43° C. One g phenyl salicylate dissolves in 6,700 mL water and 6 mL alcohol. It is very soluble in chloroform and ether (Ref. *1*).

(1) *Safety.* The mechanism of action of phenyl salicylate as an intestinal antispetic was based on its hydrolysis to phenol and salicylic acid. The usual dose was 300 mg, although doese as large as 1 g were sometimes given. Phenyl salicylate was formerly used as an enteric coating for capsules and tablets (Ref. *1*).

No data on the safety of phenyl salicylate have been submitted to the Panel, and there are only extremely limited data in the literature on the topical use of this ingredient. Presumably, and antifungal activity it may possess would occur only after hydrolysis, if indeed this does occur when phenyl salicylate is applied topically. However, in view of its oral use in the past as an intestinal antiseptic, the Panel can visualize no systemic toxicity potential by absorption through the skin in the concentrations now used. On the other hand, if hydrolysis on the skin does occur and if hydrolysis is complete, then the products of hydrolysis would be 44 percent phenol and 56 percent salicylic acid. In the concentration currently used (2 percent), the total amount of phenol and salicylic acid would not cause systemic toxicity from localized application such as to athlete's foot, jock itch, or ringworm. Local effects of the intact molecule of phenyl salicylate, such as irritation, sensitization potential, or effect on healing of cracks and fissures are unknown. Therefore, in view of the absence of data establishing the effects of phenyl salicylate mentioned above, the Panel recommends additional safety testing.

(2) *Effectiveness.* As mentioned above, phenyl salicylate hydrolyzes to yield phenol and salicylic acid. If

hydrolysis occurs after topical application, the effectiveness of phenyl salicylate should be similar to that of phenol (see part III. paragraph B.l.e. above—Phenolates (phenol and phenolate sodium)) and salicylic acid (see part III. paragraph C.l.p. below—Salicylic acid). The effectiveness of phenyl salicylate is questionable because the Panel has received no effectiveness data.

(3) *Proposed dosage*—(i) *Concentration.* Phenyl salicylate 2.0 percent.

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

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

(5) *Evaluation.* The Panel recommends testing of the local toxicity of phenyl salicylate (irritation, sensitization, and effect on broken skin). If it is established that hydrolysis on the skin occurs, the toxicity or phenol which is produced should be evaluated. (See part III. paragraph B.l.e. (1) above—Phenolates (phenol and phenolate sodium) safety.) The Panel also recommends in vitro testing and one double-blind, placebo-controlled clinical trial to determine the effectiveness of phenyl salicylate in the treatment of athlete's foot, jock itch, and ringworm. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

Reference

(1) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 911, 1973.

n. *Povidone-iodine.* The Panel concludes that povidone-iodine is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Povidone, formerly known as polyvinylpyrrolidone or PVP, was developed during World War II as a plasma expander. It is formed by reacting acetylene, ammonia, and formaldehyde under pressure, yielding a water-soluble polymer. Preparations commonly used in the United States have an average molecular weight of either 33,000 or 56,000. Povidone binds many drugs, including iodine, producing a colloidal solution in water (Ref. *1*).

Povidone-iodine is a yellowish-brown amorphous powder with a slight, characteristic odor. In aqueous solutions it is acidic. Povidone-iodine is soluble in alcohol, but is practically insoluble in chloroform, ether, and acetone. Povidone-iodine contains about 10 percent available iodine (Ref. *2*).

(1) *Safety.* The safety of povidone-iodine was reviewed by the Advisory Review Panel on OTC Antimicrobial I Drug Products in the Federal Register published September 13, 1974 (39 CFR 33129). Since then, certain new safety data have been made available to the Advisory Review Panel on OTC Antimicrobial II Drug Products.

The intravenous LD_{50} of 10 percent povidone-iodine (1 percent available iodine) in rabbits is 1.1 mL/kg. The oral LD_{50} in rats is 80 mL/kg. Safe intraperitoneal doses of povidone-iodine ranged from 2.5 mL/kg for rats to 4 mL/kg for dogs (Ref. *3* and *4*).

To determine the subacute oral toxicity of 10 percent povidone-iodine, researchers fed this drug to growing rats for 3 months. No significant effects on the rats were noted other than a temporary elevation in protein-bound iodine levels and nonspecific changes in thryoid tissue. These tissue changes returned to normal within 90 days of the last dose (Ref. *3*).

Skin irritation studies on animals and humans on both normal and damaged skin showed no significant degree of irritation from povidone-iodine (Ref. *5*). Instillation into rabbit eyes showed only slight or mild reactions which generally subsided in 24 to 48 hours (Refs. *3, 5,* and *6*).

One report of the mutagenicity potential of povidone-iodine (Ref. *7*) indicated that it was positive in a modification of the Ames *S. typhimurium* model, but these results could not be reproduced by another researcher (Ref. *3*). Another test using mouse lymphoma and Balb/3T3 cells showed that povidone-iodine has no significant mutagenic or transformation capabilities. Other data indicated that it does not produce mutagenic effects in mice or hamsters according to the dominant lethal test, micronucleus test, and chromosome analysis (Ref. *3*).

Numerous reports in the literature indicate the lack of toxicity or irritation to skin from povidone-iodine. These reports include application of povidone-iodine to eyebrows, eyelids, and mucous membrances. It was also applied to athlete's foot and used in catheter cut-downs and in preoperative preparation (Refs. *3, 5,* and *6*).

A tissue culture study (Ref. *8*) was run in which skin specimens were degermed in vivo with povidone-iodine. Growth of epithelial cells in culture was then determined. The authors reported 83 percent positive skin cultures after povidone-iodine treatment, but the Panel observes that it was applied to the intact skin (primarily stratum corneum) where available iodine would have been bound to tissue before reaching the epithelial (viable) layer.

In another study (Ref. *9*), minute cutaneous wounds were studied microscopically after application of 1:100 dilutions of povidone-iodine. Tissue injury was very slight, less than with hydrogen peroxide, quaternary ammonium compounds, or soaps. Nevertheless, the investigators that disinfectants in general (including iodine solutions) "damaged tissue and interfered with tissue function, thereby increasing the injury already existing in a damaged tissue and delaying wound healing." The Panel observes that the very high dilution of povidone-iodine used in this study does not provide adequate data on its effect on wound healing.

Another submission (Ref. *10*) resolved most of the Panel's concern about the effect of povidone-iodine on wound healing. A 10-percent povidone-iodine solution was applied to "split-skin" and "full-thickness" wounds in rats and to human skin graft wounds to determine any effects on wound healing (Ref. *11*). Control sites were treated with saline or dry Owens gauze. Treatments were given four times daily until epithelialization was complete. The results showed that povidone-iodone had no gross or microscopic effect on wound healing. In both the animal and human experiments, no statistically significant difference was seen between treated and control sites in mean healing time of wounds. Other supporting data (Ref. *10*) showed that there was no reaction when 10 percent povidone-iodine was used on varicose ulcers or wound infections. These data removed the Panel's previous concern over the effect of povidone-iodine on wound healing. However, the Panel still believes that in some instances iodine may be an irritant or sensitizer (particularly with long-term use and under occlusion). For this reason the Panel recommends that a caution be included in povidone-iodine labeling.

The Panel concludes that povidone-iodine is safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* Studies by a number of investigators (Ref. *3*) reveal that 10 percent povidone-iodine has considerable in vitro effectiveness against a wide variety of bacteria, yeast, and fungi which are commonly found in the toewebs. Povidone-iodine killed *T.*

mentagrophytes in 20 to 30 minutes, *M. audouinii* in 30 to 60 minutes, and *E. floccosum* in 3 to 4 hours. A 1:160 dilution killed *T. mentagrophytes* in 20 to 30 minutes. Ten percent povidone-iodine killed *C. albicans* (identified strains and clinical isolates) in 15 seconds. Various dilutions were also tested against clinical isolates of *C. albicans*. A 1:1 dilution required 15 seconds for fungicidal effect, and a 1:10 dilution required 60 seconds.

Meyer-Rohn and Liehr (Ref. *12*) studied 10 percent povidone-iodine solution and ointment in a plate diffusion test. They used "Kimmig" agar for dermatophytes and maltose indicator agar for *Candida*. A 14-mm punch hole was filled with 0.2 mL of the povidone-iodine solution or ointment and the plates were inoculated after 1-hour diffusion. Plates were incubated at 37° C for *Candida* and 27° C for dermatophytes. Results were read as mm of inhibition at 24 hours for *Candida* and 4 weeks for dermatophytes. *T. rubrum, T. mentagrophytes, E. floccosum,* and *M. canis* were inhibited by 10 percent povidone-iodine solution (20 mm zone). The zone of inhibition for a 1:10 dilution was 18 mm for *M. canis* and 16 mm for the other three dermatophytes. The 1:100 dilution showed no inhibition of these microorganisms. Although dilutions of povidone-iodine up to 1:5 inhibited *C. albicans*, growth was seen at 1:10.

The in vitro antibacterial activity of iodone was discussed in the report of the Advisory Review Panel on OTC Antimicrobial I Drug Products published in the **Federal Register** of September 13, 1974 (39 FR 33129). Data indicate that povidone-iodine is more active against bacteria than against fungi. This report also describes some effectiveness concerns, such as the stability of the preparation and the availability of elemental iodine from the povidone-iodine complex. This Panel has seen no data which completely resolve those concerns.

Kuttin, Beemer, and Amani (Ref. *13*) have described their experiences treating *T. mentagrophytes* infections in a laboratory rabbit colony. The animals had inflammed skin lesions and hair loss. Sometimes the nails were affected. The infection was documented by KOH preparation and culture. Seventeen of 133 rabbits in the colony (12.7 percent) developed this infection which did not appear to be self-limited. Several months after the lesions first appeared each infected rabbit was treated with a single application of 10 percent povidone-iodine solution, with no concomitant therapy. Response was swift; new hair growth was seen in 3 to 4 days, and no further lesions developed. All animals responded completely and remained free of disease for 1 year.

Rinaldi and Sabia (Ref. *14*) used 40 patients in a double-blind, controlled, and randomly assigned study of 10 percent povidone-iodine solution in the treatment of athlete's foot. A positive culture (on Sabouraud's), clinical symptoms of athlete's foot, and a history of no prior topical antifungal therapy were necessary to enter the study group. Patients were then graded clinically for symptoms and signs of pain itching, fissuring, vesiculation, erythema, scaling, etc. The treatment groups did not differ significantly in age and sex, in duration and severity of disease, or in type of organisms.

One group was treated twice daily with 10 percent povidone-iodine solution and the other group with the vehicle which had "a small amount of preservative and color" added. Feet were washed twice daily and the appropriate solution applied after drying. Patients were evaluated at 7, 14, and 25 days of therapy and 7 days after treatment stopped. Patients were considered cleared if they had no signs or symptoms of the disease and if followup cultures were negative.

After 4 weeks of treatment, 75 percent (15/20) of the povidone-iodine group and 25 percent (5/20) of the control group were clear. This difference is statistically significant ($p < 0.01$, by chi-square analysis). A followup (by telephone) 1 year later on 17 patients from each group suggested that "approximately 25 percent in each group reported later reoccurrences," but no specific data were given about how such figures were compiled. The authors concluded that povidone-iodine is effective in the treatment of athlete's foot.

The major shortcoming of the Rinaldi and Sabia study (Ref. *14*) is an inadequate followup of patients. Otherwise it generally meets the Panel's criteria. The Panel notes that none of the standard dermatology textbooks refer to athlete's foot as an indication for the use of povidone-iodine. To the Panel's knowledge, this ingredient was marketed for only 1 year (1960) for the treatment of athlete's foot. Because povidone-iodine is not generally recognized as effective in the treatment of athlete's foot, jock itch, and ringworm, the Panel requires a well-designed, controlled study to substantiate the ingredient's effectiveness in these conditions.

(3) *Proposed dosage*—(i) *Concentration.* Povidone-iodine 10 percent.

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

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

Cautions should include the following statement: "If redness or itching occurs or persists, discontinue use and consult a doctor or pharmacist."

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

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o. *Propionic acid and its salts (sodium propionate and zinc propionate).* The Panel concludes that propionic acid and its salts (sodium propionate and zinc propionate) are safe but that there are insufficient data available to permit final classification of their effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Propionic acid, $C_2H_5CO_2H$, is also known as propanoic acid. It is a colorless liquid with a characteristic odor. The sodium and zinc salts of propionic acid are colorless or white crystalline or granular powders. Propionic acid is miscible with water, alcohol, chloroform, and ether (Ref. *1*).

(1) *Safety.* Heseltine (Ref. *2*) concluded that the acute toxicity of sodium propionate in animals was so low that he considered it "neither practicable nor necessary" to determine the LD_{50} of the drug. The oral LD_{50} of propionic acid in rats is reported to be 4,290 mg/kg; the intravenous LD_{50} of sodium propionate in mice is 2,100 mg/kg (Ref. *3*). The installation of a 10-percent solution of sodium propionate into rabbits' eyes was reported to aid the healing of experimental lesions; doubling the concentration produced no harmful effects (Ref. *2*).

In humans the estimated "acceptable" daily intake of sodium, potassium, and calcium propionate is as high as 10 mg/kg (Ref. *1*). Heseltine reported that daily oral doses of 6 g sodium propionate given to an adult male patient turned the urine faintly alkaline but had no appreciable diuretic, cathartic, or other side effects (Ref. *2*). Propionic acid and its sodium and calcium salts are widely used as food preservatives (Refs. *4* and *5*).

Several studies report little local irritation from the topical use of propionates (Ref. *6*). Some of these studies consisted of treatment regimens extending over several months with continuous use of propionates.

The concentration of total propionates (propionic acid, sodium propionate, and zinc propionate) in antifungal preparations ranges from 4 to about 12 percent. Based on the total amount of propionic acid available for absorption and the absence of acute toxicity, the Panel concludes that no toxicity hazard exists from the topical application of the propionates.

(2) *Effectiveness.* Propionates were first used in the treatment of fungal diseases in 1939 after Peck et al. (Ref. *7*) reported that many short-chain fatty acid molecules were effective antifungal agents.

Propionic acid and its sodium and calcium salts have been widely used as food preservatives by the baking industry to inhibit mold growth (Ref. *1*). In vitro antifungal data suggest that propionates are bacteriostatic and fungistatic (Ref. *8*). However, the in vitro data is quite old and uses zone of inhibition and contact-time testing so that only general conclusions can be drawn. The Panel recommends further in vitro testing to characterize the activity of propionates against dermatophytes.

Keeney et al. (Ref. *9*) compared the effectiveness of 16.4 percent sodium propionate and 3.6 percent propionic acid in carbowax ointment (39 patients) to a 10-percent undecylenic acid in carbowax ointment (40 patients) and the carbowax base alone (41 patients). Athlete's foot was diagnosed by KOH preparations and by culture. During the study the patients used no medication other than the ointment, which they were instructed to apply once in the evening and wash of with soap and water in the morning. After the first examination, the patients were seen at intervals of 1, 3, 5, and 6 weeks.

