[4110-03]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 352]

[Docket No. 78N-0038]

SUNSCREEN DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Establishment of a Monograph; Notice of Proposed Rulemaking

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This proposed rule would establish conditions for the safety, effectiveness, and labeling of over-the-counter (OTC) sunscreen drug products. The proposed rule, based on the recommendations of the Panel on Review of Topical Analgesic including antirheumatic, otic, burn, and sunburn treatment and prevention drugs is part of the Food and Drug Administration's ongoing review of OTC drug products.

DATES: Comments by November 24, 1978; reply comments by December 26, 1978.

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

FOR FURTHER INFORMATION CONTACT:

William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, Department of health, Education, and Welfare, 5600 Fishers lane, Rockville, Md. 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: Pursuant to part 330 (21 CFR Part 330), the Commissioner of Food and Drugs received on December 14, 1977, a report of the Advisory Review Panel on Over-The-Counter (OTC) Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Products. In accordance with § 330.10(a)(6) (21 CFR 330.10(a)(6)), the Commissioner is issuing (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC sunscreen drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that the available data are insufficient to classify such conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel to the Commissioner. The minutes of the Panel meetings are on public display in the office of the hearing Clerk (HFA-305), Food and Drug Administration (address given above).

The purpose of issuing the Panel's unaltered conclusions and recommendations is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The Commissioner has not yet fully evaluated the report; the Panel's findings are being issued as a formal proposal to obtain public comment before the agency reaches any decision on the Panel's recommendations. The report has been prepared independently of the Food and Drug Administration (FDA). It represents the best scientific judgment of the Panel members but does not necessarily reflect the agency position on any particular matter contained in it.

The Commissioner recognizes that extensive changes will result in the current marketing practices of these products if the Panel recommendations are fully implemented. The Panel's recommendations include many labeling revisions. One of these labeling recommendations is the statement "Overexposure to the sun may lead to premature aging of the skin and skin cancer. The liberal and regular use over the years of this product may help reduce the chance of premature aging of the skin and skin cancer." As with other of the Panel's recommendations, the Commissioner is not at this time making a final decision with regard to this labeling. However, he finds it necessary to comment that the issue is important and requires careful study. Because of the critical nature of the disease conditions involved, the wording of any claim concerning them must be very carefully considered especially because three of the seven panel members oppose the use of the recommended statement. Special attention must be given to assure that consumers are not misled or confused. The Commissioner recognizes the potential for such a statement to mislead the public, and is concerned about its use. However, the issue is open and will receive the fullest attention before any claim with regard to skin cancer or aging of the skin is included in any OTC drug monograph.

After careful review of all comments submitted in response to this proposal, the Commissioner will issue a tentative final regulation in the FEDERAL REGISTER to establish a monograph for OTC sunscreen drug products.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), all data and information concerning OTC sunscreen drug products submitted for consideration by the Panel have been handled as confidential by the Panel and FDA. All such data and information will be put on public display at the office of the Hearing Clerk, Food and Drug Administration, after September 25, 1978, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address given above).

Based on the conclusions and recommendations of the Panel, the Commissioner proposes the following:

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

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

3. That the conditions excluded from the monograph because the available date are insufficient (category III) to classify such conditions either as category I or category II be permitted to remain on the market, or to be introduced into the market after the date of publication of the final monograph in the FEDERAL REGISTER, provided that FDA receives notification of testing in accordance with § 330.10(a)(13) (21 CFR 330.10(a)(13)). The Panel recommended that a period of 2 years be permitted for the completion of studies to support the movement of category III conditions to category I. The Commissioner will review that recommendation as well as all comments on this document, and will determine what time period to permit for category III testing after that review is completed.

In the FEDERAL REGISTER for January 5, 1972 (37 FR 85), the Commissioner of Food and Drugs announced a proposed review of the safety, effectiveness and labeling of all OTC drugs by independent advisory review panels. In the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), the Commissioner published the final regulations providing

for the OTC drug review under § 330.10 which were made effective immediately. Pursuant to these regulations, the Commissioner issued in the FEDERAL REGISTER of December 12, 1972 (37 FR 26456) a request for data and information on all active ingredients utilized in topical analgesic, including antirheumatic, otic, burn, sunburn prevention and treatment drug products.

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report pursuant to § 330.10(a)(1) on the safety, effectiveness and labeling of those products:

Thomas G. Kantor, M.D., Chairman, John Adriani, M.D., Col. William A. Akers, M.D., Maxine Bennett, M.D., Minerva S. Buerk, M.D., Walter L. Dickison, Ph. D., and Jerry Mark Shuck, M.D.

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

The Panel presents its conclusions and recommendations for sunscreen active ingredients in this document. The Panel's conclusions for topical otic active ingredients were published in the FEDERAL REGISTER of December 16, 1977 (42 FR 63556), and its conclusions for skin protectant active ingredients were published in the FEDERAL REGISTER of August 4, 1978 (43 FR 34628). The Panel's conclusions and recommendations for external analgesic ingredients will be presented in a later issue of the FEDERAL REGISTER.

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

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

The following FDA employees served: C. Carnot Evans, M.D., Served as Executive Secretary. Lee Geismar served as Panel Administrator. Lee Quon, R.Ph., served as Drug information Analyst until July 1975, followed by Timothy T. Clark, R.Ph., until July 1973, followed by Thomas H. Gingrich, R.Ph., until July 1976, followed by Victor H. Lindmark, Pharm.D.

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

Joseph P. Armellino, M.D., Charles Bluestone, M.D., Stuart Ericksen, Ph. D., Alexander A. Fisher, M.D., Thomas Fitzpatrick, M.D., Ph. D., J. M. Glassman, M.D., Peter Hebborn, Ph. D., George E. Heinze, Kenneth R. Johannes, Albert M. Kligman, M.D., Howard Maiback, M.D., Edward Marlowe, Ph. D., Kenneth L. Milstead, Ph. D., John Parrish, M.D., Madhue Pathak, M.D., Robert Sayre, Ph. D., Joseph P. Soyka, M.D., Garrett Swenson, Esq., Stephen M. Truitt, Esq., and Frederick Urbach, M.D.

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

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons and has considered all pertinent data and information submitted through December 14, 1977, in arriving at its conclusions and recommendations for OTC sunscreens.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to sunscreen active ingredients are set out in three categories:

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

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

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

I. SUBMISSION OF DATA AND INFORMATION

Pursuant to the notice published in the FEDERAL REGISTER of December 12, 1972 (37 FR 26156) requesting the submission of data and information on OTC topical sunscreen drugs, the following firms made submissions related to the indicated products:

A. SUBMISSIONS BY FIRMS

Firms and Marketed Products

AVA, Inc., Garland, Tex. 75040, AVA Suntan Lotion.

Bonne Bell, Lakewood, Ohio 44107, Sure Tan Gel and Sure Tan Lotion.

Paul B. Elder Co., Bryan, Ohio 43506, RVP Wide Range Sunscreen, RVP Ultra-Range Sun Protection, RVPlus, RVPaque Ultra-Violet Occlusive Agent, RVPABA Lipstick.

Elizabeth Arden, Inc., New York, N.Y. 10022, Sun Gelee and Suncare.

Greiter Corp., Inc., Weidling, Austria, Piz Buin Exclusiv Suntan Cream, Piz Buin Exclusiv Extrem Suntan Cream, Piz Buin Exclusiv Suntan Liquid Cream.

G. S. Herbert Laboratories, Irvine, Calif. 92664, Eclipse Sunscreen Lotion.

Lanvin-Charles of the Ritz, Inc., Holmdel Township, N.J. 07733, Alexandra de Markoff Lip Emollient, Alexandra de Markoff Allevia Body Treatment, Alexandra de Markoff Allevia Travel Stick, Bain de Soleil Suntan Creme White, Bain de Soleil Suntan Cream, Bain de Soleil Suntan Lotion, Bain de Soleil Leg Make-Up, Bain de Soleil Foam Concentrate, Bain de Soleil Bronzer, Imperial Nutricia Moisture Tint, Revenescence Sun Bronze, Revenescence Protective Cream for the Face, Revenescence Extra Protective Creme for the Face, Revenescence Moisture Glow-Bronze Shade, Revenescence Moisture Glow Liquid-Bronze Shade.

Menley & James Laboratories, Philadelphia, Pa. 19101, Sea & Ski Golden Tan, Sea & Ski Block Out.

Miles Laboratories, Inc., Elkhart, Ind. 46514, Sungard Lotion.

Plough, Inc., Memphis, Tenn. 38101, Coppertone Improved Shade Suntan Lotion, Coppertone Lipkote Lip Balm, Coppertone Noskote Sunscreen, Coppertone Suntan Cream, Coppertone Suntan Foam, Coppertone Suntan Lotion, Coppertone Suntan Oil, Coppertone Suntan Oil Aerosol Spray, Q.T. Foam, Q.T. Lotion, Sudden Tan, Sun Protective Foam, Sun Shielding Lotion.

Rowell Laboratories, Inc., Baudette, Minn. 56623, Duoshield One and Duoshield Two.

Texas Pharmacal Co., San Antonio, Tex. 78296, A-Fil Cream, Sundare Creamy Lotion, Sundare Clear Lotion, SunStick Lip Protectant, SunSwept Cream.

Westwood Pharmaceuticals, Inc., Buffalo, N.Y. 14213, Presun Lotion.

In addition, the following firms made related submissions:

Amerchol, Edison, N.J. 08817, Amerscreen P.

Chattem Laboratories, Chattanooga, Tenn. 37409, Alpaba.

EM Laboratories, Inc., Elmsford, N.Y. 10523, Eusolex 161, Eusolex 232, Eusolex 4360, Eusolex 6300, Eusolex 3573, Eusolex 5563.

Felton International, Inc., Brooklyn, N.Y. 11237, Sunarome.

GAF Corp., New York, N.Y. 10020, Sulisobenzone.

Givaudan Corp., Clifton, N.J. 07104, Giv-Tan-F, Parsol MCX and Parsol Hydro.

Greiter Corp., Tulsa, Okla. 74101, Exclusiv Creme, Exclusiv Milk, Exclusiv Moisture Creme, Exclusiv Oil Lotion, Exclusiv

Stick, Extrem Creme, Extrem Glacier Creme, Extrem Junior Creme, Extrem Milk, Piz Buin.
Haarmann and Reimer Corp., Springfield, N.J. 07081, Neo Heliopan AV.
Hill Top Research, Inc., St. Petersburg, Fla. 33709, Sun Block 253E, Sun Block 256E, Sun Block U-2575.
Ingram Pharmaceutical Co., San Francisco, Calif. 94111, 2-Ethylhexyl 2-cyano-3,3-diphenylacrylate.
Scher Chemicals, Inc., Clifton, N.J. 07012, Dipsal (Dipropylene Glycol Salicylate).
Van Dyk & Co., Inc., Belleville, N.J. 07109, Escalol 106, Escalol 506, Escalol 507.

B. LABELED INGREDIENTS CONTAINED IN MARKETED PRODUCTS AND OTHER INGREDIENTS SUBMITTED TO THE PANEL.

Alcohol
Allantoin
Allantoin-*p*-aminobenzoic acid complex
p-Aminobenzoic acid
Amyl dimethyl PABA
Amyl para-dimethylaminobenzoate
Amyl-*p*-dimethylaminobenzoate
Beeswax
Benzophenone-3
Benzyl alcohol
BHA
BHT
2-Bromo-2-nitropropane-1,3-diol
Camphor
Carbomer 934
Carboset
Cellulose gum
Cetyl alcohol
Cetyl palmitate
Cetyl stearyl glycol
Cinoxate
Citric acid
Clove oil
Cocoa butter
Color
Digalloyl trioleate
Dihydroxyacetone
Dimethicone
5-(3,3-Dimethyl-2-norbornyliden)-3-penten-2-one
3,4-Dimethylphenyl-glyoxylic acid sodium salt
Dimethyl polysiloxane
Dioxybenzone
Dipropylene glycol salicylate
Ethyl alcohol
2-Ethylhexyl 2-cyano-3,3-diphenylacrylate
Ethylhexyl-*p*-methoxycinnamate
2-Ethylhexyl 4-phenylbenzophenone-2'-carboxylic acid
2-Ethylhexyl salicylate
FD&C yellow No. 5
FD&C red No. 4
Fragrances
Glycerin
Glyceryl PABA
Glyceryl stearate
Homosalate
Isopropyl myristate
Isopropyl palmitate
Lanolin
Lanolin alcohol
Lanolin derivatives
Lanolin oil
Lawsone (2-hydroxy-1,4-naphthoquinone)
Menthol
Menthyl anthranilate
p-Methoxycinnamic acid diethanolamine
3-(4-Methylbenzyliden)-camphor
Methylparaben
Microcrystalline titanium-coated mica platelets
Microcrystalline wax
Mineral oil
Octyl dimethyl PABA
Oleth-3-phosphate
Oxybenzone
Padimate
Padimate A
Padimate O
Parabens
Paraffin
PEG 2 stearate
Petrolatum
2-Phenylbenzimidazole
Polyoxyl-40-stearate
Polysorbate 60
Propellant 46
Propellant 12/114
Propoxylate of *p*-aminoethylbenzoate
Propylparaben
Propylene glycol
Propylene glycol stearate
Quaternium 15
Red petrolatum
SD alcohol 40
Sesame oil
Silaca
Sodium carbomer
Sorbitan oleate
Sorbitan stearate
Stabilized aloe vera gel
Stearyl alcohol
Sulisobenzone
Synthetic spermaceti
Titanium dioxide
Triethanolamine
Triethanolamine salicylate
Triethanolamine stearate
Water
Wax
Zinc oxide

C. CLASSIFICATION OF INGREDIENTS

1. *Active ingredients.*

Allantoin combined with aminobenzoic acid (allantoin *p*-aminobenzoic acid complex)
Aminobenzoic acid (*p*-aminobenzoic acid)Cinoxate
Diethanolamine *p*-methoxycinnamate (*p*-methoxycinnamic acid diethanolamine)
Digalloyl trioleate
5-(3,3-Dimethyl - 2 - norbornyliden)-3-penten-2-one
Dioxybenzone
Dipropylene glycol salicylate
Ethyl 4-[bis(hydroxypropyl)] aminobenzoate (propoxylate of *p*-aminoethylbenzoate)
2-Ethylhexyl 2-cyano-3,3-diphenylacrylate
Ethylhexyl *p*-methoxycinnamate
2-Ethylhexyl 4-phenylbenzophenone-2'-carboxylic acid
2-Ethylhexyl salicylate
Glyceryl aminobenzoate (glyceryl PABA)
Homosalate
Lawsone with dihydroxyacetone [dihydroxyacetone; lawsone (2-hydroxy-1,4-naphthoquinone)]
Menthyl anthranilate
3-(4-Methylbenzylidene)-camphor
Oxybenzone (benzophenone-3)
Padimate A (amyl *p*-dimethylaminobenzoate, amyl para-dimethylaminobenzoate, amyl dimethyl PABA, padimate)
Padimate O (octyl dimethyl PABA)
2-Phenylbenzimidazole - 5 - sulfonic acid (2-phenylbenzimidazole sulfonic acid)
Red petrolatum
Sodium 3,4-dimethylphenyl - glyoxylate (3,4-dimethylphenyl-glyoxylic acid sodium salt)
Sulisobenzone
Titanium dioxide
Triethanolamine salicylate

2. *Inactive ingredients.*

The Panel has classified the following as inactive ingredients or pharmaceutical necessities. In some cases, depending upon dosage and claim, some of the ingredients may be classified as skin protectants, which will be discussed more fully in a later issue of the FEDERAL REGISTER.