At the beginning of treatment, only 31 percent of the propionate group had positive cultures. The researchers considered this number too small to "draw decisive conclusions" based on causative organisms. When treatment began, KOH preparations were negative in 15 percent of the propionate group, 12 percent of the undecylenic acid group, and 7 percent of the placebo group.

After the first week of thereapy, 54 percent of the patients treated with the propionate ointment and 51 percent treated with the undecylenic acid ointment were KOH negative. In the third week, KOH preparations were negative in 80 percent of those treated with propionate ointment compared to 67 percent in the undecylenic acid group. In the fifth week, KOH preparations were negative in 73 percent of the propionate group and 70 percent of the undecylenic acid group. The authors reported that after 5 weeks the patients had become careless in following instructions and that this carelessness was reflected in the study results. At the 6-week examination, 82 percent of the propionate ointment group and 59 percent of the controls were KOH negative. The undecylenic acid group could not be observed at 6 weeks. Keeney et al. concluded that the two ointments were equally effective in the treatment of athlete's foot.

The Panel notes that the above study was not double-blinded. Also, no lag period followed treatment, and culture results of the placebo group were not reported.

Keeney and Broyles (Ref. *10*) conducted an uncontrolled study on 55 naval cadets to evaluate the effectiveness of 10 percent sodium propionate ointment and powder on athlete's foot. The powder was applied in the morning and the ointment at night. Before treatment, positive KOH preparations were obtained in only 11 (20 percent) of the cases; only 9 of these produced positive cultures. It appears that athlete's foot was diagnosed mainly on clinical impression. The authors reported that after 8 weeks of treatment, 90 percent (10/11) of the cadets with "advanced" cases were "cleared" of the disease. Criteria for judging a case "cleared" were not specified.

Sulzberger, Shaw, and Kanof (Refs. *11* and *12*) evaluated the effectiveness of various preparations in the treatment of athlete's foot and jock itch. Diagnosis was made on clinical impression. No KOH preparations or cultures were done. The length of treatment time is unclear. The authors state that treatment lasted "throughout the summer." Seventy-five percent (123/164) of the patients receiving 20 percent sodium propionate powder were cured or improved at the end of treatment. This compared with 81 percent (396/489) cured or improved in the 2-percent undecylenic acid-20 percent zinc undecylenate group. Of patients receiving boric acid-salicylic acid powder, only 48 percent (106/221) were cured or improved. The researchers concluded that "undecylenic acid-undecylenate powder was slightly more effective than sodium propionate powder, which in turn was definitely more effective than the boric acid-salicylic acid powder."

Sulzberger, Shaw, and Kanof (Ref. *11*) also compared 20 percent sodium propionate in talc (17 patients) to 20 percent zinc undecylenate and 2 percent undecylenic acid in talc (44 patients) in the treatment of jock itch. They obtained the following results: 59 percent (10/17) of the patients treated with the propionate powder and 80 percent (35/44) of those treated with the undecylenate powder were reported as "cured." Unfortunately, only 17 patients received the propionate ointment, a number too small to justify valid

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Forty percent salicylic acid ointment was applied to two human patients with burn surfaces no greater than 5 to 6 percent of the body. Serum salicylate levels were determined every 8 hours for 48 hours; the highest salicylate level reached was 15 mg/100 mL. No clinical symptoms of toxicity were observed (Ref. *4*).

Signs of toxicity were noted by von Weiss and Lever (Ref. *3*) after 3 to 6 percent salicylic acid ointment was applied to psoriatic lesions over a large part of the body six times a day. Serum levels of salicylic acid ranged from 46 to 64 mg/100 mL. Toxic effects were nausea, difficulty in breathing, impaired hearing, confusion, and hallucination. Most symptoms disappeared within 1 day after treatment stopped.

A more recent report described four patients with psoriasis on more than 25 percent of their bodies (Ref. *7*). A preparation containing 6 percent salicylic acid in a gel base was applied to the entire body surface below the neck immediately after showering. The treated areas were covered with a plastic wrap for 10 hours, after which the patients were allowed to shower again. This treatment was repeated daily for 5 days. Serum salicylate levels never exceeded 5 mg/100 mL in any of the patients, although more than 60 percent of the total applied salicylic acid was absorbed. No toxicity or accumulation of salicylic acid was observed.

Salicylic acid is a keratolytic agent. At concentrations higher than 3 percent it will destroy keratinized skin. Because of its keratolytic action, salicylic acid is known to be irritating to both the skin and the eyes. However, the concentration necessary to establish clinical signs of skin irritation depends on many factors, such as the vehicle, exposure time, and surface area occlusion. In higher concentrations, salicylic acid may delay wound healing, but this has not been fully assessed in the treatment of athlete's foot.

The systemic toxicity of topical salicylic acid, like its keratolytic effects, appears to result from a combination of factors. Some of these factors are (1) a high concentration of salicylic acid in a vehicle which allows rapid absorption, (2) the frequency of application, (3) whether the surface area is occluded, and (4) the condition and area of skin to which the preparation is applied (Ref. *7*).

It is recognized that absorbed salicylic acid is rapidly metabolized and excreted (Ref. *3, 4,* and *7*). Therefore, if the area of application is small, such as in athlete's foot or jock itch, systematic toxic concentrations of salicylic acid probably would not be reached. For example, if one assumes complete instantaneous absorption of the total dose of 1 g of a 3–percent salicylic acid preparation, the maximum amount in the blood at any one time would be 30 mg. This 30 mg of salicylic acid would be distributed into 7 L of blood, resulting in a maximum blood concentration of approximately 0.4 mg/100 mL. This is well below the 30- to 50-mg/100 mL level considered to be toxic.

Therefore, considering the worst case of absorption as described above, and the known rapid elimination of salicylic acid, the Panel considers the use of salicylic acid in topical preparations to be safe if the concentration is 3 percent or less, and if the use of this drug is restricted to relatively small body areas.

(2) *Effectiveness.* Salicylic acid is generally applied in ointment form and is used in dermatology for the following reasons: (1) to produce a keratolytic or macerating action; (2) as an antiseptic and antiparasitic; and (3) on the assumption that the addition of salicyclic acid to an ointment will promote the absorption of the other ingredients. Davies and Marks (Ref. *8*), using scanning electron microscopy of skin surface biopsies, suggested that the peeling effect of salicylic acid is due to the dissolution of intercellular cement material.

In vitro studies (Refs. *9* through *13*) have indicated that salicylic acid has some fungicidal activity. Dolan et al. (Ref. *14*) conducted a "semi-in vivo" study using epidermal scales of guinea pigs infected with *T. mentagrophytes.* Scales were placed in a stainless steel tissue capsule which was immersed in the test solution for 5, 15, 30, or 60 minutes. Then the scales were cultured on a Sabouraud's agar plate to see if the *T. mentogrophytes* were still living. The results were expressed as the time it took to kill the organism while in the presence of the antifungal ingredient. Salicylic acid was reported to have fungicidal activity with *T. mentagrophytes* cultured at 15 minutes, but not at 30 minutes.

The most extensive in vivo testing of salicyclic acid was done by Hopkins et al. (Ref. *15*). Over 7,500 patients at Fort Benning, Georgia, were treated for athlete's foot during a 3-year period. Cultures were obtained before treatment, but the cultured organisms were not identified. KOH preparations were examined at each visit. Although the total number of patients in the study was large, only 258 apparently received salicylic acid. Twenty-eight patients completed 4 weeks of treatment with salicylic acid; 47 percent were clinically clear at this time. The data were presented in an ambiguous fashion so that the actual success of salicylic acid is undeterminable.

Because of the lack of data on the effectivenes of topical salicylic acid for the treatment of athlete's foot, jock itch, and ringworm, the Panel recommends additional effectiveness testing.

(3) *Proposed dosage*—(i) *Concentration.* Salicylic acid 0.05 to 3.0 percent.

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

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

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

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q. *Sulfur.* The Panel concludes that sulfur is safe but that there are insufficent data available to permit final classification of its effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm. Goodman and Gilman (Ref. *1*) summarize the history of sulfur as follows:

> Sulfur has a long history in medicine. The practice of burning sulfur for the purification of the air is mentioned in the *Odyssey.* Hippocrates considered sulfur an effective antidote against plague. For the layman, sulfur has an undeserved reputation as an intestinal antiseptic, and the practice of an annual "spring cleansing" of the intestinal

tract with sulfur and molasses was once prevalent. The legitimate medical uses of sulfur preparations are as fungicides and parasiticides and for the treatment of various cutaneous disorders (Ref. *1*).

Elemental sulfur is a dry powder made from a yellow, brittle solid of crystalline texture. It can exist in several different crystalline forms as well as an amorphous or polymeric form. The solubility may vary depending on the form of sulfur but, in general, sulfur is insoluble in water, sparingly soluble in alcohol, and soluble in organic solvents (Ref. *2*).

The four forms of elemental sulfur used in dermatology are: (1) Sublimed sulfur (flowers of sulfur), a fine, yellow, crystalline powder; (2) washed sulfur (sulfur lotum), made by washing sulfur with ammonia; (3) precipitated sulfur (milk of sulfur), a fine yellowish-white, amorphous, odorless powder with smooth texture, and (4) colloidal sulfur, in which minute particles of elemental sulfur are stabilized (prevented from aggregation) in an aqueous medium containing a colloid such as egg albumin or gelatin (Ref. *3*). Precipitated sulfur and colloidal sulfur are the forms used most commonly in dermatology.

Sulfur is contained in currently marketed antifungal products in concentrations of 0.2 to 8 percent. The Panel also received a submission on a soap containing 10 percent sulfur.

(1) *Safety.* Toxicological data on sulfur are practically nonexistent. The safety record of sulfur is based on its long and varied use. Sax (Ref. *4*) rated the toxicity of sulfur as very low. Sulfur is reported to be nontoxic for man and mammals. If taken orally in sufficient doses, however, sulfur may have a laxative or cathartic effect possibly due to formation of hydrogen sulfide in the intestinal tract (Ref. *5*). In concentrations above 15 percent, sulfur is very irritating to the skin. Also, concentrations below 15 percent applied for prolonged periods may cause severe topical irritation to some people. Sulfur may cause progressive reddening, thickening, and scaling of the skin, with eventual total body redness and scaling (erythroderma), as injury to the skin exceeds the ability of the skin to repair itself (Ref. *6*).

After a careful review of the literature, Lorenc and Winkelmann (Ref. *6*) noted that, despite the long history and almost universal acceptance of sulfur by dermatologists, there were only three references in the literature which attempted to describe the histologic effects of sulfur on the skin. One of these reported that sulfur did not injure the deeper layers of skin; the other two papers described a parakeratosis (an abnormality of the horny layer of the skin resulting in the process of keratinization) of the stratum corneum.

Lorenc and Winkelmann studied the histological effects of concentrations of 5 to 40 percent sulfur in petrolatum during a 4-week period of exposure on hairless mouse skin. These investigators concluded that the reaction caused by sulfur was a single manifestation of unknown mechanism, namely one or injury to the skin. The reported keratolytic and keratoplastic actions of sulfur are a single manifestation, but the end result depends on the concentration used. Lorenc and Winkelmann concluded that sulfur injures the epidermis; the injury is then followed by a reparative process. However, when higher concentrations of sulfur are used, the injury exceeds the reparative process and thus exfoliation (peeling) results. Hence, the terms "keratoplastic" and "keratolytic" describe certain phases of the same basic reaction. Lorenc and Winkelmann also reported that the sequence of events in the skin of hairless mice after the application of various strengths of sulfur was essentially the same as the sequence reported in the human thigh, abdomen, and scrotum.

Rossoff (Ref. *7*) reported that 5 to 10 percent sulfur preparations are keratolytic. Rossoff did not suggest that lower concentrations were primarily keratoplastic, though he did indicate that a sulfur concentration of 2 percent in combination with salicylic acid is popular in antiseborrheic preparations.

Sulfur, in various forms, has had a long history of oral and topical use. It has been reported that dermatologists almost universally accept sulfur for topical use (Ref. *6*). For these reasons the Panel concludes that topically applied sulfur does not have a serious toxicity potential and is safe at the dosage cited below.

(2) *Effectiveness.* Colloidal sulfur is the most active form of sulfur because of its minute particle size, enabling intimate contact between the sulfur and the epidermis (Ref. *8*). Although colloidal sulfur was first isolated from a sulfur spring in 1830 (Ref. *9*), it was not further studied until 1888 and 1911 or used therapeutically until the early 1930's (Refs. *8* and *10*). Before this, precipitated sulfur was considered to be the most active form of sulfur (Ref. *11*).

Hydrogen sulfide is produced when sulfur is applied to human skin and can be recognized by its characteristic "rotten egg" odor. The formation of hydrogen sulfide within the epidermis results from a biochemical reaction between sulfur and cysteine. Cysteine is the principal molecular carrier of sulfur in the epidermal protein keratin (Refs. *12* and *13*). Sulfur is absorbed by the skin (Ref. *11*) and is detectable in the epidermis about 2 hours after application. Sulfur is detectable throughout the skin after 8 hours but is gone after 24 hours (Ref. *14*). Reactions to sulfur presumably begin within the first 2 hours after application and continue until sulfur is completely absorbed by the bloodstream.

Topically, sulfur causes an injury to the epidermis, followed by a reparative reaction (Ref. *6*). The extent of injury probably depends on the amount of hydrogen sulfide produced within the epidermis, which in turn depends upon the following circumstances: (1) the concentration of sulfur applied (Refs. *6* and *10*), (2) the length of time of application (Ref. *12*), and (3) the degree of intactness of the skin surface (Ref. *10*). Low concentrations of sulfur (1 to 2 percent) cause only minor epidermal damage. This damage is soon followed by a thickening of the epidermis (acanthosis) as the process of keratin formation is stimulated. This thickening may sometimes occur atypically and incompletely (Refs. *11*, *12*, and *15*). The keratoplastic action of sulfur is most marked when sulfur is applied in a water-washable emulsion base (Ref. *12*).

Sulfur concentrations in the range of 5 to 15 percent cause more injury to the skin and are keratolytic, especially when applied in a petrolatum base (Ref. *12*). The release of hydrogen sulfide in the epidermis dissolves young prickle cells in the epidermis and causes swelling and softening of the top horny layer of the skin. These events are followed by the peeling off of the upper epidermis and stratum corneum (Refs. *6* and *10*). Hence the antifungal action of sulfur on the skin is probably largely due to its keratolytic effect. In other words, when the stratum corneum is shed, the fungal spores and hyphae embedded within it are also shed (Refs. *10* and *11*). Hydrogen sulfide may also be directly toxic to the fungus in the stratum corneum, although this remains speculative (Ref. *16*). The keratolytic action of sulfur in an alkaline medium is enhanced by heat and light (Ref. *11*).

In vitro studies with dermatophyte fungal cultures reveal that sulfur is not a potent fungicidal or fungistatic agent. In one study, precipitated sulfur in a 1:10 dilution caused no inhibition of dermatophytes (Ref. *17*). In another study a 1:50 dilution did not inhibit dermatophyte growth, and a 1:1,000 dilution of sulfur killed only 29 percent of dermatophytes tested after a 24-hour exposure (Ref. *18*). Sulfur ointment (15

percent sulfur in petrolatum) was found to have little or no fungistatic activity when tested against *M. albicans* or *T. interdigitale* (Ref. *19*).

Another study found sulfur in a 5-percent dilution to be neither fungicidal nor fungistatic to *M. tropicalis* after a 2-minute exposure. However, other 2-minute exposure tests were more favorable in that a 1-percent dilution was found to be fungicidal to *T. interdigitale* (Ref. *10*). Solutions of 1:10,000 sulfur in carbowax were found by investigators to completely inhibit a 3-hour broth culture of *C. albicans*. Higher dilutions of up to 1:200,000 sulfur in carbowax suppressed growth of *Candida* for up to 24 hours, but then lost their activity through sedimentation and allowed subsequent visible growth of the organism (Ref. *20*).

Elemental sulfur has been reported to have antibacterial activity, with the activity largely depending on the size of the sulfur particles (especially with colloidal sulfur). A calcium phosphate-sulfur precipitate, in which fine particles of elemental sulfur were embedded in a calcium phosphate gel, was found to have a strongly inhibitory action against several strains of hemolytic streptococci (Ref. *21*). This same gel had only moderate activity against *S. aureus* and no antibacterial activity against gram-negative organisms. It was postulated that sulfur might act on bacterial cells by inactivating the sulfur-hydrogen (SH) groups contained in enzyme systems of the bacteria. Indeed, the antibacterial action of sulfur was neutralized by the addition of cysteine and other SH-containing compounds to the culture medium which presumably restored the activity of the bacterial enzymes requiring free SH groups.

The popularity of sulfur baths for treating skin diseases in the 19th century probably stemmed from their success in treating scabies, a very itchy skin disease caused by a mite. However, by 1880 sulfur was also recognized as being destructive to the fungi causing the skin diseases of favus, ringworm, and tinea versicolor (Ref. *22*).

Renewed interest in sulfur as an antifungal agent occurred in the 1930's following its use against fungal diseases of plants (Ref. *10*). In 1932, sulfur was mentioned as being "of definitive value" in the treatment of tinea, although no specific types of fungal infection were documented (Ref. *11*). At the same time, sulfur was felt be beneficial in treating bacterial infections by withdrawing oxygen and moisture from the tissue to make conditions less favorable for bacterial proliferation (Ref. *11*). To this end, the use of sulfur for bacterial infections, such as boils, dates to at least the 1880's (Ref. *22*).

In 1935, colloidal sulfur in a 2- to 5-percent aqueous solution was sponged twice daily between the toes involved with athlete's foot. The results were favorable. The same solution proved satisfactory for vesicular (blistered) athlete's foot treated 7 to 10 days with wet compresses of aluminum acetate. The colloidal sulfur solution did not, however, work well on either the hyperkeratotic (thickened) or eczematized (inflamed) types of athlete's foot. Jock itch and ringworm of the body responded well to the 2- to 5-percent colloidal sulfur in an aqueous, glycerinated or cholesterolized, hydrous wool fat base. But treatment with the colloidal sulfur was not superior to other forms of treatment (Ref. *10*).

Sulfur ointment was listed as one of several possible prescriptions for athlete's foot of the hyperkeratotic variety. This preparation contained 15 percent sulfur in a base of wool fat, yellow wax, and white petrolatum. Half-strength sulfur ointment diluted with petrolatum was also effective in treating interdigital *C. albicans* infection on the hands and around the nails (paronychia) (Ref. *23*).

In 1942, athlete's foot and jock itch were treated successfully with Wilkinson's ointment diluted one-third with zinc oxide ointment (Ref. *24*). Before dilution, the original ointment consisted of 15 percent sublimed sulfur and 10 percent precipitated calcium carbonate in a mixture of 15 percent juniper tar, 30 percent soft soap, and 30 percent lard. The ointment was applied "sparingly" to prevent the development of dry scaly skin. Application of the ointment, together with daily foot baths in fresly prepared formaldehyde solution, was shown to decrease the number of cases of athlete's foot seen at a military clinic.

In 1945, about 100 British soldiers at a military clinic were treated for athlete's foot with Vleminckx's solution (liquor calcis sulphuratae, BPC) (Ref. *25*). The solution was prepared by boiling a mixture of 25 g quicklime and 50 g sublimed sulfur in 1 L water until only two-thirds of the original volume remained. The supernatant fluid was decanted and swabbed twice daily onto the feet and between the toes of the affected soldiers. The solution stung when applied to raw areas. Cases of athlete's foot were clinically cured in 3 to 10 days and no relapses were observed during variable observation periods of a few weeks to a few months. No cultures or controls were included in the study.

In 1951, *C. albicans* infections in several intertriginous skin areas were treated with carbowax-sulfur, which was prepared by heating 500 g carbowax with 5 g sublimed flowers of sulfur (Ref. *20*). Among the 35 patients treated twice daily with the carbowax-sulfur ointment, 13 were cured, 18 were markedly improved, 3 improved temporarily, and 1 developed skin irritation. The length of treatment time varied from 1 to 4 months, with one exception of intermittent treatment for 2 years. Treatment was discontinued only after cultures were negative for *C. albicans* and the skin appeared normal. Several patients had involvement of multiple areas (groin, interdigital areas, and nails) which cleared. Unfortunately, no controls were included in the study. In patients with multiple involved areas it was not possible to separate the treatment times and responses of different anatomical areas under treatment.

Based on the above available data, the Panel concludes that sulfur is of questionable effectiveness in the treatment of athlete's foot, jock itch, and ringworm. Although elemental sulfur, particularly in colloidal form, is a strong antifungal agent in plants, there are no controlled studies demonstrating that sulfur is effective in treating fungal diseases in humans. A few uncontrolled studies which did not use cultures suggest that various sulfur ointments and solutions may be beneficial in the treatment of dermatophyte fungal infections (Refs. *10, 23, 24,* and *25*). Other uncontrolled studies (Refs. *20* and *23*) suggest that sulfur may be effective in the treatment of *C. albicans* infections of the skin. In vitro studies suggest that sulfur has only mild antifungal and antibacterial activity (Refs. *17, 18,* and *19*).

(3) *Proposed dosage*—(i) *Concentration.* Sulfur 0.2 to 8.0 percent. A concentration of 8 to 10 percent sulfur may be used providing it is in a soap formulation which will be rinsed off after application.

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

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

(5) *Evaluation.* The Panel recommends in vitro testing and one double-blind, placebo-controlled clinical trial to determine the effectiveness of sulfur in the treatment of athlete's foot, jock itch, and ringworm. This study should be

conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

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r. *Triacetin.* The Panel concludes that triacetin is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

Triacetin, or glyceryl triacetate, is a colorless, somewhat oily liquid with a slight, fatty odor. It is prepared by the acetylation of glycerol. Triacetin is soluble in 14 parts water and is miscible with alcohol, ether, and chloroform (Ref. *1*).

Triacetin is contained in currently marketed products in concentrations of 15 to 33.3 percent.

(1) *Safety.* The subcutaneous LD_{50} of triacetin in mice is reported to be 2.3 mL/kg (Ref. *2*). Li et al. (Ref. *2*) also reported that triacetin in a 50-percent aqueous solution caused marked congestion and moderate edema when placed in rabbits' eyes. Triacetin was shown to be irritating to tissues and slightly hemolytic. It produces an emulsion when mixed with serum.

In contrast to this data, information supplied to the Panel indicates that triacetin, when tested as the pure compound or as a cream formulation, is completely devoid of local toxicity when evaluated on rabbit skin (both intact and abraded) and in rabbit eyes (Ref. *3*). According to a letter from the Department of the Army (private communication), ointments containing 40 to 50 percent triacetin were nonirritating to the skin when tested behind the ears of human subjects (Ref. *3*). Another private communication in this same submission reported that following the 10th consecutive application of a 25-percent triacetin cream in a repeated insult patch test, there was no evidence of primary irritation.

Because of the chemical structure of triacetin and because the hydrolytic products of this agent (glycerin and acetic acid) are known to be systemically nontoxic in the amounts used, the Panel is not concerned about systemic toxicity from triacetin. In addition, the "Dispensatory of the United States of America" (Ref. *4*) specifies that chloroazodin dissolved in triacetin 1:500 "may be used undiluted in open traumatic wounds * * *."

Therefore, in view of the evidence presented about and the rather extended history of use without significant problems of toxicity, the Panel concludes that triacetin is safe in the treatment of athlete's foot, jock itch, and ringworm.

(2) *Effectiveness.* The mechanism of action of triacetin is the apparent production of free acetic acid from the hydrolysis of the compound by esterases. When triacetin is exposed to esterase (produced by dermatophytes), acetic acid is split from the glycerin molecule until the pH of the environment is changed to about 4.0. At this pH level the activity of the esterase is inhibited, and no further acetic acid is liberated until the pH rises to the level where the esterase again becomes active.

In vitro, triacetin has shown activity (reduction of colony size) against a series of clinical isolates of dermatophytic fungi cultured on Sabouraud's agar (Refs. *5* and *6*). In general, inhibition was noted at 0.1 percent, although there was considerable variation between dermatophytes. For instance, the colony diameters at this concentration were as follows: *E. floccosum*, 19 mm; *T. mentagrophytes*, 66 mm; *T. rubrum*, 59 mm; and *M. canis*, 37 mm. Triacetin 0.5 percent completely inhibited all dermatophytes except *M. Gypseum* which had a 3-mm colony diameter. Activity against *C. albicans*, however, was minimal. Testing against bacteria was not included.

Contrary to most antimicrobial agents, triacetin's activity increases in the presence of serum. Knight (Ref. *5*) states that this is not surprising because "the ubiquitous esterase would be expected in serum." Two studies (Refs. *7* and *8*) have dealt with the effectiveness of triacetin in the treatment of athlete's foot.

A double-blind study by Cahn and Levy (Ref. *7*) in 1959 evaluated the effectiveness of triacetin in patients diagnosed with symmetrical ringworm of the body, athlete's foot, or

dermatophytosis. Cultures were performed before treatment began. The product was evaluated in ointment, liquid, and powder form (concetration not specified). The patients were used as their own controls. The lenght of treatment varied depending on the dosage form; the ointment was used for 1 to 12 weeks, the liquid for 2 to 8 weeks, and the powder for 3 weeks. Applications were made twice daily for all treatments (active ingredient and placebo). Both the subjective symptomatic relief and the objective clearing of the lesions were evaluated. Table 10 shows the results:

TABLE 10.—RESULTS OF DOUBLE-BLIND COMPARISON OF TRIACETIN IN OINTMENT, LIQUID, AND POWDER

Dosage form	Number of patients	Percent cleared	Percent no improvement
Ointment	45	46.7 (21)	*53.3 (24)
Liquid	40	60.0 (24)	*40.0 (16)
Powder	40	22.5 (9)	77.5 (31)

*NOTE: Infections due to *T. rubrum* did not respond to either the ointment or the liquid.

The authors concluded that successful responses, including symptomatic relief, usually occurred within the first week of therapy.

The Panel notes the small patient population in this study. Placebo results were not reported, and apparently neither followup cultures nor KOH preparations were performed. Also, it is unclear whether the results for the liquid and ointment are statistically significant.

A second study by Johnsom and Tuura (Ref. *8*) evaluated triacetin ointment 25 percent and triacetin liquid 5 percent in the treatment of various types of fungal infections. This study was not blinded and did not use a placebo control. Some patients received a combination of 25 percent triacetin ointment with 5 percent salicylic acid. However, results of the study were not correlated with treatment groups. Twenty-two of the 80 patients studied had athlete's foot caused by *T. mentagrophytes*. In 3 weeks, 15 of the 22 patients had negative KOH preparations and negative cultures. In seven patients the KOH preparation was positive, but the culture was negative. Four patients with *E. floccosum* infections (athlete's foot and jock itch) were cleared at the end of 3 weeks. It seems that *E. floccosum* and *T. mentagrophytes* infections of the feet clear with the topical application of triacetin. However, again, the patient population was small.

Although triacetin may clear athlete's foot caused by *T. mentagrophytes* or *E. floccosum*, the Panel concludes that a well-designed, clinical study is necessary to establish triacetin as an effective antifungal ingredient. According to the preceding studies, triacetin is not indicated in the treatment of *T. rubrum* infections.

The Panel concludes that triacetin may be effective in the treatment of inflammatory, soggy toeweb athlete's foot but should be labeled as contraindicated for the dry form of the disease (caused by *T. rubrum*).

(3) *Proposed dosage*—(i) *Concentration.* Triacetin 15.0 to 33.3 percent.

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

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

Warning: "Use only for soggy, wet forms of athlete's feet."

(5) *Evaluation.* The Panel has seen no evidence that triacetin may be effective in any fungal disease other than the soggy toeweb form of athlete's foot. Moisture may be necessary for the activity of triacetin. Because ringworm of the body is almost always dry and is generally caused by *T. rubrum*, triacetin may not be effective in this condition. The Panel therefore recommends one double-blind, placebo-controlled clinical trial of each type of fungal disease—athlete's foot, jock itch, or ringworm—to establish the effectiveness of triacetin in each particular condition. These studies should be conducted in accordance with the guidelines set forth below for OTC topical antifungal ingredients. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

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2. *Category III labeling.* The Panel concludes that the following labeling claims for products used in the treatment of athlete's foot, jock itch, and ringworm are unsupported by sufficient scientific data to permit classification in Category I. As indicated elsewhere in this document, additional data are required in order to place them in Category I. (See part III. paragraph E. below—Guidelines for Safety and Effectiveness Studies.)

a. *Product performance labeling.* Specific statements relating to product performance must be substantiated by adequate data. This includes "speed of action" claims. In general, any Category I labeling of effectiveness that includes a time, such as "cures athlete's foot in 2 weeks," automatically becomes Category III until the time claimed is substantiated.

b. *Antibacterial activity.* Some antifungal ingredients, such as miconazole nitrate and iodochlorhydroxyquin, have antibacterial activity as well as antifungal activity. Although antifungal agents may have antibacterial activity in vitro, the Panel concludes that these ingredients may not use the term "antibacterial" in the labeling without supportive clinical trials demonstrating an antibacterial effect when the ingredient is applied to the toewebs.