Alcohol
Allantion
Beeswax
Benzyl alcohol
BHA
BHT
2-Bromo - 2 - nitropropane-1,3-diol
Camphor
Carbomer 934
Carboset
Cellulose gum
Cetyl alcohol
Cetyl palmitate
Cetyl stearyl glycol
Citric acid
Clove oil
Cocoa butter
Color
Dimethicone
Dimethyl polysiloxane
Ethyl alcohol
FD&C yellow No. 5
FD&C red No. 4
Fragrances
Glycerin
Glyceryl stearate
Isopropyl myristate
Isopropyl palmitate
Lanolin
Lanolin alcohol
Lanolin derivatives
Lanolin oil
Menthol
Methylparaben
Microcrystalline titanium-coated mica platelets
Microcrystalline wax
Mineral oil
Oleth-3-phosphate
Parabens
Paraffin
PEG 2 stearate
Petrolatum
Polyoxyl-40-stearate
Polysorbate 60
Propellant 46
Propellant 12/114
Propylparaben
Propylene glycol
Propylene glycol stearate
Quaternium 15
SD alcohol 40
Sesame oil
Silica
Sodium carbomer
Sorbitan oleate
Sorbitan stearate
Stabilized aloe vera gel
Stearyl alcohol
Synthetic spermaceti
Triethanolamine
Triethanolamine stearate
Water
Wax
Zinc oxide

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

None.

D. REFERENCED OTC VOLUME SUBMISSIONS

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call for data notice published in the FEDERAL REGISTER of December 12, 1972 (37 FR 26456). The volumes will be put on public display after September 25, 1978, in the Office of the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857.

II. GENERAL STATEMENTS AND RECOMMENDATIONS

A. INTRODUCTION

As part of its review, the Panel was charged to evaluate data and information on the safety, effectiveness, and labeling of OTC sunburn prevention active ingredients. In general, the Panel found upon reviewing submissions, the scientific literature, and other evidence that over-exposure to sunlight damages the skin and can lead to various skin lesions. In the long run, suntanning is not good for the skin. The cumulative exposure to sunlight from childhood into adulthood can lead to skin cancer. Persons most at risk to the harmful effects of sunlight are those with light eyes and light skin of northern European descent who now live in sunny climates. Susceptible persons can avoid the sunshine between 10 a.m. to 2 p.m. solar time by covering their skin with clothing, wearing broad brim hats, applying opaque cosmetics, or staying indoors. Avoidance of excessive sun exposure would be best, but it is often impractical because of occupational demands or is often undesirable for leisure pursuits. Another protective measure available to the consumer is to apply sunscreens to prevent sunburn immediately and to prevent further sun damage.

The Panel recognizes that many of these products have been traditionally considered by the Food and Drug Administration as cosmetics with labeling such as "for tanning" and "for fast suntanning". This is due in part to the statutory definition of a cosmetic as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance * * *." (21 U.S.C. 321(i)). The Panel believes that, regardless of claims, products intended to be used for prevention of sunburn or any other such similar condition should be regarded as drugs. The use of sunscreens may mitigate the harmful effects of the ultraviolet (UV) radiation from the sun on the exposed skin of susceptible individuals. The Panel discusses these harmful effects elsewhere in this document. (See part II. paragraph D. below—The Harmful Effects of Sunlight on the Skin.) In fact, the statutory definition of a drug in part states "articles (other than food) intended to affect the structure or any function of the body of man or other animals * * *." (21 U.S.C. 321(g)).

The Panel has evaluated the claimed active ingredients contained in the products submitted for review. The Panel finds that these preparations reduce by varying amounts the solar radiation absorbed by the skin and thereby affect the physiological response and extent of the erythemal reaction (redness) produced. Indeed, these products affect the structure and function of the body by screening, reflecting, or scattering the harmful, burning rays of the sun. This is a desirable alteration to a normal physiological response to solar radiation for individuals with sensitive and extra sensitive skin.

The Panel has classified products intended to be used for preventing sunburn and similar conditions as drugs regardless of claims made for the products and has identified them as sunscreen products. Sunscreens may act either chemically or physically. The majority of sunscreens commonly used in the OTC drug market act chemically to absorb specific portions of the UV spectrum. An example of a chemical sunscreen is aminobenzoic acid (para-aminobenzoic acid). Physical sunscreens act by providing an actual physical barrier to solar radiation. Instead of absorbing UV light, these agents scatter and reflect such light, thereby reducing the likelihood of sunburn. An example is titanium dioxide. Regardless of the mechanism employed, the active ingredients in such products, which either absorb, reflect, or scatter UV light between 290 and 777 nanometers (nm), have been classified as drugs and identified as sunscreen agents which are more fully discussed below.

The Panel further recognizes that ingredients that are not sunscreens may be contained in sunscreen products and may also be classified as drugs. These include skin protectants, and repellants to ward off flying insects.

No perfect topical preparation for preventing sunburn is available, but there are many satisfactory preparations on the market. Interestingly, no "prescription only" products are available to protect the sunsensitive person. All currently marketed sunscreen products are sold OTC. The majority of consumers who purchase sunscreen products have no pathological conditions, but desire to acquire a suntan and to prevent a painful sunburn. Some individuals, however, are particularly susceptible to the immediate and cumulative effects of sunlight exposure and for health reasons should protect themselves from the harmful UV radiation from the sun.

B. TYPES OF SOLAR RADIATION

For practical purposes, the solar spectrum at the earth's surface consists of wavelengths of electromagnetic energy between 295 and 1,800 nanometers (nm) (ref. *1*). The sun's rays associated with diseases are related to the light sensitivity range from 290 to 800 nm. The UV spectrum lies between 290 and 400 nm, visible light between 400 and 770 nm, and the infrared rays beyond 770 nm. Ultraviolet radiation from both sunlight and artificial sources is sometimes subdivided into three bands from the longer to the shorter wavelengths as follows:

1. *UV-A (black light radiation, long-wave UV radiation, near UV radiation) wavelength 320 to 400 nm.* UV-A radiation can cause tanning of the skin, but is weak in causing reddening of the skin. About 20 to 50 Joules/cm^2 of UV-A energy is required to produce a minimally perceptible redness reaction (the Minimal Erythema Dose or MED). The Panel has further discussed MED below. (See part II. paragraph D. below—The Harmful Effects of Sunlight on the Skin.) The erythema (redness) reaction is maximal in intensity about 72 hours after exposure.

2. *UV-B (sunburn radiation, middle UV radiation) wavelength 290 to 320 nm.* Radiation causes the sunburn, reaction, which also stimulates pigmentation (tanning) in the skin. Approximately 20 to 50 millijoules/cm^2 of UV-B energy is required to produce one MED (about 1,000 times less than the dose of UV-A). The erythema reaction is maximal in intensity at 6 to 20 hours after exposure.

The action spectrum causing sunburn lies between 290 and 320 nm in the UV-B band, with a maximum effect at 296.7 nm, although the quantity reaching the earth's surface is small. Under optimal environmental conditions for sunburn, only 0.2 percent of the total solar radiation causes erythema of the skin. Ninety-five percent of this burning radiation may be absorbed by the normal white skin. Different amounts of energy reach the earth's surface at various wavelengths from 295 to 320 nm. At 307.4 nm the maximal amount of energy to cause sunburn is delivered by the sun to the skin (ref. *2*).

3. *UV-C (germicidal radiation, short UV radiation, far UV radiation) wavelength 200 to 290 nm.* UV-C radiation from sunlight does not reach the earth's surface, but artificial UV sources can emit this radiation. Although UV-C is not effective in stimu-

lating pigmentation (tanning), it does cause erythema requiring about 5 to 20 millijoules/cm² of UV-C energy to produce one MED.

REFERENCES

(1) Keston, S. F., "Diseases Related to Light Sensitivity," *Archives of Dermatology and Syphilology*, 67:284-301, 1953.

(2) Schulze, R., "Effectiveness of UV Absorbers and Commercially Available Sunscreens (Wirksamkeit von UV-Absorbern und handelsueblicher Sonnenschutzmittel)," *Journal of the Society of Cosmetic Chemists*, 14:544-565, 1963.

C. FACTORS AFFECTING THE AMOUNT OF SUNLIGHT EXPOSURE

At sea level, the UV energy of sunlight is greatest between the hours of 10 a.m. and 2 p.m. in midsummer, when the sun is overhead (ref. *1*). Even within the most intense 4-hour period, the sunlight intensity varies. Exposure at noon results in more UV-B energy falling on the skin than exposure at 10 a.m. or 2 p.m. In the morning and late afternoon, the sun is at a lower angle, sharply reducing the sunlight's intensity by 75 percent, and sunburn is not likely to occur. Atmospheric conditions similarly alter the solar erythemic intensity. Reflection of additional ultraviolet light from snow and white sand may greatly shorten the time to sunburn (ref. *2*). Depending upon the latitude, the average unprotected, untanned, white-skinned person requires approximately the following exposures in June to cause the observed reaction:

GUIDE FOR FAIR-SKINNED PEOPLE (REF. 2)

Reaction from exposure	New Jersey 40 N	Florida Keys 25 N
	(minutes)	*(minutes)*
Minimal redness (erythema) (the minimal erythema dose, MED)	21	10
Vivid redness (erythema), no pain	42	25
Painful sunburn	80	50
Blistering sunburn	165	120

An average white-skinned person would be exposed to an average of 19 MED's during the entire day atop Mauna Loa on the island of Hawaii. To date, this is the highest reading obtained by network of UV recording meters (ref. *3*). About 4 MED's are required to cause a painful sunburn; about 8 MED's will produce blistering.

REFERENCES

(1) Kreps, S. I., "Sunburn Protection and Suntan Preparations," *American Perfumer and Cosmetics*, 78:73-77, 1963.

(2) Fitzpatrick, T. B., M. A. Pathak and J. A. Parrish, "Protection of the Human Skin Against the Effects of the Sunburn Ultraviolet (290-320 nm)," *in* "Sunlight and Man," M. A. Pathak, et al., eds., University of Tokyo Press, pp. 751-765, 1974.

(3) Measurement of Ultraviolet Radiation in the United States and Comparisons with Skin Cancer Data, U.S. Department of Health, Education, and Welfare, National Institutes of Health (DHEW No. 76-1029), November 1975.

D. THE HARMFUL EFFECTS OF SUNLIGHT ON THE SKIN

The UV energy absorbed by the skin can produce an erythemal reaction (redness). The intensity of the reaction is dependent upon the amount of energy absorbed. As discussed above, UV radiation from both sunlight and artificial sources has been divided into three bands (UV-A, UV-B, and UV-C), which emit different quantities of energy and therefore produce an erythemal reaction at different time intervals after exposure. The amount of energy from any source required to produce a minimally perceptible redness reaction of the skin is termed the Minimal Erythema Dose or MED. The length of time required to produce an MED is dependent, as discussed above, on the quantity of energy emitted by the source and the response of the host's skin to sunlight. Sunscreen agents decrease the amount of energy absorbed by the skins by limiting the total amount of available energy that reaches the skin. Besides the UV source and the sunscreen agent, the pigmentation of an individual's skin determines the length of time required to produce an MED. Less time is required to produce an MED in light-skinned individuals than is required to produce an MED in dark-skinned individuals. The source of the UV radiation, the type of sunscreen agent used, and the pigmentation of the individual's skin determine the length of time required to produce an MED.

The tanning ability of an individual is genetically predetermined and is governed by the individual's capacity to produce melanin pigment within the pigment cells (melanocytes) when stimulated by UV-B and UV-A. There is a spectrum of pigmentation in humans, ranging from Negro (black) to Caucasian (white). The extent of any erythemal response is a function of skin color, and the MED for Dark-skinned blacks is about 33 times as high as that for light-complexioned Caucasians (ref. *1*).