D. Combination Products Used in the Treatment of Athlete's Foot, Jock Itch, and Ringworm.

The Panel acknowledges and concurs with the rationale expressed in the OTC drug combination policy regulation (21 CFR 330.10(a)(4)(iv)) as follows:

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

The Panel concludes that combination products for the treatment of athlete's foot, jock itch, and ringworm should contain the minimal number of ingredients necessary to achieve effectiveness. In general, the fewer the ingredients, the safer and more rational

the therapy. Consumer interests are best served by exposure to the fewest ingredients possible at the lowest possible dosage regimen consistent with a satisfactory level of effectiveness.

1. *Category I combination drug products.* a. *Combinations of antifungal ingredients.* (1) Each antifungal ingredient in the combination must be a Category I ingredient.

(2) Each antifungal ingredient in the combination must be present within the dosage range for a Category I ingredient as set forth elsewhere in this document.

(3) The combination may contain up to three antifungal ingredients provided each ingredient broadens the antifungal spectrum.

For example, the combination may contain nystatin, an anticandidal ingredient, to broaden the spectrum.

An antidermatophytic drug combined with an anticandidal drug would be a rational approach to the treatment of diseases caused by both dermatophytes and *Candida.* Because most consumers cannot distinguish between these diseases, such a combination would offer them broader therapy.

If one ingredient is shown to be very effective against a certain dermatophyte, such as *T. rubrum,* it may be useful to combine this ingredient with a Category I ingredient which is not so active against *T. Rubrum.*

b. *Combinations of antifungal ingredients with other ingredients.* Combinations may include nonantifungal ingredients which have been classified as Category I by any OTC advisory review panel and are designed to aid the antifungal agent in relieving symptoms or enhancing activity. Antiperspirants and keratolytics may each be added provided that they are safe and effective and that their inclusion in a combination product does not decrease the effectiveness of the antifungal ingredient(s) nor decrease consumer safety. In general, combination topical antifungal products should contain no more than one active nonantifungal ingredient from each of the categories mentioned below.

(1) Combinations of up to three antifungal ingredients with an antiperspirant.

One class of ingredients that may be added is antiperspirants. The Panel believes that drying the affected area will aid in the treatment of athlete's foot. Examples of acceptable antiperspirants would be aluminum salts and other similar agents that can be shown to follow the above guidelines.

(The Panel considers drying agents such as talc and bentonite as inactive ingredients present in formulations for nonantifungal purposes.)

(2) Combinations of up to three antifungal ingredients with a keratolytic agent.

Keratolytic chemicals are another permissible added ingredient class, provided that they can be shown to be safe and effective in the concentrations used. Theoretically, an effective keratolytic agent could remove the outer layers of the stratum corneum, thus better exposing the infecting fungus to the action of the antifungal ingredient. Salicylic acid is an example of such an agent. It should be recognized, however, that in carrying out their keratolytic action, many of the keratolytic agents irritate the skin.

(3) Combinations of up to three antifungal ingredients with hydrocortisone or hydrocortisone acetate, 0.5 to 1 percent.

Combinations of an antifungal agent with hydrocortisone or hydrocortisone acetate 0.5 to 1.0 percent have been submitted for evaluation of potential OTC use against fungal infections of the skin. Antifungal agents included in the various submitted combinations with hydrocortisone include iodochlorhydroxyquin, miconazole nitrate, and calcium undecylenate (Refs. *1, 2,* and *3*). Double-blind, controlled studies have been performed on each of these combinations except calcium undecylenate (Ref. *1*).

Topical hydrocortisone and hydrocortisone acetate when used alone in the management of athlete's foot significantly reduce the itch and pain as well as the signs of inflammation. Despite this reduction of signs and symptoms, the growth of the organism continues as the inflammation is reduced. A positive KOH preparation is easily obtained from a lesion of athlete's foot or ringworm of the body that has been treated with topical hydrocortisone for 48 to 72 hours. This local reduction of inflammation is occasionally followed in 48 to 72 hours by a generalized eruption of erythema multiforme (a skin disease characterized by pimply or blistery lesions and reddening or discoloring of the skin about the lesions) or an "id" reaction. Consequently, hydrocortisone should never be used alone in the treatment of athlete's foot.

The inflammation produced by the organisms causing athlete's foot may act as a barrier and prevent a weak antibacterial or antifungal agent from effectively eradicating the infection. Hydrocortisone in 0.5 to 1.0 percent concentration is an effective anti-inflammatory agent capable of reducing or eliminating the itching and burning in the skin caused by athlete's foot. It is reasonable to asume that a Category I antifungal agent for athlete's foot plus hydrocortisone would be a rational combination drug for the management of this condition.

In 1976 a combination cream containing miconazole nitrate 2 percent and hydrocortisone 1 percent was tested in a double-blind, controlled trial in Belgium (Ref. *4*). Inflamed skin lesions of bacterial and fungal origin were treated in 63 patients (ages 12 to 60 years) with either the miconazole-hydrocortisone combination, miconazole 2 percent, or hydrocortisone 1 percent cream. Each cream was applied twice daily for 4 weeks. Dermatophytic fungi were identified by microscopic evaluation or culture in 41 patients. Bacteria (staphylococci and streptococci) were isolated in 21 patients, and no growth occurred in one patient.

After 3 weeks of treatment, dermatophytes were found only in patients using hydrocortisone alone, including 11 of 13 patients. No dermatophytes were found after 3 weeks in patients using either the miconazole-hydrocortisone or miconazole creams, whereas 28 of these patients originally had dermatophyte infections. The miconazole-hydrocortisone combination was superior to miconazole or hydrocortisone alone in producing symptomatic relief of itching and redness within 1 week, and in suppressing inflammation. At the end of the trial (4 weeks), cure rates were 85.7 percent with the miconazole-hydrocortisone combination, 40.0 percent with miconazole, and 4.5 percent with hydrocortisone alone.

An unpublished, double-blind, controlled study of miconazole nitrate 2 percent-hydrocortisone 1 percent cream was performed by Taplin in Colombia, South America in 1976 (Ref. *3*). The 99 patients were male Caucasian soldiers with severe jock itch and ringworm of the body. All patients except one were infected by the dermatophyte *E. floccosum.* KOH preparations and fungal cultures were performed on days 0, 7, and 14 of treatment. Clinical evaluation of signs and symptoms was performed on days 0, 1, 2, 3, 4, 7, and 14, with scores of mild to severe included for fissuring, maceration, erythema, scaling, pustules/vesicles, erosions, and excoriations. Subjective symptoms of burning, pain, and itching were also evaluated on the same days. The clinical results are summarized in Table 11.

TABLE 11.—RESULTS OF TREATMENT WITH MICONAZOLE-HYDROCORTISONE

	Day 7		Day 14	
	Cured	Not cured	Cured	Not cured
Miconazole-hydrocortisone	27	6	32	1
Miconazole	22	11	25	7
Hydrocortisone	3	30	2	31

After 14 days, 97 percent of the combination miconazole-hydrocortisone group were cured, in contrast to 78 percent of the miconazole group and 6 percent of the hydrocortisone group. There were not enough subjects in the study to attain a "p value" of .05 between the miconazole-hydrocortisone and the miconazole-treated groups. However, Taplin felt that the 97-percent success of the combination product indicated "significantly greater efficacy" than miconazole, especially when tested under the "worst conditions of heat, humidity, and poor hygiene."

During the first 4 days of treatment the miconazole-hydrocortisone combination tended to reduce the intensity of signs and symptoms more than either miconazole alone or hydrocortisone alone. After 4 days of treatment, 16 patients in the miconazole-hydrocortisone group were free of symptoms, compared to only 8 in the miconazole group and 7 in the hydrocortisone group, but these differences were much less marked after 7 and 14 days of treatment. The fungal culture results (using DTM agar) were almost identical after 7 and 14 days of treatment, with negative clutures after 14 days in 33 of the miconazole-hydrocortisone group, 32 of the miconazole group, and only 4 of the hydrocortisone group. No followup cultures were done after treatment stopped.

In 1978 Maibach (Ref. *5*) reported a randomized, double-blind, multicenter study comparing iodochlorhydroxyquin-hydrocortisone cream with its individual components in 354 patients with fungal infections of the skin. (The Panel had previously received both published and unpublished data from this same study which had been conducted by Carpenter et al. in 1972 (Refs. *2* and *6* through *9*).) All patients had positive KOH and fungal cultures before treatment, and cultures were repeated on the final visit after 7 days of treatment. The types of fungal infections treated included athlete's foot (121), jock itch (105), ringworm of the body (80), moniliasis (37), and "other" (11), exclusive of hair and nail infections.

Patients received identical-appearing tubes of cream with instructions to apply the cream three times daily. They were randomly assigned to 4 treatment groups: 89 patients received the combination cream containing 3 percent iodochlorhydroxyquin and 1 percent hydrocortisone; 83 received 3 percent iodochlorhydroxyquin cream; 96 received 1 percent hydrocortisone cream; and 86 received the cream vehicle alone. Patients were seen on day 2 or 3 of treatment and after 7 days of treatment for evaluation of signs and symptoms. Physicians rated the overall clinical response and graded the severity of erythema, scaling, vesiculation, and exudation. Patients rated the severity of itch and their overall change in discomfort. The results of the study after 7 days of treatment are summarized in Table 12.

TABLE 12.—COMPARISON OF IODOCHLOR- HYDROXYQUIN-HYDROCORTISONE (I+HC) CREAM WITH ITS INDIVIDUAL COMPONENTS

[Percent]

Treatment	Rated "good to excellent," by M.D.	Discomfort "gone or much better"	KOH(+) to (−) conversion
3% I+HC	65	64	49
3% I	46	55	56
1% HC	32	42	19
Vehicle	25	30	28

The combination of iodochlorhydroxyquin-hydrocortisone was concluded to be consistently better than either of its active components or the vehicle alone in the treatment of athlete's foot, jock itch, and ringworm of the body. The iodochlorhydroxyquin-hydrocortisone combination was also the best treatment for cutaneous candidiasis, although the number of patients treated was small.

The Panel believes that the prophylactic use of antifungal-hydrocortisone combinations is irrational because long-term use may introduce risks to the consumer, such as possible skin atrophy and other long-term steroid effects. The Panel therefore recommends that there be no claim of prevention made for these products.

The Panel recommends that hydrocortisone and hydrocortisone acetate combination products contain the following warning: "Do not use longer than 30 days without consulting a doctor or pharmacist."

The Panel recommends that all Category I combinations be labeled according to Category I labeling for antifungal products used in the treatment of athlete's foot, jock itch, and ringworm, as outlined elsewhere in this document. (See part III. paragraph A.2. above—Category I Labeling.)

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(*7*) OTC Volume 070153.
(*8*) OTC Volume 070154.
(*9*) Carpenter, C. L., et al., "Combined Steroid-Antiinfective Topical Therapy in Common Dermatoses: A Double-Blind, Multi-Center Study of Iodochlorhydroxyquin-Hydrocortisone in 277 Patients," *Current Therapeutic Research*, 15:650–659, 1973.

2. *Category II combination drug products.*—a. *Criteria for Category II classification.* A combination is classified by the Panel as a Category II products, i.e., one that is not generally recognized as safe or effective, if any of the following apply:

(1) The combination contains any ingredient that is listed elsewhere in this document as a Category II ingredient for safety reasons. If classified by another Panel as a Category II ingredient for safety, its inclusion in a topical antifungal combination must be adquately justified.

(Ingredients in Category II for antifungal effectiveness but which the Panel has determined to be safe are permitted in combinations if they are used for nonantifungal purposes, such as keratolytic activity. See part III, paragraph B above—Category II Conditions.)

(2) The combination contains more than three antifungal ingredients.

(3) The combination contains a local anesthetic.

The Panel concludes that a combination of an antifungal ingredient with a local anesthetic, such as benzocaine, is irrational. Although local anesthetics may be useful in relieving the symptoms of athlete's foot, jock itch, and ringworm, these ingredients actually mask the symptoms of the fungal infection without helping to eradicate the fungus. Because any Category I antifungal drug will kill the fungus, thereby relieving symptoms, the Panel believes that the inclusion of local anesthetics in combination products is unnecessary. Also, through potential sensitization they may increase risk to the consumer and offer little added benefit.

b. *Category II combination product: Carbol-fuchsin solution.* The

combination of basic fuchsin 0.3 percent, phenol 4.5 percent, boric acid 1 percent, resorcinol 10 percent, alcohol, and acetone into a carbol-fuchsin paint is commonly known as "Castellani's paint" or "Magenta paint B.P.C." A paint is a medicated liquid preparation with antiseptic, astringent, caustic, fungicidal, or analgesic properties which is applied to the skin with a brush, a sponge, or a cotton applicator (Ref. *1*). Carbol-fuchsin solution is usually kept in a dark bottle with a glass stopper (Ref. *2*).

In 1928 and 1929, Castellani originally advocated the use of carbol-fuchsin solution for treatment of chronic cases of fungal infection of the feet ("epidermophytosis"), especially cases associated with secondary bacterial infection. He also used it to successfully treat jock itch and itching of the anogenital area associated with both dermatophyte and yeast-type (monilial, saccharomycetic, and cryptococcal) fungal infections (Refs. *3* and *4*).

The combination of saturated alcohol solution of basic fuchsin and 5 percent aqueous phenol gave "good results" when used in treating fungal infections, but Castellani believed that the addition of boric acid and acetone made it more penetrating and increased its action. Resorcinol was thought to further enhance the action of the paint, especially in chronic cases of athlete's foot resistant to other forms of therapy, but was not absolutely necessary for the effectiveness of the paint. The frequency of application varied from several times daily to twice weekly. For use on acutely inflamed areas, Castellani recommended diluting the paint with an equal part of water. He recognized the disadvantage of the paint, which colored the skin a deep red, but thought that most patients with chronic fungal infections would not object to it (Refs. *3* and *4*).

Carbol-fuchsin solution became a popular antifungal remedy during the 1930's and was still commonly used through the 1960's. Seale and Clark (Ref. *2*) reported on the use of carbol-fuchsin solution in 50 cases of intertriginous moniliasis (*C. albicans* infections of overlapping skinfolds under the arms, beneath the breasts, in the groin area, and between the toes). The diagnosis in each case was confirmed with KOH preparations or cultures. The paint was applied several times daily. Discomfort and intense itching were relieved within a few hours; in most cases, recovery was "complete" within a week. If lesions were widespread or acutely inflamed with raw surfaces, the paint was diluted 1:1 to 1:3 to avoid harmful effects from absorption of the 5-percent phenol in the paint.

The authors concluded that results were "usually prompt and frequently dramatic." They also concluded that basic fuchsin was not always a necessary component of carbol-fuchsin solution, because the therapeutic value of the paint was only slightly lessened if basic fuchsin was omitted from the formula. However, they observed that toewebs infected with *Candida* often have deep, erosive lesions between and beneath the toes, which respond more readily to a fuchsin-containing paint. Seale and Clark felt that basic fuchsin had a drying, adhesive quality which enabled the paint to adhere well to the toewebs. The presence or absence of basic fuchsin in the paint did not seem to alter the in vitro growth of *Candida* suspensions on Sabouraud's media. Full-strength carbol-fuchsin solution completely unhibited the growth of *Candida*. Although the Panel was impressed by the seemingly favorable response of candidal skin infections to carbol-fuchsin solution in this study, it concluded that the study was markedly deficient because of the absence of controls and followup fungal cultures.

Leyden and Kligman (Ref. *5*) searched for a substitute for carbol-fuchsin solution which would not stain the skin. They stated that "carbol-fuchsin solution (Castellani paint) deserves the esteem accorded it by generations of therapists. Not only is it drying, but basic fuchsin is a powerful antimicrobial agent." They felt that eliminating the dye would destroy the antimicrobial effect. In their experience, colorless carbol-fuchsin solution had only "feeble therapeutic value." They did find, however, that carbol-fuchsin solution was equivalent to 30 percent aluminum chloride for promoting drying of soggy toewebs and effectively treating symptomatic athlete's foot. The two solutions were tested in paired comparison studies in 10 volunteers with athlete's foot. After 1 week of treatment, improvement was equal in both feet as judged clinically. No KOH preparations or cultures were included in the study, and treatment for longer than 1 week was not reported.

Riley and Flower (Ref. *6*) compared the in vitro effects of carbol-fuchsin solution and gentian violet solution against *C. albicans*. Their study was undertaken in response to the favorable clinical trial of carbol-fuchsin solution reported by Seale and Clark (Ref. *2*). As Riley and Flower did not believe that the solution was clinically effective. In vitro studies were performed by mixing dilutions of carbol-fuchsin solution (1:50 to 1:5000) into the melted Sabouraud's agar and then plating the cultures with a saline suspension of 1:1,000 *C. albicans*. The various components of the paint were similarly tested, including a 7-percent alcoholic solution of basic fuchsin. Dilutions of 1 percent gentian violet ranging from 1:10 to 1:10,000 were similarly tested.

After 24 hours, complete inhibition of *C. albicans* was seen on all gentian violet plates and the plates containing 1:50 and 1:100 dilutions of carbol-fuchsin solution. After 48 hours, only the gentian violet plates and the 1:50 dilution of carbol-fuchsin still showed complete inhibition of growth. Among the individual components of carbol-fuchsin solution, only 7 percent basic fuchsin and 5 percent aqueous phenol in 1:25 dilutions gave complete inhibition of growth at 48 hours, while 1:25 dilutions of 8 percent aqueous resorcinol allowed only slight growth after 24 hours.

The authors concluded that gentian violet was much superior to carbol-fuchsin solution or any of its components in inhibiting *C. albicans*. They also concluded that against intertriginous candidiasis the most active component of the paint was basic fuchsin. They were unable to explain the effectiveness reported by Seale and Clark (Ref. *2*). They postulated that the therapeutic effectiveness of carbol-fuchsin solution was probably due to its drying qualtities and keratolytic ability (Ref. *6*).

Carbol-fuchsin solution was evaluated for its antibacterial effectiveness by Marples and Kligman (Ref. *7*), using occlusion tests on human forearms. The paint contained 0.4 percent basic fuchsin, 4.5 percent phenol, and 10 percent resorcinol in acetone-water and was extremely effective in preventing multiplication of bacteria in the occlusion test and in reducing the number of bacteria in the expanded flora test. The solution did not allow overgrowth of gram-negative bacteria, as did basic fuchsin when tested alone.

Carbol-fuchsin solution was evaluated in infants in the treatment of diaper rash and seborrheic dermatitis (often infected with *C. albicans*) of other intertriginous areas (Ref. *8*). For many years the standard treatment at a hospital in Belfast had included twice daily applications of the paint for 48 hours, followed by nystatin cream or ointment. It had been observed that children who had fair complexions or had been bathed just before being painted became mildly shocky and drowsy.

A 6-month-old infant whose entire body had been painted with carbol-fuchsin became drowsy, had shallow

respiration, and passed blue urine 12 hours after painting. Central nervous system depression secondary to the paint was suspected. The painting was stopped, and the infant recovered. Because phenol toxicity was suspected, 16 infants, ages 2 to 5 months, with seborrheic dermatitis were monitored with 24-hour urine collections for phenol after 11 to 15 percent of their body surfaces were painted with carbol-fuchsin solution. Phenol was detected in the urine of four children. This led to discontinuation of the treatment in infants. The authors pointed out that the paint is usually applied to intertriginous areas of skin for its drying ability and anti-yeast and antibacterial actions, and that these areas are ideal for absorbing chemicals found in the paint. They also stated that carbol-fuchsin solution was withdrawn from production because of the presence of carcinogenic compounds involved in its synthesis (Ref. *8*).

The Panel concludes that carbol-fuchsin should be placed in Category II for safety. The concentration of phenol (4.5 percent) exceeds the minimal safe concentration of 1.5 percent previously set by the Panel. Also, the concentration of resorcinol (10 percent) is not safe for OTC antifungal use. A third safety problem involves basic fuchsin, considered to be a potential carcinogen. The Panel also concludes that the effectiveness of carbol-fuchsin solution in the treatment of athlete's foot, jock itch, and ringworm is questionable because of the lack of any placebo-controlled, double-blind clinical trials. The Panel recognizes, however, that carbol-fuchsin has been widely used for over 50 years without apparent documented toxic effects in adults. The Panel concludes that the use of carbol-fuchsin solution, prescribed and supervised by a physician, might be an appropriate treatment for some cases of athlete's foot and jock itch.

References

(*1*) Welsh, A. L., *"The Dermatologist's Handbook,"* Charles C. Thomas Publishing Co., Springfield, IL, p. 36, 1957.

(*2*) Seale, E. R., and W. A. Clark, "Treatment of Intertriginous Moniliasis," *Southern Medical Journal,* 41:926–930, 1948.

(*3*) Castellani, A., "Carbolfuchsin Paints in the Treatment of Certain Cases of Epidermophytosis," *American Medicine,* 34:351–352, 1928.

(*4*) Castellani, A., "Further Observations on the Treatment of Epidermophytosis of the Toes (Mango Toe) and Certain Other Forms of Epidermophytosis by a Fuchsin Paint," *Journal of Tropical Medicine and Hygiene,* 32:77–79, 1929.

(*5*) Leyden, J. J., and A. M. Kligman, "Aluminum Chloride in the Treatment of Symptomatic Athlete's Foot," *Archives of Dermatology,* 111:1004–1010, 1975.

(*6*) Riley, K., and A. H. Flower, "A Comparison of the Inhibitory Effect of Castellani's Paint and of Gentian Violet Solution on the In Vitro Growth of *Candida albicans," Journal of Investigative Dermatology,* 15:355–361, 1950.

(*7*) Marples, R. R., and A. M. Kligman, "Methods for Evaluating Topical Antibacterial Agents on Human Skin," *Antimicrobial Agents and Chemotherapy,* 5:323–229, 1974.

(*8*) Rogers, S. C., F. G. Burrows, and D. Neill, "Percutaneous Absorption of Phenol and Methyl Alcohol in Magenta Paint B. P. C.," *British Journal of Dermatology,* 98:559–560, 1978.

3. *Category III combination drug products*—a. *Criteria for Category III classification.* A combination is classified as a Category III product if any of the following apply:

(1) The combination contains one or more Category III antifungal ingredients. (Category III ingredients are permitted in combinations if they are safe and are used for nonantifungal purposes, such as keratolytic activity. See parts III. paragraph C. above—Category III Conditions.)

(2) The concentration of any Category I antifungal ingredient is below the minimal effective dosage set by the Panel for such ingredient.

(3) The combination contains an antibacterial ingredient.

The Panel concludes that a broad-spectrum antibacterial ingredient which is active against gram-positive and gram-negative bacteria combined with an antifungal ingredient is a rational combination for the treatment of athlete's foot.

In 1973, Amonette and Rosenberg (Ref. *1*) demonstrated that characteristic recalcitrant eruptions of the toewebs, with "soggy wetness" and denuded skin, were associated with infection by gram-negative bacteria. The infection occurred mainly in adult males and could be present concurrently with athlete's foot caused by dermatophytes. Either *P. aeruginosa* or *Proteus mirabilis* or both were cultured from all 12 patients with the soggy toeweb infections. Treatment was difficult and required a combination of bed rest, exposure to air, and various applications of silver nitrate solution, Castellani's paint, and gentamicin sulfate cream to be successful.

Leyden and Kligman (Ref. *2*) demonstrated that the bacterial population of toewebs greatly increases with experimental occlusion of the feet or toes, similar to conditions produced by hot weather, sweating, exercise, and tight shoes. They further showed that if dermatophytes were present before occlusion, the toewebs became red, macerated, keratotic, and symptomatic (uncomfortable), whereas normal toewebs without fungi did not develop such changes despite the expanding bacterial flora. They believe that the fungi probably damaged the stratum corneum, enabling the high level of bacterial growth to aggravate the "athlete's foot" between the toes.

The bacteria most commonly isolated from toewebs were diphtheroids, but as moisture and maceration increased in the toewebs, *S. aureus* and gram-negative bacteria (*Proteus* and *Pseudomonas* species) greatly increased. As the bacteria increased, the athlete's foot became more severe and the recovery of dermatophytes markedly decreased, with fungi being found in only 36 percent of the toewebs in severe cases in contrast to 84 percent in the mild cases. (Although the fungi are still present in the skin (as shown by biopsy), they are apparently forced deeper into the stratum corneum in the soggy toewebs and are often not evident on either KOH preparation or culture.)

In the same study, antibacterial agents (hexachlorophene 5 percent and neomycin 1 percent) were applied to occluded toewebs infected with dermatophytes and also to some toewebs that were not infected. The hexachlorophene suppressed gram-positive bacteria, but allowed proliferation of gram-negative bacteria in the toewebs. Although all toewebs infected with dermatophytes became red, macerated, and hyperkeratotic, the hexachlorophene-treated areas did not develop the foul odor and intense itching characteristic of untreated infected toewebs. Normal toewebs (without contaminating dermatophytes) treated with hexachlorphene developed only a white, moist appearance despite the heavy growth of *Pseudomonas.* The treatment of toewebs with neomycin was beneficial in the wet, macerated form of athlete's foot but not in the dry, scaling form. Leyden and Kligman concluded that topical antibacterial agents produced definite clinical benefit in the treatment of athlete's foot, although the disease was "not cured, merely curbed."

The combination of neomycin 1 percent and tolnaftate 1 percent in ointment was also evaluated in the same study. The combination was thought to be clinically more effective than either treatment alone in both the wet and dry forms of athlete's foot involving toewebs. The combination of the antibiotic and the antifungal agent resulted in "swifter and greater resolution of signs and symptoms" of macerated interdigital athlete's foot (Ref. *2*).

A previous study by the same authors demonstrated that 30 percent aluminum chloride (hexahydrate form) produced resolution of macerated hyperkeratotic toewebs after 7 to 10 days of twice daily application (Ref. *3*). This effect was attributed to the local drying and astringent effect, as well as the antimicrobial effect of aluminum chloride.

The Panel concludes that the combination of an antifungal ingredient with a broad-spectrum antibacterial agent is sometimes desirable for the treatment of athlete's foot characterized by soggy toewebs. Before such an ingredient could be included, however, the Panel would require a double-blind, controlled clinical study demonstrating effectiveness. There is no evidence that an antifungal-antibacterial combination is beneficial in the treatment of jock itch or ringworm of the body. The Panel therefore concludes that until such a combination is proven effective, it is not rational for the treatment of jock itch or ringworm.

The Panel does not approve the inclusion of either hexachlorophene or neomycin as an antibacterial agent in athlete's foot products, but has cited them merely as examples of antibacterial agents used in previous studies. The Panel concludes that any antibacterial agent considered for inclusion in a combination antifungal product should be safe and effective. The Panel is particularly concerned that chronic use of certain antibacterial ingredients could result in potential toxicity, including contact sensitization. This sensitization is likely to occur on the feet because of prolonged contact between sensitizers and the skin under conditions of heat, moisture, and occlusion produced by shoes. The Panel further concludes that antibiotics (with the exception of nystatin) should not be included in athlete's foot products because of the potential hazard of developing widespread antibiotic-resistant strains of bacteria.

b. *Category III combination product: Whitfield's ointment.* Whitfield's ointment has been a popular antifungal ointment since the 1930's. It was originally made of benzoic acid 12 percent, salicylic acid 6 percent wool fat 5 percent, and white petrolatum. The composition has been modified; Whitfield's ointment USP XVI contained benzoic acid 6 percent and salicylic acid 3 percent in polyethylene glycol.

Molinas (Ref. *4*) evaluated the effectiveness of various antifungal ointments in an in vivo guinea pig study. Treatment was begun immediately after inoculation with the test organism, *T. mentagrophytes.* The in vivo study was followed by in vitro testing on the same compounds using agar cup plate and wet filter paper methods. Whitfield's ointment (12 percent benzoic acid-6 percent salicylic acid) compared favorably with the control (5 percent undecylenic acid-20 percent zinc undecylenate) in all tests.

Dolan et al. (Ref. *5*) evaluated the activity of several antifungal agents by measuring the immersion time necessary to kill *T. mentagrophytes* in infected epidermal scales obtained from guinea pigs. The fungicidal effect depends upon the penetration and fungicidal activity of the test material, which the authors believed correlated well with actual clinical conditions. Whitfield's ointment (12 percent benzoic acid-6 percent salicylic acid) allowed growth at 5 minutes, but inhibited *T. mentagrophytes* at immersion times of 15 minutes and longer. The same results occurred with 5 percent undecylenic acid, implying similar antifungal activity. Salicylic acid 5 percent was also tested and found to be fungicidal. It required 30 minutes' immersion time to inhibit growth.

In an uncontrolled study, Hopkins et al. (Ref. *6*) evaluated the modified Whitfield's ointment (6 percent benzoic acid-3 percent salicylic acid) in the treatment of athlete's foot. Forty-eight percent of the 29 patients had negative KOH preparations after 1 to 2 weeks of treatment, although only 10 percent were reported as clinically cleared. Fifteen patients remained in the study for up to 4 weeks. Of these, 40 percent were KOH negative, and 27 percent were clinically cleared. Eight percent of the cases treated showed mild irritation from Whitfield's ointment. The authors noted that benzoic acid rarely caused irritation. Salicylic acid was thought to be more irritating because of its keratolytic action. Whitfield's ointment was also tested in patients with jock itch. It was more effective in treating jock itch than in treating athlete's foot, but was also more irritating in the groin. Twenty-two percent of 65 patients reported irritation, with severe irritation in 5 percent.