The Panel finds that the current labeling of sunscreen products makes no reference to skin color because such products are actually intended for individuals whose skin color falls within the pigmentation spectrum that would have an erythemal response to the UV light of the sun. The Panel emphasizes that despite the fact that deeply pigmented skin has more inherent protection, it is still susceptible to sunburn and the effects of overexposure as discussed below.

Urbach stated, "All of us, even those with dark complexions, can develop skin cancer if we expose ourselves to the sun long enough. But that would take 200 to 300 years in some cases, and we just don't live that long" (ref. *2*).

Some commercial preparations on the OTC drug market today that permit suntanning without painful sunburn fall into four groups, each aimed at a certain consumer group.

MARKETED SUNSCREEN PREPARATIONS (REF. 3)

Indication and Solar Transmission

For quick tanning—Transmit about 15 percent of the sunburning rays.
For normal skin—Transmit from 4 to 8 percent of the sunburning rays.
For sensitive skin—Transmit from 1 to 4 percent of the sunburnig rays.
For extra sentive skin—Transmit under 1 percent of the sunburning rays.

The Panel emphasizes that sunscreen preparations only extend the time it takes the sun to produce a sunburn. Tanning cannot be rushed, taking about 2 weeks in most white people, if painful erythema is to be avoided. The most rapid way to cause tanning is to allow the sun to produce erythema of the skin. Erythema sufficient to induce tanning yet not so severe as to cause pain requires only one-half of the time of exposure that is required to produce a painful sunburn. Suntanning can occur at UV wavelengths from 320 to 400 nm, but develops slowly under natural conditions. Tanning most commonly develops after exposure to the "sunburn" UV wavelengths between 290 and 320 nm, the UV-B band.

As previsously noted, sunscreen preparations contain certain chemicals which absorb UV light at various wavelengths or contain an opaque substance that physically reflects or scatters the UV light rather than absorbing the rays (refs. *4* and *5*).

In our cosmetically conscious society, most persons consider a suntan to be healthy. Certainly, sun exposure forms vitamin D in the skin, and this enhances absorption of calcium from the intestine and prevents rickets. However, dermatologists are well aware that light-eyed and fair-skinned individuals are particularly susceptible to premature aging of the skin and skin cancers caused by sunlight (ref. *3*).

A recent study in the United States reported a high incidence of sun-induced cancer in susceptible people (ref. *6*). In 1973, in the United States alone, 1,409 deaths were due to sun-induced skin cancers (excluding melanomas) in susceptible people (ref. *7*). Annually in the United States with a population of over 210,000,000, an esti-

mated 9,000 individuals develop cutaneous malignant melanoma, 300,000 develop other skin cancers, and 600,000 develop cancers of all other organs exclusive of the skin (ref. *8*). Other specific diseases of congenital, metabolic, toxic, immunologic, allergic, or idiopathic origins are caused or aggravated by sunlight exposure. The pain and blistering of sunburn from overexposure is known to many. The Panel discusses below, in detail, the more common harmful effects that may be induced by the UV radiation from the sun, i.e., skin cancer and premature aging of the skin.

1. *Skin cancer in susceptible individuals.* As described above, one of the risk factors of chronic exposure to the sun is the development of keratoses and skin cancer. Epidemiological evidence shows that the incidence of skin cancer is increased in populations located in the southern latitudes as compared with populations in northern latitudes. Auerbach (ref. *9*) showed a constant rate of increase of skin cancer incidence approaching the equator from north to south; the incidence doubled for every 3° 48′ reduction in latitude. This geographical relationship has been accepted as indirect evidence that skin cancer in man is related to the greater exposure of individuals to sunlight in southern latitudes than in northern latitudes. Several epidemiological studies reinforce the conclusion that prolonged sun exposure is a factor in the etiology of skin cancer (refs. *9* through *14*). The damage due to sunlight is insidious and cumulative.

Retrospective studies have been done to identify those characteristics in individuals that may increase their susceptibility to skin cancer if overexposed to sunlight. These contributory factors proved to be age, sex, skin pigmentation, and occupation. The general conclusion drawn from these studies was that they corroborated the evidence for a cumulative influence of sun exposure on tumor development and that they indicated the protective effect of pigmented skin. For example, the incidence of cancer was reported to increase with age among Caucasian adults in a rural county of Tennessee (ref. *12*). The incidence increased from 0.7 per 100 up to the age of 44 years to 13.6 per 100 between age 65 and 74 years for males. For females in these age groups, the incidence of skin cancer increased from 0.4 per 100 to 6.8 per 100. The incidence for males was higher than the incidence for females. Other studies indicated a higher incidence of skin cancer in whites than in nonwhite populations (refs. *14* and *15*), implying that the dark pigmentation of nonwhites protects against the harmful effects of the UV radiation. The higher incidence in males than in females may be explained by the increased exposure of males to the sun from their outdoor occupations. Skin cancer occurs most frequently in those areas of the body that are exposed to the sun, such as the neck, head, arms, and hands. Consequently, the frequency of skin cancer is higher in farmers, sailors, and construction workers (ref. *12*).

The Panel agrees with the concept that sunlight plays an important role in the etiology of skin cancer in man. The Panel recognizes the epidemiological evidence for the carcinogenic properties of UV radiation from the sun and the relationship to human skin cancer, such as premalignant keratoses, and malignant basal cell epitheliomas and squamous cell epitheliomas. The Panel is particularly concerned about recurrent sunburn and overexposure to the sun throughout the years, because the lower wavelength limit of cancer-producing radiation on the skin of mice and rats has been shown to be 325 nm, i.e., the same spectral range that produces sunburn in human skin (ref. *16*). Although the epidemiological evidence favors a casual relationship between sunlight and skin cancer in man, prospective direct evidence to substantiate the relationship will be difficult to obtain for ethical and moral reasons. However, the evidence indicates that there is a lower risk in heavily pigmented individuals; that there is a continued rise in the incidence with increasing age, thus indicating a cumulative effect from sunlight exposure; and that the incidence rate is higher among susceptible populations living in subtropical and tropical latitudes. Physical, genetic, and environmental factors interact, apparently, to alter the causal effect of sunlight on tumor development (ref. *10*).

In addition, factors unrelated to sunlight may operate in the development of basal cell carcinoma in man. This conclusion is based on the observations that one-third of all basal cell carcinomas occur in areas of the skin receiving little or no UV radiation. The ratio of the incidence of basal cell carcinoma to squamous cell carcinoma shows a great north-south difference varying from approximately 10 to 1 in favor of basal cell carcinoma in northern cities, to 4 to 1 in northern and central rural areas, and to 2 or 3 to 1 in southern rural areas (ref. *9*). These observations suggest that increasing exposure to sunlight has a greater effect on the development of squamous cell carcinoma than on that of basal cell carcinoma. nevertheless, some association between basal cell carcinoma and sunlight is indicated from epidemiological studies.

The Panel recognizes the influence of genetic factors on the development of skin cancer, i.e., the protective mechanism of skin pigmentation which is genetically determined. The susceptibility to skin cancer is decreased in individuals with deeply pigmented skin. Epidemiological evidence indicates that susceptible individuals have a fair complexion, light hair, blue or gray eyes, tan less and to a lighter color, and sunburn more easily and more severely than individuals not developing skin cancer. Studies show that skin cancer patients have greater outdoor exposure than those not affected.

The Panel concludes that continuous and prolonged exposure over the years to sunlight increases the risk of skin cancer in susceptible individuals and that the use of sunscreens by such individuals may mitigate the harmful effects of overexposure to the sun. Below, the Panel assesses the overall harmful effects of sunlight exposure and recommends that the labeling of sunscreen products, alert the consumer to these harmful effects.

2. *Premature aging of the skin in susceptible individuals.* Another harmful effect that may result from the cumulative action of chronic prolonged exposure to the UV radiation from the sun is a condition which has been commonly referred to as premature aging of the skin. Premature aging of the skin refers to the thinning, dryness, and fine wrinkling produced by the exposure of the skin to sunlight. Although the external characteristics of this condition, i.e., dry, wrinkled, thin skin with a loss of elasticity, are similar to the characteristics of the aging process, premature aging of the skin due to UV radiation has histological and biochemical characteristics that differ qualitatively and quantitatively from those seen in the aging process. The changes that are associated with premature aging of the skin are seen in the dermis of the skin. In addition to these dermal changes are the effects that UV radiation induces in the epidermal layer of the skin, where the basal and squamous cell epitheliomas (skin cancers) casually related to sunlight exposure occur. The relationship between the changes in the dermal connective tissue of the skin and epidermal carcinogenesis are not understood, although dermal changes associated with premature aging of the skin have often been associated with skin cancer formation (ref. *17*).

The dry, wrinkled, atrophic condition of sunlight-exposed skin was first reported by Unna from observations in sailors. Since that observation, biochemical and histological studies have been done comparing the changes in sunlight-exposed and unexposed skin of white and nonwhite individuals. Prolonged UV radiation from the sun

on the dermal layer of exposed skin ultimately produces elastic degeneration and elastic tissue dissolution. This effect is qualitatively and quantitatively different from the aging unexposed skin of white individuals and, in addition, is less pronounced in both the exposed and unexposed skin of nonwhite (pigmented) individuals (ref. *18*).

The quantity of elastic tissue in the dermis of sunlight-exposed skin increases with age in both white and nonwhite individuals. This elastic tissue hyperplasia is greater than that seen in unexposed skin and is apparently accompanied by a decrease in collagen and eventually culminates in the disintegration of the elastic fibers into an amorphous mass as seen in stained histological tissue sections. The loss of the elasticity of exposed skin is the result of the dissolution of the elastic fibers. Quantitative biochemical changes occur in elastic degeneration of exposed skin that differs from that seen in the aging process in unexposed skin. In contradistinction to aging unexposed skin, it has been shown that in chronically sunlight-exposed skin the concentration of hexosamine is increased and the concentration of hydroxyproline is decreased. Glucosamine is also increased in chronically exposed skin which is thought to correlate with the increased staining for mucopolysaccharides in the skin (refs. *19* and *20*).

Just as in studies on the effect of pigmentation on the incidence of skin cancer in man, it has been reported that biopsies of exposed skin of elderly nonwhite individuals showed little of the elastic degenerative changes seen in biopsy specimens obtained from similar exposed regions of elderly white individuals, and that biopsy specimens of unexposed areas were almost identical in similar age groups of both white and nonwhite individuals. The evidence pointed to a correlation between the degree of pigmentation and the degree of elastosis. The less pigmented individuals showed a greater amount of degeneration. The reports indicate that pigmentation has a protective effect and that the elastotic degenerative effects of UV radiation from the sun are not simply the result of the aging process.

The Panel concludes that because pigmentation of the skin appears to have an influence in preventing the harmful effect of elastotic degeneration in sunlight-exposed skin, the use of sunscreens may mitigate elastotic degenertion in light skinned individuals (susceptible individuals). It appears that elastotic degeneration (premature aging of the skin) is more likely to occur in individuals with the characteristics that make them susceptible to the harmful effects of chronic exposure to UV radiation from the sun, as discussed above.

3. *Conclusions.* The Panel recognizes the epidemiological evidence that skin cancer, and degenerative skin changes (elastotic degeneration) commonly referred to as premature aging of the skin are causally related to chronic exposure to the UV radiation from the sun. The Panel is concerned that because it is difficult to substantiate this evidence by adequate and direct information, susceptible individuals will continue to be subjected to the harmful effects of continuous sun exposure without using whatever protection is presently available. The Panel is fully aware of the limitations of the present sunscreens, i.e., primarily the inability to remain on the skin under diverse conditions, and the apparent irreversibility of UV radiation damage to the skin.

However, the Panel feels that because skin cancer is extremely common in susceptible individuals, amounting to one-third to one-half of all cancers of all anatomical sites as reported in the United States (ref. *10*), the use of sunscreens properly and regularly applied may aid in reducing this high incidence.

The Panel believes that sunscreens would be beneficial for children and adolescents with the susceptible skin coloration, genetic background, and geographical environments making them likely to be subject to repeated sunburns. The damage is cumulative and 20 to 50 years may pass before skin changes including skin cancers appear.

Experimental studies in mice have been reported to show that the topical application of 3-benzoyl-4-hydroxy-6-methoxy-benzenesulfonic acid and aminobenzoic acid decreased the erythematous and carcinogenic effect of UV radiation (ref. *21*). Whether such results derived from animal studies can be extrapolated to chronic sun exposure in man remains, of course, undetermined, but the Panel feels that the topical application of sunscreens by susceptible individuals may mitigate the harmful effects of chronic exposure to the sun.

Dermatologists routinely instruct their patients who have skin cancer of the sun-exposed areas to wear long sleeves and a wide-brim hat, to avoid sun exposure between 10 a.m. to 2 p.m. solar time, and to use a sunscreen liberally every day (women may substitute a heavy opaque makeup) "even just to take out the garbage." Most physicians recommend sunscreens for skin cancer patients, not to heal damage that occurred years earlier, nor to prevent skin cancers due to the lag time of 10 to 30 or more years between the time the damage occurred and the tumor appears, but to prevent skin cancer from today's exposure appearing 10 to 20 years hence.

Therefore, the Panel recommends the following statement in the labeling for all sunscreen products: "Overexposure to the sun may lead to premature aging of the skin and skin cancer. The liberal and regular use over the years of this product may help reduce the chance of these harmful effects." or "Overexposure to the sun may lead to premature aging of the skin and skin cancer. The liberal and regular use over the years of this product may help reduce the chance of premature aging of the skin and skin cancer."