Holti (Ref. *7*) conducted a double-blind trial comparing the effectiveness of the modified Whitfield's ointment (6 percent benzoic acid-3 percent salicylic acid) and pecilocin in the treatment of athlete's foot (12 patients) and ringworm (2 patients). The organisms cultured were either *T. rubrum* or *T. interdigitale.* Treatment was for 8 weeks. Patients were assessed clinically and by cultures 1 month after treatment stopped. If the disease was still present, the patient was then treated with the other ointment. Followup continued at 3-month intervals for the next 2 years.

The two patients with ringworm were treated with pecilocin. They were free of infection on the first examination and did not relapse. Of the 12 with athlete's foot, 5 had been treated with pecilocin and 7 with Whitfield's ointment. Only two patients (one Whitfield's and one pecilocin) required a switch to the other treatment. After 6 months, the two still had positive cultures. Three other patients (two treated with Whitfield's and one with pecilocin) who had been clear at 3 months were found to have positive cultures at 6 months. The remaining seven patients maintained negative cultures at 6 months.

Holti concluded that Whitfield's ointment and pecilocin were equally effective fungicidal ointments. He believed that nail involvement was responsible for the recurring athlete's foot infections. Although the study design was adequate, patient numbers were small and a placebo control was not used.

The Panel concludes that Whitfield's ointment (6 percent benzoic acid-3 percent salicylic acid) is of questionable effectiveness in the treatment of athlete's foot, jock itch, and ringworm. It recommends one double-blind, placebo-controlled trial to determine the effectiveness of this ointment.

References

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

(*2*) Leyden, J. J., and A. M. Kligman, "Interdigital Athlete's Foot. The interaction of Dermatophytes and Resident Bacteria," *Archieves of Dermatology,* 114:1466–1472, 1978.

(*3*) Leyden, J. J., and A. M. Kligman, "Aluminum Chloride in the Treatment of Symptomatic Athlete's Foot," *Archives of Dermatology,* 111:1004–1010, 1975.

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E. Guidelines for Safety and Effectiveness Studies

The following guidelines are for studies which the Panel recommends be

conducted in order to move a Category III topical antifungal drug product into Category I. These guidelines are in accord with the present state of the art, but do not preclude the use of any advances or improved technology.

The Panel's approach has been to completely study the potential toxicity of active ingredients used in topical antifungal products. Even though these ingredients are to be used topically, their oral toxicity should be studied for the following reasons: (1) To identify the target organ or system and having identified it, to (2) determine the safety factor which permits safe use when absorption and systemic toxicity occur.

1. *Safety guidelines.* The Panel recommends that the following studies be performed to evaluate topical antifungal ingredients classified in Category III because of inadequate safety data.

a. *Acute studies in animals.* (1) Determine the acute oral toxicity of the total formulation in appropriate species to define the response curve and allow determination of the LD_{10}, LD_{50}, and LD_{90}.

(2) Conduct short-term topical toxicity tests on the total formulation on both intact and abraded skin.

(3) Conduct an appropriate rabbit skin irritation study on intact and abraded skin on the vehicle and total formulation.

(4) Conduct an appropriate rabbit eye irritation study on the vehicle and total formulation.

(5) Conduct a skin sensitization study in guinea pigs on the total formulation and its vehicle.

b. *In vitro screening for carcinogenic potential.* (1) A bacterial mutagenesis assay would be a logical first step in screening for carcinogenic potential. One of the assays using the *Salmonella* histidine auxotroph back mutation, such as that described by Ames (Ref. *1*) or Frantz and Malling (Ref. *2*), would be suitable. Because the compounds in question are likely to be antibacterial, parallel dose-response curves for viability must be done. Where obvious antibacterial activity occurs, other cellular testing procedures should be used.

(2) Depending on the properties of the chemical tested and the results of the bacterial mutagenesis assay, other in vitro tests could be conducted for clarification. These tests should use a mammalian cell culture system designed to test either mutagenicity or transformation. Strategies for selecting tests in this rapidly developing field can be found in current literature.

c. *Subchronic studies in animals.* Conduct a 28-day dermal toxicity study in the rabbit or other appropriate species on abraded skin at suitable dose levels to ensure adequate exaggeration of normal "use" levels. At the conclusion of this study, conduct a full pathological assessment on vital organs and skin. It would be desirable to evaluate the direct effects on the skin following application for a longer period of time, but the Panel is not aware of a suitable model for such a study.

(2) Conduct a subchronic (90 days or longer) feeding study with the total formulation. Determine blood levels and conduct full pathology at termination of the study. This study should attempt to determine the "no effect" blood level of the total formulation. Determine the target organ(s) for toxic effects.

d. *Chronic studies in animals.* (1) Conduct a 1-year chronic feeding study with at least two dose levels. Monitor blood levels at 3-month intervals. Conduct a full pathology evaluation at conclusion of study.

(2) a carcinogenicity evaluation following dermal application will be necessary only if the appropriate in vitro screening assays are positive or have yielded questionable results. For example, antifungal agents may have bacterial activity which can cause false negative or misleading results in the *Salmonella* mutagenicity test because the assay procedure involves bacterial enumeration.

e. *Studies in humans.* (1) Determine the irritation potential of the vehicle and the total formulation using the best current procedures.

(2) Conduct an appropriate sensitization potential study on the total formulation using the most reliable procedure for identifying both potent and weak sensitizing potential(s). It is especially important to test for sensitization in ingredients that are intended for prophylactic use.

(3) Because absorption studies in animals do not necessarily parallel those in humans, appropriate transepidermal studies should be conducted in humans. These studies should be conducted only where the safety of the ingredient has been adequately established in animals.

References

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(*2*) Frantz, C. N., and H. V. Malling, "The Quantitative Microsomal Mutagenesis Assay Method," *Mutation Research*, 31:365–380, 1975.

2. *Effectiveness guidelines.* An antifungal ingredient must have at least one well-designed clinical study demonstrating effectiveness in the treatment of athlete's foot as the minimal indication of effectiveness. It is generally accepted that fungal infections of the feet may be more difficult to control than those of the groin. For this reason the Panel believes that any ingredient that is effective in the treatment of athlete's foot will also be effective in the treatment of jock itch or ringworm. It is important to note, however, that any ingredient with effectiveness demonstrated only in jock itch or ringworm and supported by a clinical trial may use "jock itch" or "ringworm" but not "athlete's foot" as a labeled indication.

The study population for any clinical study of athlete's foot, jock itch, or ringworm infections should be carefully selected. Certain populations may be desirable because environmental conditions and regimented routines and dress may predispose these groups to develop infections; military populations are an example. University dormitory or athletic populations may be acceptable if proper control can be instituted.

Other studies have used accessible patients, such as those referred to clinics or large dermatology centers in universities. This patient population frequently includes those with chronic fungal disease who are most difficult to treat satisfactorily.

a. *Helpful procedures in performance of trial.* Regardless of the study population selected, the patients must have significant disease. In all cases, a positive KOH and culture is an essential requirement for admission to a study. Symptoms alone are not a reliable basis for entering a study because different diseases may have similar symptoms.

An anatomical diagram (map) of the foot is helpful when it is used to indicate the sites from which skin scrapings were taken for KOH preparations and cultures. These sites should be sampled again for cure cultures. Any additional sites should also be marked on the map. This technique provides a permanent record for each patient.

The preferred site is the one the clinician determines to be most likely to produce a fungal isolate. Mushy toe sites should not be used because the rate of fungal isolation is low. Sampling of this preferred site and one other site on all patients, as opposed to sampling a standardized site on every patient, shows the highest number of recoveries.

Numerical grades for evaluating the severity of each symptom and definitions of these grade values should be recorded, thereby providing defined grading scores. Investigators should be

trained and experienced on the grading scale to be used.

Clinical photography with paired photographs may also be helpful in the preparation of a final record. These photographs are not essential, but when they are used, they should be standardized.

The Panel recommends that the following studies be performed to evaluate topical antifungal ingredients classified in Category III because of inadequate effectiveness data.

b. *Criteria for determining antifungal activity.* To determine the specific antibacterial and antifungal activity of ingredients, specific in vitro testing procedures will be required. These procedures will also apply when these ingredients are tested against clinical isolates during clinical testing.

In in vitro testing, the antifungal ingredient should be tested in the concentration used in the formulated product. The testing procedure should state whether the single ingredient or the formulated product was tested. It is often useful to establish an activity curve so that tests need not be limited to this single concentration. Test data should also include specific details of the organisms, the media, and the neutralizers that were used.

Some ingredients reviewed by the Panel may have antifungal activity, but were included at very low concentrations. These are recognized by microbiologists as preservative levels, i.e., they have been included to maintain the quality of the product and to prevent contamination on repeated use. It is necessary to establish whether an ingredient is included in an antifungal preparation as an antifungal agent or as a preservative. The results of in vitro testing and determination of the spectrum of the chemical should reveal this.

An ingredient included as a preservative should be present at a level necessary for adequate preservation of the product. The minimal effective preservation level can be determined by the standard preservative effectiveness test contained in the "United States Pharmacopeia" (Ref. *1*) or the CTFA preservatives test (Ref. *2*). Modifications of this procedure allow more accurate estimation of the effectiveness of a preservative ingredient and involve rechallenge and organic load testing.

c. *Characterization of clinical isolates.* When clinical studies are performed, the microorganisms infecting each patient should be identified. When a specimen is taken for culture, the researcher should specify the medium used, the type of inoculation, the temperature and time of incubation, and the identification of isolates.

Several media and techniques for isolating clinical specimens are decribed in the literature. Because there is considerable disagreement on the best procedure for in vitro testing, alternative procedures are presented. References are included in which supporters of each technique discuss the specific attributes of that particular technique.

(1) *Dermatophytes.* The Panel stresses the importance of the isolation of a positive culture as part of any protocol for an acceptable clinical study. The testing procedures should indicate the degree of susceptibility of various clinical isolates to the antifungal ingredient being tested. This includes the ingredient and the final product formulation. Specific suggestions concerning susceptibility testing procedures are discussed below.

(i) For clinical isolation of dermatophytes, Dermatophyte Test Medium (DTM) is strongly recommended. It offers advantages since it contains specific inhibitors for other microorganisms and in comparative trials has shown a higher rate of positive cultures (Ref. *3*). However, some clinics may prefer to use another suitable medium for isolation. If so, the rate of isolation and method of identification should be reported.

(ii) Identification of the isolate from DTM should be made according to Rebell and Taplin (Ref. *4*).

(2) *Candida.* The following specific information and procedures should be used in order to identify isolates believed to be *Candida.*

(i) Perform KOH or wet mount to determine whether the isolate is yeastlike.

(ii) Identify the specific strain of *Candida* as follows: Pagano-Levine medium should be used because specific and positive identification of *C. albicans* can be made with this medium based on the presence of chlamydospores. If another similar suitable medium is used for isolation, the rate of isolation and method of identification should be reported. Other biochemical tests exist for the identification of other less frequently isolated candidal species, such as *Candida parapsilosis, Candida tropicalis,* or *Candida stelladoitea* (Ref. *5*) which do not produce chlamydospores.

(iii) Determine whether the isolate is pathognomonic according to yeast morphology and site of isolation.

(3) *Bacterial isolates.* If the sampling of mushy toes is avoided, as mentioned above, and the specific media mentioned are used, bacteria will not ordinarily be isolated. If they are found, they frequently gram negatives, especially *Pseudomonas.* (Ref. *6*).

References

(*1*) "The United States Pharmacopeia," 20th Ed., United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 873–874, 1979.

(*2*) "A Guideline for the Determination of Adequacy of Preservation of Cosmetics and Toiletry Formulations," *Toilet Goods Association Cosmetic Journal,* 2:20–23, 1970.

(*3*) Taplin, D., et al., "Isolation and Recognition of Dermatophytes on a New Medium (DTM)," *Archives of Dermatology,* 99:203–209, 1969.

(*4*) Rebell, G., and D. Taplin, "Dermatophytes: Their Recognition and Identification," 2d Ed., University of Miami Press, Coral Gables, FL, 1970.

(*5*) Winner, H. I., and R. Hurley, "Candida Albicans," J. and A. Churchill, Ltd., London, 1964.

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

d. *In vitro testing of antifungal ingredients.* Many ingredients placed in Category III have never been adequately characterized for their antifungal activity. The Panel has indicated that some agents have specific activity where only minimal testing has been done. Knowledge of the type of inhibitory activity or killing activity is required to adequately test and formulate ingredients. The results of well-conducted in vitro testing may help one prudently decide whether to invest funds in clinical trials. Also, data derived from activity testing permit a significant increase in predictability when the ingredient is used.

Culturing and susceptibility testing procedures in hospital settings have not been well developed for antifungal agents because diseases caused by fungi, although often serious, are less common than infectious diseases of bacterial origin. The development of testing procedures has also been discouraged in dealing with potentially active ingredients because the correlation of the results of in vitro testing with clinical effectiveness has not been high for antifungal agents. Improved procedures now permit more rapid, reliable, and simplified culturing. The Panel has attempted to describe techniques which may help improve the correlation between in vitro and in vivo activity.

(1) *Testing for fungicidal or fungistatic activity.* Identification of the specific type of activity is important. Fungistatic agents probably are effective because they keep the fungus from reproducing while allowing body responses to act effectively in

eliminating the fungus. Frequently, fungistatic agents are not as immediately effective as are agents which eliminate the fungus rapidly. Although these two activities have been considered divergent, in reality there may only be a difference in the rate at which fungal cells are killed.

(2) *Preparation of inoculum.* The following comments on the preparation of inoculum apply to all testing of antifungal agents including antifungal activity and susceptibility testing.

The inoculum size and incubation time directly affect the in vitro activity of antimicrobial agents (Ref. *1*). Consequently, it is essential to determine the number of colony-forming units in the inoculum. A colony-forming unit is either one single cell or a single clump of cells. Spores are often used in the preparation of inocula instead of mycelial growth because they are more often single and distinct and provide easier handling for dispersion and enumeration.

The Panel recognizes that there may often be specific problems in developing techniques for the preparation and standardization of inocula. The highly variable culturing results which have been obtained with dermatophytic fungi make it necessary to develop a method that works for each specific dermatophytic organism. One method may not necessarily work for all, but as methods are refined, more uniform procedures are possible.

The inoculum preparation and standardization can be controlled using the following suggestions. The Panel recommends that for each microorganism to be tested, the following considerations be included in a protocol:

(i) Specify the incubation time of the inoculum.

(ii) Inoculum size. Specify the number of colony-forming units by performing a viable cell count. Determining the inoculum size is necessary to obtaining the optimal results in the actual test procedure.

(iii) Freshly prepared agar plates should be used.

(iv) Known and confirmed strains of fungi should be tested.

(v) A suggested control isolate is helpful.

(vi) Comparative culture testing. A known test culture run at the same time as the isolate is helpful to ensure that all aspects of the test are controlled.

(3) *Media selection.* (i) A standardized medium is absolutely essential. The more reproducible the medium, the better.

(ii) The media now in use for growing the clinical isolate are Sabouraud's with dextrose plus yeast extract and brain-heart infusion plus 50 μg/mL ampicillin. Meuller-Hinton medium has also been used. (This is standard antibiotic susceptibility testing medium.)

The Panel generally recommends Sabouraud's with dextrose plus yeast extract, although other appropriate media may be used. Comparative effectiveness for growth and susceptibility testing should be done where new media are considered. Some agars will selectivity pick up ingredients from the formulation that is being tested on them. (The active ingredient binds to agar.)

(iii) Comparative data have shown that DTM is superior for clinical isolation. In use, DTM suppresses the bacterial flora and allows growth of the dermatophytes. If clinical specimens are being prepared for culture and subsequent susceptibility testing, the following suggestions should be considered: (*a*) No transport medium should be used.

(*b*) A temperature of 30° C is the standard. Any variation in temperature should be noted.

(*c*) The time of incubation should be at least 2 weeks. Cultures should be read at 5, 10, and 14 days.

(*d*) Sabouraud's medium rather than DTM should be used for nail cultures.

(*e*) A suggested alternative is Sabouraud's with 100 μg/mL gentamicin and yeast extract.

(4) *Examples of susceptibility testing procedures.* (i) Drop test. This procedure has been described by Miles and Misra for bacteria (Ref. *2*).

(ii) Agar dilution. If agar dilution is used, a problem may develop when the inoculated fungal mycelium grows to the surface of the plate and spreads.

(5) *Organisms to test to enure reliability of the procedure*—(i) *E. floccosum.*

(ii) *T. mentagrophytes* (granular).

(iii) One suggested *T. metagrophytes* strain is D-1-ATCC 18748 (Vietnam).

(iv) *T. rubrum*—sporulating (organism difficult to sporulate).

(v) *Trichophyton tonsurans* (clinical isolate).

(vi) *C. albicans.*

(vii) More than one type of organism should be tested. Examples are *M. canis* and *T. mentagrophytes* for ringworm; *T. rubrum* and *E. floccosum* for jock itch; and *T. mentagrophytes* and *T. rubrum* for athlete's foot.

(6) *Test details.* (i) The test should be repeated to ensure reproducibility.

(ii) A recognized active antifungal agent as control should be tested with a reference strain of organism of known susceptibility and with the clinical isolates.

(iii) Incubate at 30° C.

(iv) A specific endpoint should be slelected; 5 days is suggested. Cultures should be held and read at 2 weeks for any changes that may occur.

(v) If the active ingredient is diluted for the test, the vehicle should be used as a diluent.

(vi) The vehicle should be tested alone.

(vii) The activity of the final product must be greater than the activity of the vehicle alone.

(7) *Zone of inhibition testing.* Historically, many types of direct contact testing are related to the zone of inhibition test. Often, materials have simply been placed on culture plates.

A zone of inhibition test is not likely to be decisive because many molecules are large, and the solubilities of ingredients vary greatly. Although this type of test is still used, it is not recommended. It alone is not sufficient to characterize antifungal activity.

(8) *Activity testing.* A distinct test to determine the type of action of the active ingredient should be done. Endpoints may be difficult to determine with antifungal agents (for instance, with imidazoles). The stability of the antifungal agent must be considered in any test procedure. The following procedures may be used when testing for fungicidal and fungistatic activity:

The fungistatic and fungicidal concentration against known organisms can be determined and recorded in standard units (μg/mL or U/mL). These concentrations are most often determined using a multiple tube method. Subculturing is usually carried out from "test" tubes to determine whether activity is fungicidal. Descriptions of testing procedure can be found in standard references such as the "United States Pharmacopeia." Other suggestions are made in the following pages.

When establishing antifungal activity, the antifungal action of the specific ingredient must be tested using all the following fungi: *T. mentagrophytes, T. rubrum, E. floccosum, M. canis,* and *Candida.* Testing a wide selection of organisms helps to establish the spectrum of a specific ingredient.

The following suggestions may be helpful in conducting these tests:

(i) After sufficient incubation of the agar dilution or other test cultures to allow growth in the absence of inhibitory chemicals, a subculture should be made. It should include an effective neutralizer. The neutralizer is required to stop the action of the inhibitory chemical.

(ii) Liquid test medium can be removed by filtration and the membrane filter placed on fresh medium to check for growth.

(iii) A plug of agar can be leached of active ingredients and this plug added to fresh medium and incubated for growth.

Unfortunately, with antifungal agents and even with the best testing procedures, some agents will show in vitro activity but will not show effectiveness in a clinical test.

(9) *Antifungal activity—testing the clinical isolate.* The testing of recent clinical isolates of fungal cultures is very important. The considerations for selecting media and inoculum preparations (discussed above) also apply to clinical isolates. DTM has been shown to be superior for clinical isolation, but difficulty in batch-to-batch reproducibility has prevented widespread acceptance. Consequently, Sabouraud's is still commonly used for primary clinical isolation, though it is not as reliable.

Reference

(1) Waitz, J. A., E. L. Moss, and M. J. Weinstein, "Chemotherapeutic Evaluation of Clotrimazole [Bay b 5097, 1)*o*-Chloro-alpha-alpha-Diphenylbenzyl) Imidazole]," *Applied Microbiology*, 22:891–898, 1971.

(2) Miles, A. A., and S. S. Misra, "The Estimation of the Bactericidal Power of the Blood," *Journal of Hygiene*, 38:732–749, 1938.

e. *Effectiveness standards for labeling indications of antifungal drug products.* The Panel recommends that all OTC topical antifungal products be labeled in a manner which will clearly indicate their ability to effectively treat jock itch or ringworm and treat and prevent athlete's foot. This label claim should be based on a well-designed, controlled, clinical trial of the active ingredient in the treatment of prevention of established fungal infections.

(1) *Treatment.* To be moved into Category I, the effectiveness of a Category III OTC ingredient used for the treatment of athlete's foot, jock itch, and ringworm must be demonstrated in a study of infected human subjects which meets the following criteria:

(i) The disease must be diagnosed clinically and confirmed by positive KOH preparation and culture of skin scrapings. Clinical signs and symptoms, such as redness, cracking, fissuring, scaling, swelling, itching, burning, or pain, should be present.

(ii) Patients with active disease should be randomly assigned to total formulation or vehicle groups and treated and evaluated in a double-blind fashion.

(iii) Total formulation should be compared to the vehicle, preferably in parallel groups of patients and not with a paired comparison test. Paired comparisons allow contamination of vehicle-treated sites with active ingredients. It is desirable to confirm the in vitro minimal inhibitory concentration of the test ingredient for the clinical isolate in refractory cases.

(iv) The final evaluation of clinical results should be corroborated with the finding of a negative KOH preparation and culture at least 2 weeks after therapy stops.

(2) *Analysis of results.* A sufficient number of subjects should be studied to yield a statistically significant result. Significance should be found at the $p=.05$ level. A realistic projection of the degree of effectiveness of the ingredient compared to the vehicle should be made before starting the clinical trial. A drug that is projected to have borderline effectiveness will require larger numbers of patients in the trial.

The domonstration of effectiveness in a clinical trial designed to include the following points provides the minimal acceptable data for consideration in order to move an ingredient from Category III to I. However, final judgment will depend on clinical judgment. Ingredients so tested should be significantly more effective than the vehicle which is used to disperse them. Patients will be considered clear of fungal infection when the following criteria are met:

(i) For the feet, a 4-week treatment period followed be 2 weeks without treatment, with KOH preparation and culture at 0, 4, and 6 weeks. The 4-week and 6-week readings are to be negative for both KOH preparation and culture. Signs and symptoms must be cleared.

(ii) For the groin, a 2-week treatment period followed by 2 weeks without treatment, with KOH preparation and culture at 0, 2, and 4 weeks. The 2-week and 4-week readings are to be negative for both KOH preparation and culture. Signs and symptoms must be cleared.

(iii) For ringworm of the body, a 4-week treatment period followed by 2 weeks without treatment. KOH preparation and culture should be done at 0, 4, and 6 weeks. The 4-week and 6-week readings are to be negative for both KOH preparation and culture. Signs and symptoms must be cleared.

The Panel recognizes the difficulty and expense of conducting this type of study; however, it cannot rely solely on in vitro or in vivo animal studies as proof of effectiveness.

The Panel agrees that experimentally induced fungal infections in humans may be used to study the effectiveness of OTC antifungals but that the results of such studies cannot be used as sole support of claims of effectiveness. It believes that therapeutic studies of the naturally occurring fungal infections yield more meaningful results.

The Panel agrees that a drug shown to be effective in the treatment of fungal infections of the feet will also be effective in the treatment of fungal infections of the groin or other parts of the body, excluding the scalp and nails, when these infections are caused by susceptible organisms. The Panel does not insist that label claims of effectiveness in treating athlete's foot, jock itch, and ringworm be supported by controlled studies done at each site.

(3) *Prevention.* The principles for a well-designed prophylactic trial of a drug are not unique for antimicrobial agents. Such studies should be ethically justifiable and use adequate patient-protection procedures including informed consent and guarantees of confidentially. It is not the intent of this Panel, however, to deny the value of data from early studies even though they do not meet current standards.

The basic question the investigator wishes to answer is: Do patients who are given the prophylactic agent have fewer recurrences than those who are not?

(i) *Selection of patients.* The fixed population at risk will generally include two types of patients. Type one is the group with recurrent interdigital athlete's foot with minimal involvement of the remaining skin of the foot. This group would not have chronic fungal infection in the toenails. Type two includes those patients who have had the eruption in a "moccasin" distribution over the skin of the foot. This group will usually have fungal disease in the toenails. Although the Panel recognizes two patient types, it believes that random patient selection suffices for a prophylactic trial.

There are frequent outbreaks of disease in most of the population after a change in environmental conditions or a change in physical activity. The Panel also recognizes that segments of the population have dramatically increased their participation in sports and in group physical activities, thus increasing the likelihood that an individual may develop dermatophytic fungal infection. The incidence of infection in populations such as those in university dormitories or military groups is high enough to use comparative groups in a prophylactic study in which all subjects begin the study free from disease.

Because an adequate prophylactic trial is one of the most difficult studies to perform and because of the lack of chronic toxicity data, the Panel

concludes that any ingredient to be labeled for prophylactic use must have studies that conform to the guidelines establishing both safety and effectiveness. The Panel recognizes that many Category I drugs effective in treatment might also be effective in the prevention of athlete's foot. For most of these drugs, however, the Panel has found no human studies to support this belief. The long-term effects of prophylactic drugs on the feet or on the fungi which cause athlete's foot are also unknown. The Panel recognizes the difficulty in organizing a human study to produce such data.

Another consideration is that there are so many variables that can influence the growth of fungi: type and amount of clothing; activity level of an individual; the skin temperature, skin moisture, or natural immunity of an individual; the virulence of the organism; and the possibility of the presence of other complicating organisms.

The Panel recognizes that in vivo studies in animals of the effectiveness of Category I antifungal ingredients cannot duplicate or substitute for the study of human fungal infections to support claims of effectiveness in prophylaxis. For this reason a clinical trial will be required to justify prophylaxis labeling claims, e.g., "prevents athlete's foot."

The Panel also believes that nonantifungal drugs (such as drying agents) and antifungal drugs which have not been proven effective (Category III) may play a role in the prevention of athlete's foot. However, no evidence has been found to either support or disprove this idea. The Panel does not believe that it is scientifically valid to accept data obtained from animal studies as proof of prophylaxis in humans.

For prophylactic trials, the Panel recommends that KOH and cultures be performed on specific anatomical sites. One recommended site is the space between the third and fourth toe. The goal of prophylaxis should be the prevention of signs and symptoms. Patients studied should have no symptoms on admission to the study, but should have a high likelihood of developing an infection.

(ii) *Prophylactic trial.* (*a*) The trial should involve a sufficient number of subjects established by using accepted statistical procedures.

(*b*) Patients should be randomly assigned to total formulation or vehicle groups.

(*c*) A vehicle control group is used.

(*d*) Comparability of the total formulation and vehicle groups is established by analysis of pertinent variables.

(*e*) Both investigators and subjects are unaware of who is receiving the total formulation or the vehicle (double-blinding).

(*f*) Efficacy is established by analysis of the incidence of infection in the two groups of the study.

(*g*) A precise definition and objective measure of the presence or absence of the disease is decided before the study.

(*h*) The length of the trial should be a minimum of 12 weeks.

(*i*) Regular followup of the groups is preferably carried out at 4 and 8 weeks. Local adverse effects and compliance should be observed. KOH and cultures should be done at baseline and at 12 weeks. Observations should be systematically recorded.

(*j*) The number of patients should be estimated from the expected difference between the formulation and vehicle groups.

(4) *Premarketing effectiveness testing.* The Panel recognizes that differences in pharmaceutical formulation can cause significant differences in the availability and activity of antifungal ingredients.

An objective effectiveness study (see below) comparing an old and new formulation or dosage form not previously marketed is required before such formulation changes may be made. Although some effects and incompatibilities are known, the effect produced by changes in concentration or by deletion and addition of ingredients is entirely unknown.

Limited clinical trials have historically replaced bioavailability studies for topically applied drugs. Ideally, the specific test to determine the effectiveness of altered or new formulations should be relatively simple. It should not require a very large number of subjects and should not be time consuming or expensive because such requirements discourage innovation.

The Panel recommends that in vitro studies be performed to establish that the antifungal ingredient is available when alterations in formulation are made.

Following these procedures, the innovator may choose one of the tests described and affirm that the new formulation is equal in effectiveness and safety to the formulation being replaced.

(i) *Criteria for changes in vehicles.* In its report on OTC topical antibiotics published in the **Federal Register** on April 1, 1977 (42 FR 17647), the Panel recognized that there may be a significant influence of vehicle on effectiveness. The Panel still maintains the viewpoint that an antifungal ingredient may demonstrate varying results as a consequence of altering the vehicle carrying the antifungal ingredient. It is concerned that vehicles other than those used in clinical studies reviewed by the Panel may be used as carriers for a Category I ingredient without adequate studies demonstrating bioavailability. For example, if a powder formulation of an antifungal agent was shown to be safe and effective, there is no scientific reason to assume that any or all other dosage forms will be as safe or effective as the one that was evaluated by the Panel.

On the other hand, the Panel sees no legitimate reason to recommend full clinical studies or full safety studies on a Category I antifungal ingredient because of alterations in the dosage form of a proven antifungal. The Panel recommends that any change in a currently marketed dosage form of a Category I ingredient be subjected to an adequately controlled in vivo study to demonstrate equivalent bioavailability (±20 percent is the standard for bioequivalence).

An in vitro study using the already evaluated formulation as the standard and the proposed formulation as the test system may be helpful in determining whether to proceed with a formulation change. The new vehicle should also be used as a vehicle control.

After routine in vitro tests have indicated that the agent is available, one of the described procedures can be used to demonstrate the equivalence of the new formulation.