4. *Minority report.* The Panel voted 4 to 3 to support a claim which can be used on labels of all sunscreen products. This claim suggests that skin cancer may be prevented by the use of any of these products. The claim presupposes that the person using the product will use it correctly. It also presupposes that alterations in the skin are not yet present which could result in skin cancer, whether the product is used or not. Because data are not yet conclusive that skin cancers are preventable by these OTC products, the minority suggests that a claim of "may reduce harmful effects of the sun" is acceptable, but the final step of preventing cancer is unwarranted at this time. The consumer representative concurs with the minority report.

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E. SUN PROTECTION FACTORS

The "Sun Protection Factor" (SPF) is used in Europe on sunscreen products. The Sun Protection Factor, which is related to the Protective Index gives the consumer a guide as to how the product will act on his skin. The SPF value may be defined as the ratio of the amount of energy required to produce a minimum erythema dose (MED) or minimal sunburn through a sunscreen product film to the amount of energy to produce the same MED without any treatment. The following equation represents this ratio:

SPF value=MED Protected Skin/MED Unprotected Skin

The European experience over the past 20 years has shown the following protection factors based upon skin types (ref. *1*):

SPF value and skin type

SPF 3—For nonsensitive skin and skin already accustomed to the sun (minimal protection).

SPF 4—For normally sensitive skin (moderate protection).

SPF 6—For sensitive skin (extra protection).

The Panel finds SPF values to be a practical guide and has included them in the labeling to aid the consumer in selecting the most suitable sunscreen for his/her own purposes.

F. SUNSCREEN AGENTS

The Panel has discussed the use of OTC sunscreen drug products in reducing by varying amounts the solar radiation absorbed by the skin. The amount of UV light from the sun that penetrates the skin depends upon the amount of energy selectively screened by the product. Consequently, the physiological effect on the skin, manifested as erythema, is determined in large part by the quantity of radiation of the sunscreen product permits the skin to absorb, or conversely, the quantity of UV energy the product prevents the skin from absorbing. The intensity of the erythemal response correlates with the amount of radiation absorbed by the individual's skin. Therefore, the Panel has classified sunscreen active ingredients into categories based upon their UV screening capacity.

The scientific literature contains definitions of sunscreen types, describing the chemicals and substances used to prevent sunburn. However, information from consumer groups revealed that the terms used, such as "sunscreen," "sunshades," and "sunblock" might not be meaningful to the general population. The Panel considered many terms in an effort to find a noun or adjective that would describe the use of these preparations.

The Panel adopts the following definitions for therapeutic sunscreen types:

1. *Sunscreen sunburn preventive agent.* An active ingredient that absorbs 95 percent or more of the light in the UV range at wavelengths from 290 to 320 nm and thereby removes the sunburning rays.

2. *Sunscreen suntanning agent.* An active ingredient that absorbs at least 85 percent of the light in the UV range at wavelengths from 290 to 320 nm, but transmits UV light at wavelengths longer than 320 nm. Such agents permit tanning in the average individual and also permit some reddening (erythema) without pain.

3. *Sunscreen opaque sunblock agent.* An opaque agent that reflects or scatters all light in the UV and visible range at wavelengths from 290 to 777 nm and thereby prevents or minimizes suntan and sunburn. Transparent sunblock agents are not yet available in the OTC drug marketplace.

The Panel realizes that these definitions are based on the UV-absorbing properties of a single active ingredient of a sunscreen product and not on how an ingredient may perform in a formulation or in a combination product during actual use on the skin. Therefore, the Panel has recommended final product testing of each formulation to assure proper use. (See part III. paragraph D. below—Sunscreen product testing procedures for determination of the sun protection factor (SPF) value and related labeling claims.)

G. CATEGORIES OF SUNSCREEN PRODUCTS

To aid the consumer in selecting the type of sunscreen product best suited to the individual's complexion (pigmentation), response to UV light and the type of outdoor activity, the Panel recommends the following product category designations (PCD's) for the product or formulation to be marketed:

1. *Minimal Sun Protection Product.* Sunscreen products that provide an SPF value of 2 to under 4, and offer the least protection, but permit suntanning.

2. *Moderate Sun Protection Product.* Sunscreen products that provide an SPF value of 4 to under 6 and offer moderate protection from sunburning, but permit some suntanning.

3. *Extra Sun Protection Product.* Sunscreen products that provide an SPF value of 6 to under 8, offer extra protection from sunburning and permit limited suntanning.

4. *Maximal Sun Protection Product.* Sunscreen products that provide an SPF value of 8 to under 15, offer maximal protection from sunburning, and permit little or no suntanning.

5. *Ultra Sun Protection Product.* Sunscreen products that provide an SPF value of 15 or greater, offer the most protection from sunburning and permit no suntanning.

The Panel reviewed the effects of UV light on the skin (ref. *2*). The Panel has summarized the following compilation of skin types, sunscreen Sun Protection Factors, and Product Category Designations discussed in this document:

Skin types and recommended sunscreen products

Skin type	Sunburn and tanning history	Recommended sun protection factor and product category designation
I	Always burns easily; never tans (sensitive).	8 or more (maximal, ultra).
II	Always burns easily; tans minimally (sensitive).	6 to 7 (extra).
III	Burns moderately; tans gradually (light brown) (normal).	4 to 5 (moderate).
IV	Burns minimally; always tans well (moderate brown) (normal).	2 to 3 (minimal).
V	Rarely burns; tans profusely (dark brown) (insensitive).	2 (minimal).
VI	Never burns; deeply pigmented (insensitive).	None indicated.

[1]Based on first 30 to 45 minutes sun exposure after winter season or no sun exposure.

The Panel recommends that the following compilation of skin types and product category designations be appropriately included in labeling as a guide:

RECOMMENDED SUNSCREEN PRODUCT GUIDE

Sunburn and Tanning History and Recommend Sun Protection Product

Always burns easily; never tans.—Maximal, Ultra.
Always burns easily; tans minimally.—Extra.
Burns moderately; tans gradually.—Moderate.
Burns minimally; always tans well.—Minimal.
Rarely burns; tans profusely.—Minimal.

The Panel believes this "Recommended Sunscreen Product Guide" will benefit the consumer. On first using this scale some people may misjudge the reactivity of their skin to sunlight. Elevated heat and humidity, sweating, and swimming may lower the SPF value at any one time for an individual. In practical terms, a person who usually gets red in the sun after 20 minutes should be able to stay in the sun for 120 minutes (2 hours) if he applies a sunscreen of extra protection (SPF 6), i.e., 20 minutes X 6, provided the product is not washed or sweated off.

As noted above, the Panel suggests five PCD categories, i.e., minimal, moderate, extra, maximal, and ultra protection. The maximal protection (SPF 8) category would protect, for 320 minutes, the average person who would be burned in 40 minutes or through the dangerous sunburning hours of 10 a.m. to 2 p.m. Once the skin has become accustomed to the sun, the individual's self-protection period is longer, and in practice this means that gradually a product with a lower PCD can replace a product with a higher PCD because the risk of sunburn has become smaller.

The Panel recommends the use of the guideline outlined above with the inclusion of the ultra protection (SPF 15 or more) category for highly sensitive individuals needing this degree of protection against UV light. The Panel emphasizes that the PCD for the package labeling is determined for the final product or furmulation, not the active ingredient alone.

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H. LABELING OF SUNSCREEN PRODUCTS

1. *Indications.* The indications for use of a sunscreen are to be simply and clearly stated. Statements of indications for use are to be specific and confined to the conditions for which the product is recommended. The directions for use are to be clear and provide the user a reasonable expectation of the results anticipated from use of the product.

The indications for use may contain any of the following:

a. *For all (minimal, moderate, extra, maximal, and ultra) sunscreen products.* (1) "Sunscreen to help prevent sunburn."

(2) "Filters (or screens) out the sun's burning rays to prevent sunburn."

(3) "Screens out the sun's harsh and often harmful rays to prevent sunburn."

(4) "Overexposure to the sun may lead to premature aging of the skin and skin cancer. The liberal and regular use over the years of this product may help reduce the chance of these harmful effects."

(5) "Overexposure to the sun may lead to premature aging of the skin and skin cancer. The liberal and regular use over the years of this product may help reduce the chance of premature aging of the skin and skin cancer."

b. *Additional indications.* In addition to the indications provided above in item a., the following may be used: (1) *For minimal sunscreen products.* (i) "Affords minimal protection against sunburn."

(ii) "Prolongs exposure time before sunburn occurs."

(iii) "Permits tanning (or suntanning) and reduces chance of (or minimizes) sunburning."

(iv) "Helps prevent sunburn on limited exposure of untanned skin."

(v) "Helps to protect the skin against sunburn while permitting tanning."

(vi) "Allows you to stay in the sun 2 times longer than without sunscreen protection."

(vii) "Provides 2 times your natural protection from sunburn."

(2) *For moderate sunscreen products.* (i) "Affords moderate protection against sunburn."

(ii) "Prolongs exposure time before sunburn occurs."

(iii) "Permits tanning (or suntanning) and reduces chance of (or minimizes) sunburning."

(iv) "Helps prevent sunburn on moderate exposure of untanned skin."

(v) "Allows you to stay in the sun 4 times longer than without sunscreen protection."

(vi) "Provides 4 times your natural protection from sunburn."

(3) *For extra sunscreen products.* (i) "Affords extra protection against sunburn."

(ii) "Prolongs exposure time before sunburn occurs."

(iii) "Permits limited tanning (or suntanning) and reduces chance of (or minimizes) sunburn."

(iv) "Helps prevent sunburn."

(v) "For sun-sensitive skin."

(vi) "Extra protection against sunburn for blondes, redheads and fair-skinned persons."

(vii) "Allows you to stay in the sun 6 times longer than without sunscreen protection."

(viii) "Provides 6 times your natural protection from sunburn."

(4) *For maximal sunscreen products.* (i) "Affords maximal protection against sunburn."

(ii) "Prevents sunburn and limits tanning."

(iii) "For sun-sensitive skin."

(iv) "Maximal protection against sunburn for blondes, redheads and fair-skinned persons."

(v) "Allows you to stay in the sun 8 times longer than without sunscreen protection."

(vi) "Provides 8 times your natural protection from sunburn."

(5) *For ultra sunscreen products.* (i) "Affords the most protection against sunburn."

(ii) "Prevents tanning and sunburn."

(iii) "For highly sun-sensitive skin."

(iv) "Greatest protection against sunburn for blondes, redheads and fair-skinned persons."

(v) "Provides the highest degree of sunburn protection and permits no tanning."

(vi) "Provides the highest degree of sunscreen protection and permits no tanning."

c. *For all (maximal and ultra) sunscreen products that contain sunscreen opaque sunblock ingredients.*

"Reflects the burning rays of the sun."

2. *Statement on product performance*—(a) *Product Category Designation (PCD).* The Panel concludes that improved, more informative labeling should be provided to the consumer to aid in selecting the most appropriate sunscreen product. The Panel recommends that the following labeling statements be prominently placed on the principal display panel of appropriate products:

(1) Products containing active ingredients that provide a SPF value of 2 to under 4: "Minimal Sun Protection Product (SPF 2)—Stay in the sun twice as long as before without sunburning."

(2) Products containing active ingredients that provide a SPF value of 4 to under 6: "Moderate Sun Protection Product (SPF 4)—Stay in the sun 4 times as long as before without sunburning."

(3) Products containing active ingredients that provide a SPF value of 6 to under 8: "Medium Sun Protection Product (SPF 6)—Stay in the sun 6 times as long as before without sunburning."

(4) Products containing active ingredients that provide a SPF value of 8 to under 15: "Maximal Sun Protection Product (SPF 8)—Stay in the sun 8 times as long as before without sunburning."

(5) Products containing active ingredients that provide a SPF value of 15 or greater: "Ultra Sun Protection product (SPF 15)—Stay in the sun 15 times as long as before without sunburning."

(b) *Labeling claims related to the PCD and SPF value.* The Panel recommends any of the following labeling claims for sunscreen products that satisfy the sunscreen product testing procedures described elsewhere in this document. (See part III. paragraph D. below—Sunscreen product testing procedures for determination of the sun protection factor (SPF) value and related labeling claims.)

(1) *For all (minimal, moderate, extra, maximal, and ultra) sunscreen products that satisfy the water resistance testing procedures.* (i) "Water resistant."

(ii) "Retains its sun protection for at least 40 minutes in the water."

(iii) "Resists removal by sweating."

(2) *For all (minimal, moderate, extra, maximal, and ultra) sunscreen products that satisfy the waterproof testing procedures.* (i) "Waterproof."

(ii) "Retains its sun protection for at least 80 minutes in the water."

(iii) "Resists removal by sweating."

(3) *For all (minimal, moderate, extra, maximal, and ultra) sunscreen products that satisfy the sweat resistance testing procedures.* (i) "Retains its sun protection for at least 30 minutes of heavy sweating."

(ii) "Sweat resistant."

3. *Warnings*—(a) *For all (minimal, moderate, extra, maximal, and ultra) sunscreen products.* The labeling of all sunscreen products should contain the following warnings:

(1) "For external use only, not to be swallowed."

(2) "Avoid contact with the eyes."

(3) "Discontinue use if signs of irritation or rash appear."

(b) *Specific warnings*—(1) *For sunscreen products providing an SPF value of 2 to under 4:* "Use on children under 2 years of age only with the advice of a physician."

(2) *For sunscreen products providing an SPF value of 4 or greater.* "Use on children under 6 months of age only with the advice of a physician."

4. *Directions for use.* The Panel believes than many consumers use inadequate amounts of sunscreen. Offering more detailed guidelines would benefit the consumer.

Based on a review of the available data, the Panel recommends that the "Directions for Use" state: "Apply liberally before sun exposure and reapply after swimming or after excessive sweating."

However, for sunscreen products that satisfy the water resistance, waterproof, and sweat resistance testing procedures described elsewhere in this document, the directions for use in the labeling of these products may be modified in accordance with the results of the test. (See part III. paragraph D. below—suncreen product testing procedures for determination of the sun protection factor (SPF) value and related labeling claims.) The Panel recommends that for sunscreen products that satisfy these testing procedures the following labeling modifications replace the directions-for-use labeling indicated above:

(a) *For all (minimal, moderate, extra, maximal, and ultra) sunscreen products that satisfy the water resistant testing procedures.* "Apply liberally before sun exposure and reapply after 40 minutes in the water or after excessive sweating."

(b) *For all (minimal, moderate, extra, maximal, and ultra) sunscreen products that satisfy the waterproof testing procedures.* "Apply liberally before sun exposure and reapply after 80 minutes in the water or after excessive sweating."

(c) *For all (minimal, moderate, extra, maximal, and ultra) sunscreen products that satisfy the sweat resistance testing procedures.* "Apply liberally before sun exposure and reapply after 30 minutes of excessive sweating."

I. SUNSCREEN PRODUCTS CONTAINING DIHYDROXYACETONE

Dihyroxyactone (DHA) is an ingredient included in sunscreen preparations. Based upon the discussion below, the Panel concludes that DHA is a cosmetic in all cases except when used in sequential conjuction with lawsone.

DHA is also know as 1,3-dihydroxy-2-propanone. It is produced from glycerol by Aerobacter species under aerobic conditions. It is a fairly hygroscopic, crystalline powder having a characteristic odor and a sweet and cooling taste. DHA normally occurs as a dimer in which form it is slowly soluble in 1 part water and 15 parts alcohol. When freshly prepared, DHA reverts rapidly to a monomer in solution, in which form it is very soluble in water, alcohol, ether, and acetone. DHA is a three-carbon sugar and is an intermediate in the metabolism of carbohydrates in higher plants, animals, and man (refs. *1* and *2*).

DHA has a unique property of producing a reddish brown color when in direct contact with the keratin of the skin. The mechanism of action for producing this color is not completely understood, but most studies agree that DHA reacts with certain amino acids of the stratum corneum to form the color, the intensity of which is directly related to the skin's thickness (refs. *1*, *3*, and *4*). Because the epidermis containing keratin varies over different areas of the body, different degrees of coloration may result. Areas such as the palms of the hands, warts, and caloused skin react to a greater extent than surfaces where skin is thinner. Scar tissue does not react to the extent of normal skin and may show up as a light-colored contrast. The nails and hair of the body show less affinity for DHA and therefore do not react as readily to coloration. Repeated application will cause an increased progressive darkening, as also will an increase in concentration. Alcohols, change in pH, and surfactants may also increase the rate of reaction. It should be noted that human sweat also contains the amino acids necessary to promote coloration (refs. *1*, *3*, and *4*).

One manufacturer submitted data for a sunscreen product composed of two separate lotions containing DHA and lawsone, respectively. The lotions are to be applied to the skin only in the stated sequence. Labeling for the product includes claims such as "sunscreen lotion," "for protection of sunsensitive skin," and "water-resistant barrier to sun's ultraviolet rays." Therefore, the Panel addressed the product not as a cosmetic, but as a sunscreen. Safety and efficacy of DHA in conjunction with lawsone is discussed below. (See part III. paragraph

B.1.1. below—Lawsone with dihydroxyacetone.)

DHA has not been shown to be effective as a topical sunscreen when used alone. Current scientific evidence shows that DHA, except in conjunction with lawsone, has no appreciable sun-screening activity.

Shaffer et al., using 10 white male volunteers, tested the sunscreening properties of DHA. Each subject had three test areas, each measuring 1 inch by 1 inch, marked on the arm. One of the test areas contained aminobenzoic acid, the second area contained 2 percent DHA in isopropyl alcohol, and the third area was used as a control. The areas were subjected to a 4+ erythema dose of UV light with a fluorescent UV lamp. Observations from the test showed the aminobenzoic acid test area with no erythema; the control area developing a 4+ erythema; and the DHA area showing 6 subjects with 4+ erythema, 2 subjects with 3+ erythema, and 2 subjects with 2+ erythema (ref. *5*).

Studies performed by Fusaro et al. (ref. *6*) and Rice (ref. *4*) demonstrated that test sites treated with single active ingredient preparations of DHA or lawsone were essentially unprotected when compared with those sites treated with both ingredients either in a freshly prepared combination preparation or in separate vehicles.

Mumford (ref. *7*) states that DHA does not diminish the response to UV radiation. Comparative testing showed equal erythema when applied to painted and unpainted skin. Repeated application of DHA to recently excised human mammary skin did not appear to develop melanin type of pigment.

Maibach and Kligman tested sunscreening with 5 percent DHA. The backs of 10 white male subjects, half of the back of which were painted with 5 percent DHA, and the other half serving as a control, were subjected to UV radiation and observed for erythema. Results of this test procedure found that DHA neither increased nor decreased the erythema or tanning response to UV light (ref. *8*).

There were no product submissions made to the Panel using DHA as a single ingredient. However, sunscreen products containing DHA were submitted to the Panel for review in combination with the sunscreen ingredients homosalate and padimate A. These products are not for sequential use. The safety and effectiveness of the sunscreens homosalate and padimate A are reviewed separately below. (See part III. paragraphs B.1.k. and o. below—Homosalate; Padimate A). These submissions label DHA a cosmetic and do not make any claims showing that DHA will afford any additional sun-screening protection.

Studies were performed to determine the protective effectiveness of two sunscreen lotions, each containing 8 percent homosalate with and without 3.5 percent dihydroxyacetone, against erythema induced by UV light exposure on nontanned and dihydroxyacetone-tanned skin (ref. *9*). In the first study, a strip of skin on the lower abdomen of a subject was tanned by six applications of a dihydroxyacetone lotion over a 6-hour period. The next day a template was used to mark off eight comparable areas, four nontanned and four dihydroxyacetone-tanned. Within each set, two areas were used as controls, one area was covered with the homosalate/dihydroxyacetone lotion, and the remaining area was covered with the homosalate lotion. All areas were then exposed to 1 hour of late morning sunlight and were scored 24 and 48 hours afterwards on a scale from 0 (no erythema) to 4+ (deep red and painful blisters). The previously tanned control areas showed slight erythema (1+) at 24 hours and were lighter (0.5+) by 48 hours, whereas the nontanned control areas were scored 3+ (deep red with slight pain) at 24 and 48 hours. Those areas treated with the two sunscreens showed no erythema except for the nontanned areas treated with the homosalate lotion, which were scored 1+ (definite pink or light red) at 24 and 48 hours. Similar results were obtained in another study wherein the undersides of three subjects' forearms were prepared in the above-described manner and exposed to the light of a sunlamp at a distance of 12 inches. In a third study a strip across the back of each of 12 subjects (six male and six female) was tanned with two applications of a dihydroxyacetone preparation, one application in the forenoon and a second later in the afternoon. The next day, templates were used to mark off three 1 inch squares each of nontanned and tanned skin. Within each set, one area served as a control; one was treated with the homosalate/dihydroxyacetone lotion; and the remaining square was treated with the homosalate lotion. Owing to rain conditions, a sunlamp instead of natural sunlight was used as the light source, with the nontanned control areas being irradiated for 4 minutes while all other areas were irradiated for 8 minutes at a distance of 12 to 14 inches. All areas were scored 24 and 48 hours afterwards using the above-described scale. The pretanned control areas (1.67+ average) showed slightly less erythema than the nontanned control area (2+ average), even though the pretanned areas were irradiated twice as long. The protective action of pretanning with dihydroxyacetone was demonstrated by those areas treated with the two sunscreens. In this study, however, the homosalate lotion (average of 0.42+ and 0.96+ for pretanned and nontanned areas, respectively) provided slightly better protection than the homosalate/dihydroxyacetone lotion (average of 0.17+ and 0.62+ for pretanned and nontanned areas, respectively). This difference was explained by the variable thicknesses at which these sunscreen lotions were applied.

The Panel concludes that DHA alone is not a sunscreen, but a cosmetic. The Panel further concludes that DHA is a sunscreen when used sequentially with lawsone.

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J. COMBINATIONS

1. *Combinations of sunscreen active ingredients.* The Panel has reviewed the submitted data and finds that a majority of marketed sunscreen products contain only one or two sunscreen active ingredients. Additional sunscreen active ingredients are included primarily to enhance the performance of the final product formulation. Because each final product formulation intended for OTC use is requred to comply with the testing procedure provided for in the OTC sunscreen monograph described below, the Panel has established no upper limit to the number of sunscreen active ingredients a product may contain. However, the Panel believes it is reasonable to require that additional sunscreen active ingredients must make a contribution to the designated indications for the product and not merely be included for marketing promotion purposes.

The Panel concludes that two or more sunscreen active ingredients may be combined provided that:

a. Each is present in sufficient quantity to act additively or by summation to produce the claimed therapeutic effect when the ingredients are within

the effective concentration range specified for each ingredient in the monograph.

b. The ingredients do not interact with each other and one or more do not reduce the effectiveness of the other or others, by precipitation, change in alkalinity or acidity, or in some other manner that reduces the claimed therapeutic effect.

c. The partition of the active ingredients between the skin and the vehicle in which thay are incorporated is not impeded and the therapeutic effectiveness of each remains as claimed or is not decreased.

2. *Combinations of sunscreen and nonsunscreen active ingredients.* The Panel also concludes that sunscreen active ingredients may be combined with other active ingredients, e.g., skin protectants, provided that the ingredients are generally recognized as safe and effective, i.e., Category I active ingredients.

III. SUNSCREENS

A. GENERAL COMMENT

A considerable number of OTC sunscreen preparations are now available to the American public for prevention of sunburn. As was mentioned above, other ingredients that are not sunscreens may be included in marketed products. These may also be active ingredients, but not sunscreens, or declared as inactive ingredients used as emollients or moisturizers. Regardless of composition, the final formulation for marketing should be evaluated by the procedures described below. (See part III. paragraph C. below—Data Required For Evaluation.) As background to a survey of the safety and efficacy of such preparations, it is necessary to understand certain aspects of the anatomy and physiology of the skin, as well as give some consideration to the penetration of materials into and through the skin barrier.

1. *The skin.* The anatomy and physiology of the skin was considered by the Panel using standard references and texts. Concerning certain features on which there was little objective data, the following decisions were made:

a. *Age.* The Panel accepted adult human skin to be older than 6 months of age. It is possible that geriatric skin requires special consideration, the parameters of which are poorly understood. Human skin, under the age of 6 months, may well have different absorptive characteristics. The Panel concludes that products providing a mainimal SPF value of 2 to under 4 should not be used on children under 2 years, and products providing a minimal SPF value of 4 should not be used on children under 6 months of age.

To provide an added margin of safety, the ingredients reviewed below are not to be used on children under the age of 6 months. This margin of safety is considered important because of the problems of medicating young children. Biologic systems which metabolize and excrete drugs absorbed through the skin may not be fully developed in children under the age of 6 months.

b. *Sex.* Although obvious differences are known between male and female skin, the Panel believes that these are not likely to affect the safety or efficiacy of the various ingredients considered as sunscreens.

2. *Skin penetration.* The Panel has recommended that sunscreens be discontinued if signs of irritation or rash appear. However, possible penetration of sunscreens through the intact skin was considered by the Panel.

Skin penetration is a complex process that is modified by numerous factors. Three portals of entry are possible through the human skin. They are the epidermal barrier, the hair follicles, and the sweat glands. For practical purposes, all absorption occurs through the epidermal barrier and sweat glands. The epidermal barrier consists of the stratum corneum, which is a keratophospholipid complex up to 1,500 microns thick. Absorption through these barriers depends primarily on the physicochemical structure of the drug and less so on the vehicle is which it is contained. However, the vehicle is important and will be considered later.

Three important conditions of the skin affect drug penetration. The conditions are physiological, physicochemical, and abnormal skin.

a. *Physiological conditions.* (1) Skin age which is discussed above.

(2) Blood flow within the skin may increase or decrease penetration, but this effect is questionable and may not directly affect absorption by the flow rate alone.

(3) Data on penetration based on skin site is conflicting and includes variations of absorption in the same site for reasons that are unclear. Studies in cadaver skin suggest that absorption is directly related to skin thickness and that it is greater in areas where large hair follicles are present.

Various skin sites have considerable difference in dermal thickness, in secondary skin appendages including the number of sweat glands and hair follicles, and in the physical location of the skin. For example, in areas well supplied with sweat glands in close apposition to other skin areas, such as the axilla (armpit) and the groin (crotch), medications applied may be more irritating than in other locations because of the presence of constant moisture and friction. Specialized sweat glands, as found in the ear canal, produce a waxy, protective secretion which may further limit the juxtaposition of medication to the skin surface; mucous membranes in close apposition to the skin as found in the mouth, the inner aspects of the labia, and the inside of the eyelids, commonly absorb medications many times more readily than does the skin.

(4) Human skin appears to be unique, and its characteristics and relation to drug absorption are not mimicked exactly by any other species.

b. *Physicochemical conditions.* (1) The skin can absorb considerable quantities of water. By hydrating the skin, absorption is facilitated. Complete occlusion by physical means can increase absorption 100-fold.

(2) The varying temperatures ranges obtainable in human environments greatly affect absorption.