(ii) *The use and validation of animal models.* Historically, animal models have been used in studies which cannot be done in humans. Frequently these procedures have involved inoculation with many organisms or the use of very large numbers of animals. They are often used as a means of screening prior to human studies. Animal models are also used because it is not practical to perform a clinical trial for minor alterations in formulation.

In order to be reliable, comparability between the model and the clinical entity must be determined. In some models the disease is self-limiting so that the exposure time to any drug is limited.

The following considerations should be applied if a model is used to determine any changes in effectiveness of a formulation:

(*a*) The model must be validated against a human clinical trial.

(*b*) The specific details of the model, for example, the number of animals, method of preparation, and inoculation, should be detailed because several variations of models have been used.

(c) The drug level required to obtain a difference in the test results should be determined.

(d) If the new formulation exceeds the criterion of ±20 percent of the activity of the old formulation, additional testing may be required.

(e) The procedures and calculations involved in the statistical analysis of the model studies should be determined and specified before performing the test.

(iii) *In vivo guinea pig testing.* The in vivo study in guinea pigs infected with the fungi specified in the protocol and using the original formulation as the standard and the proposed formulation containing the Category I drug as the test system may be used. The proposed vehicle would also be used as a placebo control. If equivalent bioavailability can be demonstrated, the vehicle may be changed. If equivalent bioavailability cannot be demonstrated using an in vivo test, the Panel recommends that a full clinical study be conducted as outlined elsewhere in this document. (See part III. paragraph E.2. above—Guidelines for Safety and Effectiveness Studies.)

There are four situations in which in vivo guinea pig testing would be particularly useful:

(a) Continued marketing of all formulations of Category I ingredients which have not been specifically demonstrated effective in clinical trials.

(b) Introduction of new dosage forms of Category I ingredients.

(c) Significant formulation modifications of existing products, i.e., change in active ingredient concentrations within Category I range or significant inactive ingredient adjustments.

(d) Initial marketing of a formulation containing a Category I ingredient.

Each of the above must be shown to be as effective as a standard of the same Category I ingredient. Either of the following standards may be used: (a) *Primary standard.* This is a formulation, containing the same Category I active ingredients, which has been shown effective in a clinical study.

(b) *Secondary standard.* This is a formulation, containing the same Category I active ingredients, which has been shown statistically equivalent to a primary standard in the guinea pig test.

(3) *The use of an excised skin model.* Reference is made to the description of Stoughton's procedure (Refs. *1* through *4*). Rather sophisticated measurements can be made using this system.

(4) *Limited clinical trials.* This kind of study may be desirable where the new formulation offers a significant advance over the existing one. This method of assuring bioavailability has been used for products submitted under new drug applications.

Reference

(*1*) Stoughton, R. B., "Bioassay of Antimicrobials. A Method for Measuring Penetration of Agents into Human Skin," *Archives of Dermatology*, 101:160–166, 1970.

(*2*) Stoughton, R. B., and G. S. Stoughton, "Topical Control of Skin Bacterial Growth with Hexachlorophene in Dimethylacetamide," *Journal of Investigative Dermatology*, 50:332–335, 1968.

(*3*) Munro, D. D., and R. B. Stoughton, "Dimethylacetamide (DMAC) and Dimethylformamide (DMFA) Effect on Percutaneous Absorption," *Archives of Dermatology*, 92:585–586, 1965.

(*4*) Stoughton, R. B., "Hexachlorophene Deposition in Human Stratum Corneum," *Archives of Dermatology*, 94:646–648, 1966.

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

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)), under 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 (see 46 FR 26052; May 11, 1981), 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 in Part 333, new Subpart C, to read as follows:

Subpart C—Topical Antifungal Drug Products

Sec.

333.201 Scope.
333.203 Definitions.
333.210 Antifungal active ingredients.
333.220 Permitted combinations of active ingredients.
333.250 Labeling of antifungal drug products.

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 C—TOPICAL ANTIFUNGAL DRUG PRODUCTS

§ 333.201 Scope.

(a) An over-the-counter antifungal drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this subpart and each general condition established in § 330.1 of this chapter.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 333.203 Definitions.

As used in this part:

(a) *Antifungal agent.* An agent which either kills or inhibits the growth and reproduction of fungal cells.

(b) *Athlete's foot.* The term "athlete's foot" refers to enfections of the feet caused by dermatophytic fungi.

(c) *Candida.* A yeast type of fungus, which under certain circumstances may cause infection.

(d) *Dermatophyte.* A fungus that is parasitic upon the skin, hair, or nails of humans or animals.

(e) *Fungus.* Any of a large division of plants, including dermatophytes, yeasts, and molds, characterized by a simple cell structure and the absence of chlorophyll.

(f) *Jock itch.* The term "jock itch" refers to a chronic and recurrent dermatophyte infection which occurs in men and affects the upper, inner thighs and sometimes extends to the groin and the pubic area.

(g) *Ringworm.* The term "ringworm" applies to skin infections cause by dermatophytic fungi.

(h) *Unit of nystatin.* A measure of the potency of nystatin as defined in § 430.6(a)(3).

§ 333.210 Antifungal active ingredients.

The active ingredients of the product consist of any of the following when used within the dosage and labeling limits established for each ingredient.

(a) Haloprogin 1 percent.

(b) Iodochlorhydroxyquin 3 percent.

(c) Miconazole nitrate 2 percent.

(d) Nystatin 100,000 unit/gram in accordance with § 333.220(a) or § 333.250(b) (3) and/or (4).

(e) Tolnaftate 1 percent in accordance with § 333.220(a), (b)(1), (b)(2), and (b)(3), or § 333.250(b)(1) and/or (2).

(f) Undecylenic acid, calcium undecylenate, copper undecylenate, and zinc undecylenate may be used individually or in any ratio which provides a total undecylenate concentration of 10 to 25 percent.

§ 333.220 Permitted combinations of active ingredients.

(a) *Combinations of antifungal active ingredients.* Two or three antifungal ingredients identified in § 333.210 may be combined provided each ingredient broadens the antifungal spectrum and provided the product is labeled according to § 333.250(b)(1).

(b) *Combinations of antifungal active ingredients with nonantifungal active ingredients.* (1) Any single antifungal active ingredient identified in § 333.210 (a), (b), (c), (e), or (f) or any combination identified in § 333.220(a) may be combined with any single antiprespirant active ingredient which is generally recognized as safe and effective in an OTC final monograph provided the combination is labeled according to § 333.250(b)(1).

(2) Any single antifungal active ingredient identified in § 333.210(a), (b), (c), (e), or (f) or any combination identified in § 333.220(a) may be combined with any single keratolytic active ingredient agent which is generally recognized as safe and effective in an OTC final monograph provided the combination is labeled according to § 333,250(b) (1).

(3) Any single antifungal active ingredient identified in § 333.210(a), (b), (c), (e), or (f) or any combination identified in § 333.210(a) may be combined with either hydrocortisone or hydrocortisone acetate 0.5 to 1 percent provided the product is labeled according to § 333.250(b) (1).

§ 333.250 Labeling of antifungal 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 "antifungal."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" and is limited to the following:

(1) *For products containing any ingredient identified in § 333.210(a), (b), (c), (e), or (f) or any combination of ingredients identified in § 333.220 for the treatment of athlete's foot, jock itch, and ringworm.* As appropriate, combine one or more of the terms describing antifungal product action in § 333.250(b)(1)(i) with one or more of the terms describing conditions for use in § 333.250(b)(1)(ii).

(i) *Product action.* (*a*) "Treats * * *"
(*b*) "For the treatment of * * *"
(*c*) "Cures * * *"
(*d*) "For the cure of * * *"
(*e*) "Clears up * * *"
(*f*) "Proven clinically effective in the treatment of * * *"
(*g*) "For effective treatment of * * *"
(*h*) "Kills * * * fungi."
(*i*) "Proven to kill * * * fungi."

(ii) *Conditions for use.* (*a*) "Athlete's foot"
(*b*) "Athlete's foot (dermatophytosis)"
(*c*) "Athlete's foot (tinea pedis)"
(*d*) "Tinea pedis (athlete's foot)"
(*e*) "Jock itch"
(*f*) "Jock itch (tinea cruris)"
(*g*) "Tinea cruris (jock itch)"
(*h*) "Ringworm"
(*i*) "Ringworm (tinea corporis)"
(*j*) "Tinea corporis (ringworm)"

(2) *For products containing tolnaftate identified in § 333.210(e) as a single ingredient labeled for the prevention of athlete's foot.* Use any one of the phrases describing product action in § 333.250(b)(2)(i) with any one of the phrases describing the condition for use in § 333.250 (b) (2) (ii).

(i) *Product action.* (*a*) "Clinically proven to prevent * * * With daily use."
(*b*) "Prevents * * * with daily use."
(*c*) "Proven effective in the prevention of * * * with daily use."
(*d*) "Helps prevent * * * with daily use."
(*e*) "For the prevention of * * * with daily use."
(*f*) "For the prophylaxis (prevention) of * * * with daily use."
(*g*) "Guards against * * * with daily use."
(*h*) "Prevents the recurrence of * * * with daily use."

(ii) *Condition for use.* (*a*) "Athlete's foot"
(*b*) "Athlete's foot (tinea pedis)"
(*c*) "Tinea pedis (athlete's foot)"
(*d*) "Athlete's foot (dermatophytosis)"

(3) *For products containing either haloprogin, miconazole nitrate, or nystatin identified in § 333.210(a), (c), or (d) as a single ingredient labeled for the treatment of external feminine itching associated with vaginal yeast (candidal) infection.* "For the treatment of external feminine itching associated with vaginal yeast (candida) infection."

(4) *For products containing either haloprogin, miconazole nitrate, or nystatin identified in § 333.210 (a), (c), or (d) as a single ingredient labeled for the treatment of superficial skin infections caused by yeast (Candida).* "For the treatment of superficial skin infections caused by yeast *(Canadida).*"

(5) *Other allowable statements for any antifungal product.* Any of the phrases describing product action in § 333.250(b)(5)(i) may be combined, as appropriate, with any of the terms or phrases describing symptoms in § 333.250(b)(5)(ii) provided that the resulting phrases are used in conjunction with the indications identified in § 333.250(b)(1), (3), and (4).

(i) *Product action.* (*a*) "Relieves * * *"
(*b*) "For relief of * * *"
(*c*) "For effective relief of * * *"
(*d*) "Soothes * * *"

(ii) *Symptoms.* (*a*) "Itching"
(*b*) "Scaling"
(*c*) "Cracking"
(*d*) "Burning"
(*e*) "Redness"
(*f*) "Soreness"
(*g*) "Irritation"
(*h*) "Discomfort"
(*i*) "Chafing associated with jock itch"
(*j*) "* * * itchy, scaly skin between the toes."
(*k*) "* * * itching, burning feet."

(6) *Other allowable statements for products containing haloprogin identified in § 333.210(a), miconazole nitrate identified in § 333.210(c), or any combination identified in § 333.220 that contains nystatin identified in § 333.210(d).*

(i) "Kills dermatophytic fungi and yeast (causes of athlete's foot, jock itch, and ringworm)."

(ii) "Proven to kill dermatophytic fungi and yeast (causes of athlete's foot, jock itch, and ringworm)."

(7) *Other allowable statement for products labeled according to § 333.250(b)(2).* "Clears up athlete's foot infection and with daily use helps keep it from coming back."

(8) *Product attributes.* Terms to describe certain physical and chemical qualities may be used as long as these terms do not imply any therapeutic effect and are distinctly separated from the indications identified in § 333.250(b)(1), (2), (3), and (4). These terms are intended to provide consumer information and relate to a product's color, odor, or feel. The following or similar terms may be used:

(i) "Colorless"
(ii) "Odorless"
(iii) "Pleasantly scented"
(iv) "Greaseless"
(v) "Usually does not sting"
(vi) "Non-staining"
(vii) "Drying"
(viii) "Cooling"
(ix) "Cools hot, tender feet."
(x) "Helps keep feet dry."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing any ingredient identified in § 333.210.* (i) "Do not use in children under 2 years of age except under the advice and supervision of a doctor."

(ii) "For external use only."

(2) *For products labeled according to § 333.250(b)(1) for the treatment of athlete's foot and ringworm.* "If irritation occurs or if there is no improvement within 4 weeks, discontinue use and consult a doctor or pharmacist."

(3) *For products labeled according to § 333.250(b)(1) for the treatment of jock itch.* "If irritation occurs or if there is no improvement within 2 weeks, discontinue use and consult a doctor or pharmacist."

(4) *For products labeled according to § 333.250(b)(2) for the prevention of athlete's foot.* "If irritation occurs, discontinue use and consult a doctor or pharmacist."

(5) *For products labeled according to § 333.250(b)(3) for the treatment of external feminine itching associated with vaginal yeast (candidal) infection or when labeled according to § 333.250(b)(4) for the treatment of superficial skin infections caused by yeast (Candida).* "Do not use this product for more than 14 days without consulting a doctor or pharmacist if condition persists or recurs."

(6) *For combinations containing hydrocortisone or hydrocortisone acetate identified in § 333.220(b)(3).* "Do not use longer than 30 days without consulting a doctor or pharmacist."

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions." Depending on dosage form, directions may vary, e.g., "Spray affected area * * *"

(1) *For products labeled according to § 333.250(b)(1) for the treatment of athlete's foot, jock itch, and ringworm.* "Cleanse skin with soap and water and dry thoroughly. Apply a thin layer over affected area morning and night or as directed by a doctor. For athlete's foot, pay special attention to the spaces between the toes. It is also helpful to wear well-fitting, ventilated shoes and to change shoes and socks at least once daily. Best results in athlete's foot and ringworm are usually obtained with 4 weeks' use of this product, and in jock itch, with 2 weeks' use. If satisfactory results have not occurred within these times, consult a doctor or pharmacist. Children under 12 years of age should be supervised in the use of this product. This product is not effective on the scalp or nails."

(2) *For products labeled according to § 333.250(b)(2) for the prevention of athlete's foot.* "To prevent fungal infection of the feet (athlete's foot), cleanse skin with soap and water and dry thoroughly. Apply a thin layer to feet once or twice daily, paying special attention to the toenails and the spaces between the toes. It is also helpful to wear well-fitting, ventilated shoes and to change shoes and socks at least once daily."

(3) *For products labeled according to § 333.250(b)(3) for the treatment of external feminine itching associated with vaginal yeast (candidal) infection, or when labeled according to § 333.250(b)(4) for the treatment of superficial skin infections caused by yeast (Candida).* "Cleanse skin with soap and water and dry thoroughly. Apply a thin layer over affected area morning and night or as directed by a doctor. If satisfactory results have not occurred within 2 weeks, consult a doctor or pharmacist."

Interested persons may, on or before June 21, 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 July 21, 1982. Received comments may be seen in the Office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: January 19, 1982.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: March 16, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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