(3) In general, increasing concentration leads to increased absorption of drugs applied to the skin. However, in almost every instance, a plateau effect occurs because there may be a reduced rate of absorption in high concentration due to the effects of the drug on the skin itself.

(4) The Panel accepts the Meyer-Overton theory that lipid-soluble substances diffuse through the lipid portion of the skin barrier and water soluble substances diffuse through the hydrated component of the proteins found within this barrier (ref. *1*). The partition coefficient is rate-limiting when related to the drug in its vehicle and the stratum corneum.

Substances soluble in both water and lipid readily penetrate the skin barrier.

(5) Generally, smaller molecules penetrate more rapidly than larger molecules; substances up to the size of 1,000 daltons are usually well absorbed, while larger ones have more difficulty. Polar groups show less absorption than nonpolar groups. Although molecular configuration unquestionably affects absorption, the mechanisms involved are not well understood.

(6) Vehicles are important in determining the state of the drug with respect to absorption and will be considered below.

The vehicles in which drugs are contained are secondary in importance to other conditions discussed, but they are important nonetheless. For example, a drug should not bind too strongly to any component of its vehicle so that its partition with respect to the skin barrier favors the vehicle. Low vehicular affinity is desirable.

Although the original charge to the Panel was to review only the active ingredients for safety and effectiveness, the Panel believes that the vehicle in which the ingredient or combination of ingredients resides may have con-

siderable effect on the effectiveness of the ingredient or ingredients involved.

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

The rate of diffusion of a drug within its vehicle bears a direct relationship to its ability to penetrate the skin barrier, as does the rate of release of the drug from the vehicle. The vehicle may have an effect on the hydration of the stratum corneum. In general, vehicles which increase or maintain hydration promote drug absorption, but this is not universally true.

Surface-active agents (surfactants) within the vehicle may change the physical state of the water within the skin and thereby increase absorption of polar compounds. Cationic and nonionic groups are considerably less active than anionic groups. Most vehicles consist of emulsions in which there is at least one immiscible liquid within another consisting of a discontinous, internal, or dispersed phase and a continous, external, or nondispersed phase. At the interface, surface tensions are smaller than the largest value of any of the elements of an emulsion. Within an emulsion, there may be surface-active agents which are compounds strongly absorbed at surfaces which have polar and/or nonpolar groups.

Other ingredients combined with an active ingredient may also affect effectiveness by altering the pH of the medium in which the active ingredient is incorporated, thereby changing its ionization and lipophilic qualities. An active ingredient which is effective in the form of a free base may be less effective or ineffective as a salt.

Other semisolid dermatological vehicles, which may or may not be emulsions, are classified as follows: Ointments; cerates or pastes (stiffer than ointments); oleaginous or hydrocarbon vehicles (generally consisting of fatty acids which may become rancid); absorption bases which specifically absorb water; emulsion bases; vanishing creams which contain approximately 75 percent water; and completely water soluble agents such as low molecular weight carbowaxes or polyethylene glycol. Some of the latter, with molecular weights of 1,500 daltons or more, have approximately the same solid characteristics as petrolatum.

An ideal sunscreen vehicle would be stable, neutral, nongreasy, nondegreasing, nonirritant, nondehydrating, nondrying, odorless, efficient on all kinds of human skin, hold at least 50 percent water, be easily compounded of known chemicals, and have infinite stability during storage. There is no ideal vehicle. Vehicles in common use represent a compromise of advantages against disadvantages, many of which have been noted previously. It is difficult to predict with any degree of accuracy the influence of vehicular formulations on the percutaneous absorption of drugs. Many authorities believe that medicinals are absorbed more readily from animal or vegetable oils than from petrolatum bases.

Vehicles for topical delivery of active ingredients are complex mixtures of substances designed to impart a certain characteristic to the finished product. Although classified as inactive or inert ingredients, many vehicles are involved in physical and chemical interactions with the outer layer of human skin (the stratum corneum). The persistance, penetration, and resistance of the active ingredients to abrasion, sweating, and washing often depends upon the vehicle. Ingredients reviewed by this Panel were categorized on the basis of their currently employed topical vehicles.

The Panel strongly recommends that all inactive ingredients, including those in the vehicle, be listed with or without a statement of their quantity. The consumer, his/her physican, or his/her pharmacist may need to know all the ingredients in a product for a variety of reasons, including possible adverse responses on the part of the user.

Therapeutic claims cannot be made on the basis of inactive ingredients or vehicles alone. Because these substances are intended for topical application where cosmetic elegance and cosmetic acceptance are considerations for the consumer, a fair statement describing the vehicle formulation is reasonable, such as nongreasy, nonstaining, oily, greaseless, velvety, emollient, moisturizer, nonsticky, etc.

c. *Abnormal skin.* Any skin abnormality tends to increase absorption of chemicals through it, but a few skin abnormalities decrease absorption.

The Panel recognizes that drugs effective on the mucous membrane may not be effective on the intact skin. In some cases, concentrations effective on mucous membranes may be inadequate on the skin. Therefore, trials of drug absorption on mucous membranes are not acceptable indications for use on intact or damaged skin.

3. *Determination of safety and effectiveness—a. Safety.* It was decided by the Panel that all materials applied to the human skin should also be tested for toxicity in test animals given the ingredient internally, by either the oral route or by injection. Such animal testing is necessary, whether or not substantivity or absorption has been shown, because individuals, especially children, may accidentally ingest or inhale the agents, or absorb them through the skin.

Clinical use and marketing experience were also used by the Panel in establishing the safety of sunscreen ingredients. The Panel accepted the data on "complaints per unit sold," submitted by the various companies, as one indicator of human safety for final preparations. However, anecdotal descriptions of toxicity were not seriously considered by the Panel unless they were supported by data that included the units of actual use.

When a drug is available for widespread use as in OTC sunscreen products, its safety must be well-documented by data on its toxicology, excretion, and pharmacologic action. The Panel evaluated the submitted toxicological data and classified the ingredients as described below.

A number of patch test methods are applicable to human safety testing of category III ingredients or final products. These tests have proven valuable in predicting skin irritancy and sensitization. The Panel recommends the following methods of patch testing:

(1) The Draize human skin irritancy and sensitization tests and the various modifications utilizing the subject's back or arm may be used (ref. *2*).

(2) The method of Shelanski and Shelanski (ref. *3*) is one in which the active ingredient or formulation is applied regularly to the test site for 3 to 4 weeks. Then, following a rest period of 2 weeks, a single challenge application of the drug or formulation is made (ref. *3*). The early applications are to detect primary skin irritants and initiate sensitization. The challenge dose is to detect skin sensitizers.

(3) The maximization procedure of Kligman or its modifications uses an irritant on the test site, thereby hastening and accentuating the skin sensitizing potential of a substance (ref. *4*).

b. *Effectiveness.* The effectiveness of all category I sunscreens has been demonstrated by appropriate studies. The UV absorbance of the individual sunscreen between 290 and 320 nm was established. In addition, in most instances data were available for human subjects treated either with artificial sunlight or with natural sunlight.

4. *Percutaneous absorption.* As noted above, certain ingredients are efficacious in relation to their percutaneous absorption which may also be related to toxicity. Therefore, the Panel considers certain in vitro studies to be applicable both for safety and efficacy. Penetration studies of drugs in

animals are, unfortunately, not directly applicable to man. Some drugs can be applied to large surface areas of the body, and drug penetration can be determined from blood level and excretion detection. Inferences of safety can then be made based on the drug levels obtained when related to toxicity studies. Methods to detect minute quantities of some substances are not available, and in general, no standard procedure to measure skin penetration ...an exists. Animal studies should ...formed as a preliminary to ... vivo testing.

...ensitization. Photosensiti... ...oad term used to describe ...c abnormal or adverse cutan... ...reaction to light energy including ...oth the more common phototoxic and the uncommon photoallergic responses.

a. *Photoallergy.* Photoallergy (ref. *5*) is an acquired altered photoreactivity dependent on an antigen-antibody or cell-mediated hypersensitivity state. The reactions may be produced by the sun alone or may depend on the presence of a photosensitizer. The clinical pattern may range from immediate urticarial lesions to delayed papular and eczematous lesions. The Panel knows of no universally acceptable test to detect potential photoallergy in man.

b. *Phototoxicity.* Many dermal preparations fluoresce under UV light stimulation, and the energy produced may cause lesions. This process is called phototoxicity. Tests for phototoxicity are extant in animals and man. Sunlight-induced injury of the skin is generally toxic and independent of allergic mechanisms. It can be likened to a primary irritant reaction. The responses are characterized clinically by erythema and edema which may occur within minutes after irradiation, but are usually delayed. The usual response appears as an exaggerated sunburn.

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B. CATEGORIZATION OF DATA

1. *Category I conditions under which sunscreen active ingredients are generally recognized as safe and effective, and are not misbranded.* The Panel recommends that the category I conditions be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

CATEGORY I ACTIVE INGREDIENTS

The Panel has classified the following sunscreen active ingredients as safe and effective and not misbranded:

Aminobenzoic acid
Cinoxate
Diethanolamine *p*-methoxycinnamate
Digalloyl trioleate
Dioxybenzone.
Ethyl 4-[bis(hydroxypropyl)] aminobenzoate
2-Ethylhexyl 2-cyano-3,3-diphenylacrylate
Ethylhexyl *p*-methoxycinnamate
2-Ethylhexyl salicylate
Glyceryl aminobenozate
Homosalate
Lawsone with dihydroxyacetone
Menthyl anthranilate
Oxybenzone
Padimate A
Padimate O
2-Phenylbenzimidazole-5-sulfonic acid
Red petrolatum
Sulisobenzone
Titanium dioxide
Triethanolamine salicylate

a. *Aminobenzoic acid.* The Panel concludes that aminobenzoic acid is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

There are three isomers of aminobenzoic acid—the ortho, meta, and para. The ortho and meta isomers have little, if any, use in human therapeutics. The Panel recognizes only the para isomer, para-aminobenzoic acid, in its deliberations. Aminobenzoic acid has been the official name for this compound since the publication of the National Formulary (NF XII) in 1965. Prior to that time the official name was PABA (*p*-aminobenzoic acid). This obsolete designation occasionally still appears in the published literature.

Aminobenzoic acid is an aromatic acid. It is widely distributed in plant and animal tissues besides being a structural component of the vitamin folic acid, a member of the vitamin B complex. Aminobenzoic acid consists of white to slightly yellowish crystals or crystalline powder. It discolors on exposure to air and light. One g dissolves in about 170 ml of water, in 8 ml of alcohol, and in 50 ml of ether. It melts at 188° C.

(1) *Safety.* Clinical use and marketing experience have confirmed that aminobenzoic acid is safe in the dosage range used as an OTC sunscreen.

Acute toxicity studies have been done in the mouse and rat with an alcoholic solution of aminobenzoic acid. The oral LD_{50} for the mouse and the rat were 17 g/kg and 6 g/kg, respectively (ref. *1*). The percutaneous (topical) LD_{50} was determined in mice by repeated applications of the alcoholic solution of aminobenzoic acid every 15 minutes to the shaved skin of the animals. The percutaneous LD_{50} was 180 g/kg. Death occurred within 24 to 48 hours and was preceded by ataxia and coma (ref. *1*). The toxicity was attributed to the alcohol in the aminobenzoic acid solution.

In monkeys, a commercial preparation of aminobenzoic acid applied directly to the eyes, produced reversible corneal opacity of short duration, minimal conjunctivitis, and moderate chemosis. At the end of the test on day 7, no toxic effects remained. In a second monkey study, a 5 percent aminobenzoic acid solution in alcohol was instilled in the eyes. Observations were made at 10 minutes, 1 hour, 24 hours, and 2, 3, 4 and 7 days posttreatment. Corneal haze, fluorescein staining, minimal conjuctivitis, minimal chemosis, and corneal epithelial haze were seen in some monkeys. The corneal damage was transient, with no permanent damage. The effects on the conjuctiva were minimal and cleared readily (ref. *1*). In a third eye irritation study in rhesus monkeys, it was concluded that an immediate precipitation of some component in the compound caused the corneal and epithelial damage, possibly the result of an additive effect of the test compound and the vehicle. The opacity that occurred could severely restrict vision in man, but this effect seems to be transient. Possible secondary damage could not be excluded (ref. *1*).

In an oral toxicity study, rats were fed 2 g/kg aminobenzoic acid daily for 1, 2, 3, or 6 months. No significant differences from controls were reported with respect to body weight, rate of growth, organ weights, or reproduction. Histological changes were only seen in the thyroids of the treated rats (ref. *2*).

Prior to the broad spectrum antibiotics, aminobenzoic acid was used to treat rickettsial diseases and typhus. Later it was used in treating diseases such as scleroderma and chronic fibrotic disease as an antifibrotic agent.

Aminobenzoic acid has the ability to cross-sensitize to a limited number of structurally similar analogs. Aminobenzoic acid belongs to a group of aromatic amines and nitro compounds capable of cross-reaction with each other because of similar chemical configuratons. The cross-reacting is dependent on previous sensitization to the other related chemical compounds which include sulfonamides, aniline dyes, paraphenylenediamine, "caine" anesthetics, and others. Theoretically, an individual with contact allergic hypersen-

sitivity to any one of these chemicals might develop an allergic dermatitis upon exposure to aminobenzoic acid. Despite this potential for phototoxicity, contact sensitization and allergic reaction, "a review of the literature to date reveals no case reports of phototoxicity and extremely few case reports of questionable photocontact allergy and contact allergy to aminobenzoic acid and its esters" (ref. *3*). Willis has concluded "that PABA possesses only the weakest potential for sensitization. It is indeed fortunate that we have such a highly effective sunscreening agent which appears not to cause any serious side effects in the majority of users."

In a study with 46 individuals hypersensitive to para-phenylenediamine with which aminobenzoic acid reacts, only 3 individuals cross-reacted following the application of 5 percent aminobenzoic acid (ref. *4*). Although aminobenzoic acid has been determined to be the allergen in some cases of photosensitivity, Kligman (ref. *5*) in a study with 25 subjects reported no sensitization in maximization tests using 20 percent aminobenzoic acid. He observed no sun sensitization over several years of testing.

Ten percent concentration of aminobenzoic acid produced no reactions of a phototoxic nature when occlusive applications were made to cellophane tape-stripped sites of 10 subjects who were irradiated with the photoactivating range of the ultraviolet spectrum. No inflammatory reactions greater than the unirradiated control were induced. Ten percent concentrations in petrolatum also showed no significant potential for inducing photocontact allergy (ref. *6*).

Kilgman (ref. *5*) has stated that:

* * * field experience has documented the claim that 5 percent hydroalcoholic solutions of aminobenzoic acid are substantially superior to any other marketed sunscreen. Evidence is accumulating that such solutions are beneficial in other light-sensitive dermatoses * * *. Though we must now concede that an occasional subject will become sensitized, it is our opinion that the merit of the product outweighs this risk.

The prevention of acute sunburn is perhaps the least important of the benefits provided. Our major interest in developing superior sunscreens has been to prevent the aging changes that underlie cancers and precanceroses in sunlight-sensitive subjects. In this context, we would prefer to have such products regarded as drugs rather than cosmetics. Their important role is to prevent disease and not simply to please.

As a general rule, low molecular weight substances with both lipid and water solubility are most likely to penetrate the horny layer. Aminobenzoic acid is none of these agents. Aminobenzoic acid permeability is about that of water which penetrates the horny layer well. Even for these low molecular weight substances, diffusion does not reach a steady state until 1 to 2 hours after application. Aminobenzoic acid diffuses into the horny layer as a reservoir type of sunscreen. A reservoir type of sunscreen is strongly resistant to sweating and partially resistant to immersion (ref. *6*).

No systemic or dutaneous side effects were noted in the course of an investigation in which 30 ml of a 5 percent alcohol solution of aminobenzoic acid was applied once daily to the face, neck, truck, and upper extremities of 10 healthy adult men for 30 days. No changes occurred in blood cell count, urinalysis, blood protein level, albuminglobulin ratio, blood urea nitrogen, fasting blood glucose, serum glutamic oxaloacetic transaminase and serum creatinine levels.

Ninety ml of aminobenzoic acid lotion were applied to the entire body 3 times at 30 minute intervals in 4 subjects. Blood alcohol levels were determined at 15, 30, 60, 240 minutes and pretreatment controls. All failed to show any detectable amount of alcohol.

Five subjects tested with 5 percent aminobenzoic acid lotion for 21 days failed to show any significant irritation of this particular preparation (ref. *1*).

Aminobenzoic acid has been used on thousands of patients with only a rare individual intolerance. The incidence of adverse reaction is low indeed. Aminobenzoic acid has also been used as a systemic and antifibrotic agen.

The Panel concludes that extensive animal and human toxicological and pharmacological data attest to the safety of aminobenzoic acid as a sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are studies documenting the effectiveness of aminobenzoic acid as an OTC sunscreen.

The effectiveness of aminobenzoic acid as a sunscreen agent is demonstrated by its in vitro UV light absorption characteristics. Qualitative spectrographic methods have demonstrated that aminobenzoic acid totally absorbs radiation between the wavelengths of 260 nm and 313 nm of the mercury spectrum, with a maximum absorption at 288.5 nm (ref. *7*). The curve is broad and such that at the wavelengths effective for erythema, the absorption spectrum is enormous and completely encloses the sunburn action spectrum. In vitro study recognizes aminobenzoic acid as a potential protective against sunburn. It has a cutoff point at 313 nm which allows UV rays with beneficial biologic effects to be transmitte (ref. *8*). Its in vivo efficacy can be affected by variables in formulation and the effects of physiological conditions, such as perspiration and sebum on the skin. The solvent in which the sunscreen is applied also influences effectiveness through dielectric effects, solvent-solute interaction, variations in pH and solvent concentration (ref. *1*). Aminobenzoic acid does not penetrate the human skin in any detectable level. One g of aminobenzoic acid dissolves in 170 ml water and in 8 ml ethanol aminobenzoic acid is currently marketed as a hydroalcoholic solution and foam. It has been employed in 5 to 15 percent concentrations in creams and ointments.

Aminobenzoic acid has been used successfully as an effective sunscr
up to approximately 315 nm ar
fords protection for the short
burn wavelength range of
nm.

For over 40 years, amin
has been known to be an
screen. Recent studies
superior to many of the
screens marketed today for
sunburn.

The efficacy of aminobenz
due to diffusion into the hor
of skin and acting as a reservo
of sunscreen. The agent is mor
cient when applied 2 hours befor
exposure, to allow for maximal diffusion. This feature results in longer protection and there is continuing sunscreen effectiveness after sweating and to a lesser extent after immersion.

The sunscreening efficacy of aminobenzoic acid in ethanol has been studied in experimental animals following exposure to artifical light sources. (ref. *1*). The results demonstrated that aminobenzoic acid protected the animals against 40 to 50 minimal erythermal doses (MED) in one study and against 30 to 38 MED's in another study. In studies done under simulated swimming and sweating conditions, the protection of aminobenzoic acid as a sunscreen was diminished, but still remained (ref. *1*). Cellophane stripping of the stratum of the skin in hairless dogs showed that aminobenzoic acid does substantially penetrate the horny layer (ref. *9*).

In albino mice, 5 percent aminobenzoic acid applied daily to the ears followed by 20-minute exposure to UV irradiation, over a period of 5 months, indicated that the carcinogenic and erythematous effects of UV light can be reduced by the topical application of aminobenzoic acid. The authors concluded that aminobenzoic acid is a highly effective sunscreen that is capable of providing adequate protection against the damaging effects of sunlight in man (ref. *10*).

In a study comparing an aminobenzoic acid lotion (5 percent aminobenzoic acid in alcohol) and an aminobenzoic acid foam (5 percent in alcohol) in rabbits, the foam preparation was 5 times more effective as a UV blocking agent than the lotion. The lotion had a protective efficacy of 7.9; the foam

38.19. After elution, the lotion had a protective efficiacy of 2.91; the foam 2.96. Apparently the primary blocking was enhanced by the vehicle. (The protective efficacy represents the number of MED's against which the sunscreeen will protect (ref. *11*).)

The sunscreening effectiveness of a 5 percent hydroalcoholic solution of aminobenzoic acid was demonstrated by Pathak, Fitzpatrick, and Frank (ref. *12*) and later confirmed by other investigators. Its effectiveness is such that it is the recognized comparison standard for sun-screening efficacy.

Pathak et al. (ref. *12*) compared the efficacy of 5 percent aminobenzoic acid in 95 percent ethyl alchohol with 24 commercially available sunscreen preparations and various chemical agents in a 3-year study (1965–1968). The effectiveness of a single application of the 5 percent solution of aminobenzoic acid was greater than that of the other UV-absorbing compounds and brand name preparations tested. It afforded very significant (p is less than 0.05) and effective protection. In vitro tests demonstrated that the prolonged effectiveness of aminobenzoic acid results from adsorption of aminobenzoic acid by the intact epidermis and partial chemical conjugation of aminobenzoic acid with constituents of the horny layer. An alcoholic solution of aminobenzoic acid at pH 4.5 to 4.8 was found to be substantive to the horny layer even after repeated washings with water. In Arizona, where the study was conducted, a single application of aminobenzoic acid provided total, daylong protection for subjects who were not swimming or engaged in activity. During periods of sweat-producing exercise, aminobenzoic acid gave 100 percent protection from erythemogenic solar radiation for 2 hours and over 75 percent protection thereafter. These investigators estimated the amount of protection mainly by visually rating the degrees of redness.

In contrast to the findings by Pathak et al., Willis and Kligman (ref. *6*) reported that after immersion, they found aminobenzoic acid less effective than did the former authors. Willis and Kligman estimated the amount of protection by use of the individually determined MED, which they defined as the least amount of radiation that will just produce a uniform redness with sharp borders. They stated that "Claims of effectiveness after swimming must be strongly qualified."

Amounts of 0.12 ml and 0.3 ml of 5 percent aminobenzoic acid in 70 percent ethanol were applied on the backs of 13 normal subjects over a fixed area of the skin. The area was irradiated at 305 nm with a 1,600 watt xenon arc. The efficacy of aminobenzoic acid was higher than other sunscreens tested and was maintained for 7 hours following applications (ref. *13*). The protective action was reduced upon induced sweating and fell to zero following showering.

A 5 percent solution of aminobenzoic acid in 55 percent alcohol with emollients was evaluated with the xenon arc lamp in 8 subjects. The protection was enhanced by applying greater amounts of solution. An application of 60 $\mu l/cm^2$ afforded protection against 25 to 30 MED's. Protection following immersion was reported to be greatest when 2 hours elapsed following application. Three applications at 2-hour intervals was superior to one (ref. *14*). Aminobenzoic acid was found to be more effective than three brand name sunscreen products.

In a study by Rossman, Knox and Freeman (ref. *15*), aminobenzoic acid was reported to be more effective as a sunscreen than over 100 other sunscreen formulations tested. Ten percent aminobenzoic acid in a vanishing cream base was effective in excess of 12 minutes in 17 patients irradiated with the Hanovia hot quartz mercury vapor lamp, and extended from 20 to 60 minutes in 13 additional patients as compared with an approximate minimal erythemal dose of 15 seconds on unprotected skin.

Rothman and Henningsen (ref *16*) studied the effectiveness of 15 percent aminobenzoic acid in Ruggles' cream in a film thickness of 0.03 mm. They found that these conditions increased the amount of irradiation from a mercury vapor lamp necessary to produce threshold erythema 50 to 100 times the amount of irradiation producing the same effect when the vehicle alone is used in the same film thickness. In the same study, these authors found that in 32 subjects highly sensitive to the erythemal action of UV light, an 0.08 mm aminobenzoic acid film provided complete protection to natural sunlight exposure. The experimental data suggest that the sunburn-protecting action of aminobenzoic acid is intense enough to protect the skin againt sunburn in case of extremely strong UV irradiation such as found on glaciers or on the ocean.

Five subjects received 12 g aminobenzoic acid daily in divided doses for 10 days. The immediate protective index was determined before dosing and again on the last day. The protective index was not increased after oral administration of aminobenzoic acid.

Aminobenzoic acid has been found to be an effective sunscreen in concentrations from 2 percent. Effectiveness increases linearly up to 2.5 percent with a clear-cut tendency to plateau at 5 percent. Doubling the concentration does not afford twice the protection. It was found that for equal amounts of aminobenzoic acid, the protection was the same whether this was achieved by a single or multiple applications. In a formulation, erythemal protection has been found to be maximal in vehicles containing between 50 percent and 60 percent alcohol. However, in some studies, concentrations of 10 percent and 15 percent aminobenzoic acid have been reported to be effective as sunscreen agents in a cream base.

The Panel concludes that aminobenzoic acid is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 5 to 15 percent aminobenzoic acid: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 5 to 15 percent aminobenzoic acid: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.)

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b. *Cinoxate.* The Panel concludes that cinoxate is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

Cinoxate is also known as 2-ethoxyethyl-*p*-methoxycinnamate. Cinoxate is a practically odorless, slightly yellow, viscous fluid, with a specific gravity of 1.000. It is stable to sunlight for 30 days. The empirical formula is $C_{14}H_{18}O_4$, with a molecular weight of 250.29. The UV absorption at 1 percent concentration is 270 to 328 nm, being total from 280 to 320 nm with a maximum at 310 nm. Cinoxate is miscible in 95 percent ethanol, 99 percent propylene glycol monomuristate, isopropyl myristate, oleyl alcohol and soya vegetable oil. It is slightly soluble in water (0.05 percent), 0.5 percent in glycerol, and 3 percent in mineral oil (ref. *1*). Cinoxate can be formulated as an aerosol, oil, hydroalcoholic lotion, and as an emulsified lotion and cream.

(1) *Safety.* Clinical use and marketing experience have confirmed that cinoxate is safe in the dosage range used as an OTC sunscreen.

Cinoxate has low toxicity on animal testing. Human toxicology tests, clinical trials and wide use attest to its safety for human use.

Acute toxicity studies have been done in rats with full strength cinoxate. The oral LD_{50} for the rat was 3.8 ml/kg (ref. *2*). In a single dose acute oral toxicity study of 2 percent cinoxate in a lotion, a single dose level of 5 g/kg administered to 10 rats caused no fatalities during the 14-day observation period or gross organ abnormalities at autopsy (ref. *3*). The Draize rabbit eye irritancy test revealed no irritation when 3 percent cinoxate in equal parts of mineral oil and corn oil was instilled into the rabbits' eyes (ref. *4*).

The repeated insult patch method of Shelanski and Shelanski in 50 subjects revealed that 2 percent cinoxate in an oil and lotion formulation was not a primary irritant, fatiguing agent, or sensitizer. In this test, the active ingredient and the vehicles were applied on 15 separate occasions under an occlusive patch (ref. *5*).

After applying 2 percent cinoxate in a cream base to both arms of six volunteers, 96 percent of the cinoxate was recovered after 4 hours contact with the skin. A photoreactivity test at 1, 25, and 60 MED in 26 subjects with 4 mg cinoxate/cm^2 applied to the back revealed no photoxicity (ref. *6*). One documented case of photodermatitis to cinoxate has been reported (ref. *7*).

Cinoxate is used as a sunscreen in several commercial preparations. One manufacturer reported receiving no complaints per 400,000 units of a 2 percent cinoxate sunscreen lotion sold, and 8 minor complaints and one allergic contact dermatitis per 2,100,000 units of a 1.7 percent cinoxate solution sold, with a ratio of complaints per 100,000 units sold of 0.41 (refs. *8* and *9*).

The Panel concludes that the animal and human toxicological data and the widespread use of cinoxate since its introduction in the late 1950's with few adverse reports attest to the safety of cinoxate as a sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are studies documenting the effectiveness of cinoxate as an OTC sunscreen.

The UV absorbance of cinoxate at 1 percent concentration in isopropyl myristate is less than 10 percent at 270 and 338 nm, but total between 280 to 320 nm with the maximum at 310 nm. Two percent cinoxate in seven experimental vehicles was applied to the backs of seven volunteers and the treated sites were exposed to 7 MED's from fluorescent sunlamps. On a scale of 0 (best score) to 6 (worst score), protection varied according to the formula, with the highest erythema index being 2.25 and the lowest 0.5 (ref. *8*).

A 2 percent cinoxate lotion was compared with a 1.75 percent cinoxate solution in a controlled study in 10 subjects at a medical school. After exposing the treated sites to fluorescent sunlamps, the lotion afforded 5.1 times greater MED protection than the vehicle, while the solution afforded 3.3 time greater MED protection than its vehicle (ref. *10*).

Two dermatologists independently evaluated a 2 percent cinoxate lotion in 48 patients (27 with photosensitivity) during the summer. There were 33 females and 15 males, with a mean age of 23 (range 3 to 52 years of age). Results of use were rated by the investigators as 31 (of 48) excellent, 12 good, and 5 fair. Thirty-four of 41 patients rated suntanning as good to excellent (ref. *11*). Of 150 patients evaluated clinically by six physicians in a company-sponsored, uncontrolled clinical trial, after using the 1.75 percent cinoxate solution for 10 days to over 1 year, results were rated as 111 (of 150) excellent, 35 good, 1 fair, 1 poor, and 2 not rated (ref. *9*). In an independent clinical trial done overseas, 85 of 86 patients reported adequate protection from sunlight and no important adverse effects (ref. *12*).

Based upon the available data, the Panel concludes that cinoxate is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) For products containing a minimum SPF value of 2 under 4 containing 1 to 3 percent oxate: Adult and children over of age topical dosage is liberal tion before sun exposure and after swimming or after sweating. There is no rec dosage for children under age except under the advic vision of a physician.

(ii) For products provi mum SPF value of 4 con percent cinoxate: Adult over 6 months of age topi liberal application before and reapply after swimm excessive sweating. There is recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.)

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c. *Diethanolamine p-methoxycinnamate.* The Panel concludes that diethanolamine *p*-methoxycinnamate is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

Diethanolamine *p*-methoxycinnamate is also known as *p*-methoxycinnamic acid diethanolamine salt.

Diethanolamine *p*-methoxycinnamate is a pale tan microcrystalline powder which is readily water soluble. Its molecular weight is 283.33 and its fusion point at 87.0° C minimum. It is stable to light and moderate heat and is not hygroscopic. It is suitable for use in aqueous or alcohol/water formulations, gels, and emulsions (ref. *1*).

(1) *Safety.* Clinical use and marketing experience have confirmed that diethanolamine *p*-methoxycinnamate is safe in the dosage range used as an OTC sunscreen.

Animal and human toxicological data attest to its safety for human topical application. The oral LD_{50} is greater than 5 g/kg in male rats and 3.7 g/kg for female rats (ref. *2*).

Application of a 2.0 percent diethanolamine *p*-methoxycinnamate solution on guinea pig epidermis was found to be nonirritating following a single application, and after repeated applications for 21 consecutive days. Repeated applications of 6 and 20 percent solutions on 21 consecutive days produced very light medicament carrier irritation. Sensitization tests on guinea pigs treated for 3 weeks with 2, 6, and 20 percent concentrations determined that allergic sensitization did not occur. Draize tests measuring the irritation of the rabbit's eye revealed that a 1 percent perfumed solution of the ingredient can be tolerated without reaction following a single and repeated (7 days) applications, whereas 3 and 10 percent concentrations produced weak irritation of the conjunctiva (ref. *2*). A commercial sunscreen lotion containing 10 percent diethanolamine *p*-methoxycinnamate applied twice to rabbits' eyes caused a reddening of the margin of the eyelid and the conjunctiva for the duration of 4 hours, after which any irritation effect disappeared (ref. *2*).

A Draize repeated insult patch test on 53 (42 female and 11 male) subjects was performed to evaluate the irritative and sensitizing potentialities of a 2 percent diethanolamine *p*-methoxycinnamate solution. Each patch contained 0.5 ml of the test material and was secured to the test site by overlying strips of occlusive adhesive tape. The patches were alternately placed on the medial surface of the right and left deltoid area. Because of the two holidays and a weekend which occurred during the study, the period of contact and rest period could not consistently be 48 hours and 3 of the 10 applications were 1, 3, and 4 days. Readings were recorded each time the patches were removed. After a 2-week rest period, challenge patches were applied to both inner deltoid areas and were removed 2 days later, with readings being recorded immediately and 24 hours afterwards. No reactions were observed during any of the above readings following the removal of either the sensitization or challenge patches. It was concluded that the test material did not manifest either primary irritation or sensitizing effects (ref. *3*).

Another Draize repeated insult patch test on 54 subjects (17 males and 37 females) was conducted in the same manner as the above test except that a 7.5 percent diethanolamine *p*-methoxycinnamate in water solution was employed, and the patches were removed every 48 hours, except for three 72-hour weekend periods and a 24-hour period at the outset, to observe whether the full group presented any irritative or sensitization reactions before proceeding further with the test. Except for 16 patients who experienced reactions to the adhesive tape used to secure the patches, no reactions to the test material were noted following the removal of the sensitization and challenge patches, thereby leading to the conclusion that the test material was neither a primary irritant nor an allergic sensitizing agent (ref. *4*).

Based upon the available data, the Panel concludes that diethanolamine *p*-methoxycinnamate is a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are studies documenting the effectiveness of diethanolamine *p*-methoxycinnamate as an OTC sunscreen.

Its absorbance is between 280 and 310 nm, with the maximum absorbance at 290 nm. Readily water soluble, it is practically insoluble in nonpolar organic solvents, oil, and fatty materials. It can be incorporated into gel, lipstick emulsion, and aqueous formulations (ref. *5*).

In several studies by Pathak, Fitzpatrick and Parrish (ref. *1*), the same formulation containing diethanolamine *p*-methoxycinnamate gave the following results:

Using a hot quartz mercury arc lamp on 12 subjects and comparing 8 different sunscreen formulations against 5 percent animobenzoic acid in ethanol, diethanolamine *p*-methoxycinnamate was shown to have a protective index range of 4 to 15, with a mean minimum of 7.37 and a mean maximum of 10.3 (8 or more is 100 percent protection). All products were found to give significant protection against erythemogenic radiation.

Eight subjects were used under conditions of passive sunbathing to test four formulations. It was found that all were superior to a commercial preparation containing 5 percent aminobenzoic acid. Eleven subjects, also under conditions of passive sunbathing, were used in testing 12 products. The mean indices for the product containing diethanolamine *p*-methoxycinnamate were 1.5 after 30 minutes of exposure, 3.0 after 60 minutes and 4.2 and 4.6, respectively, after 90 and 120 minutes.

In a forth study using the same formulation the product had a mean protective index of 4.6.

Based upon the available data, the Panel concludes that diethanolamine *p*-methoxycinnamate is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) for products providing a minimum SPF value of 2 to under 4 containing 8 to 10 percent diethanolamine *p*-methoxycinnamate: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 8 to 10 percent diethanolamine *p*-methoxycinnamate: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

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

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(4) OTC Volume 060110.
(5) "Efficacy Data," Draft of unpublished paper in OTC Volume 060083.

d. *Digalloyl trioleate.* The Panel concludes that digalloyl trioleate is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

Digalloyl trioleate is a mixture of several derivatives of tannic acid. It is the triester produced by the reaction of digallic acid and oleic acid and conforms generally to the formula $C_{68}H_{106}O_{12}$. It is a clear, viscous, brown liquid with a slight smell. It is insoluble in water but soluble in vegetable oils, 95 percent alcohol, and mineral oil to which has been added 10 to 15 percent vegetable oils. It is incompatible with alkalies, tannic acid, and triethanolamine. The specific gravity is 1.040 to 1.045, and the refractive index is 1.515 to 1.525 (ref. *1*). Digal-

loyl trioleate can be formulated as an oil, emulsified lotion or cream, ointment, alcoholic solution, and lipstick.

(1) *Safety.* Clinical use and marketing experience have confirmed that digalloyl trioleate is safe in the dosage range used as an OTC sunscreen.

Extensive animal and human toxicological testing attests to its safety for topical application.

Acute toxicity studies have been done in mice and rats with digalloyl trioleate. The oral LD_{50} for both mice and rats was 24.5 g/kg (ref. *1*). In a chronic topical application study, eight groups of three rabbits per group had digalloyl trioleate applied as follows: 0.5 ml/kg of bodyweight neat (straight chemical as applied) for 90 days; 4.0 ml/kg of bodyweight neat for 31 days; in lotion 4.0 ml/kg of bodyweight for 90 days and one group with 2 hours of sunlight exposure daily; in ointment 4.0 ml/kg of bodyweight for 93 days plus one group with sunlight exposure; and in cetyl alcohol-ethanol vehicle 4.0 ml/kg of bodyweight for 93 days; and two groups of vehicles applied alone. No dermal toxicity not effect upon the hemogram occurred. The 4.0 ml/kg dose produced some erythema; and due to its physical nature, some matting of the fur which, when removed, resulted in some depilation. No visible toxicity resulted, and the fur regrew normally. The 0.5 ml/kg application caused some erythema, but no toxicity. The vehicle containing a cetyl alcohol-ethanol combination also caused erythema. All animals remained in good condition, gained weight, and showed no gross pathology on autopsy (ref. *1*). Three almost-albino shoats had a weighed amount of 2.5 percent digalloyl trioleate in a lotion, ointment, and cetyl alcohol-ethanol vehicle applied daily to the back, shoulder, and neck for 82 applications. Three swine and a control boar received 2 hours of sunlight daily. After 93 days, all animals were in good condition, gained weight, showed no severe skin irritation or toxicity, and demonstrated no gross or histological pathology of the skin or visceral organs at autopsy. The cetyl alcohol-ethanol treated animal showed some visible irritation (ref. *1*). A modified Landsteiner technique for skin sensitization was negative in 10 guinea pigs injected intracutaneously with 0.1 ml of 0.1 percent digalloyl trioleate in cottonseed oil on alternate days for 10 injections and a final injection 10 days later (ref. *1*).

An independent study in 200 subjects revealed no primary irritation, while one subject developed a sensitivity reaction to digalloyl trioleate. The closed-patch test consisted of applying a 1-cm blotting paper disc saturated with digalloyl trioleate under a patch for 48 hours on days 1 and 7, and reading the results on days 3, 9, and 11 (ref. *1*). A repeated-insult irritation study in 10 white men revealed no irritation or toxicity to a product containing 3.5 percent digalloyl trioleate as the sole active ingredient. One subject developed some erythema on the 9th day (ref. *2*).

The medical literature contains one verified case report of contact photoallergy (ref. *3*). This case has been mentioned directly or indirectly in 16 other publications (ref. *4*). Another reported case of possible contact photoallergy to digalloyl trioleate in a 5-year-old boy with solar dermatitis had no documentation (ref. *5*).

From 1952 through 1972, nearly 4,000,000 units of a sun-protective lipstick product containing 2.5 percent digalloyl trioleate were distributed. Only one complaint of "irritation" had been received by the company from all sources (ref. *6*). During a 20-year period, almost 2,000,000 units of a sunscreen lotion containing 3.5 percent digalloyl trioleate were distributed. The company received a total of six complaints from consumers, yielding a rate of 0.3 per 100,000 units distributed. Of the six complaints, four were concerned with irritation or sensitization. Only one of the four complaints seemed to be a legitimate contact photosensitization, though this was not proven. One person developed redness, but was also "allergic to weeds," while two reported a "reaction." Correspondence with these complainants requesting more details went unanswered (ref. *4*). The Panel received no submissions from other companies who use digalloyl trioleate in their products.

The Panel concludes that the animal and human toxicological data and the extensive use of the substance with few reported complaints attests to the safety of digalloyl trioleate as a sunscreen agent for OTC use.

(2) *Effectiveness.* There are studies documenting the effectiveness of digalloyl trioleate as an OTC sunscreen.

A 1 percent digalloyl trioleate concentration in ethanol absorbs UV light from 270 to 320 nm, with the maximum at 300nm. It has been in use since the early 1930's. No complete data on controlled clinical trials in man were submitted. The United States Army tested and selected 3 percent digalloyl trioleate as one of the four "approved" sunscreens for acquisition under Military Specifications Sunburn Preventative Preparation Cream Base MIL-S-11262 (Quartermaster Corps) July 10, 1951, and MIL-S-11262A March 10, 1953 (refs. 7 and *8*). The efficacy data were not available to the Panel. Abbreviated results were given of a sunscreen test on the backs of men and women employing 2.5 percent digalloyl trioleate in a lotion and a cetyl alcohol-ethanol vehicle on two treated sites with each site compared to an untreated site. Both preparations offered adequate screening against 5 minutes' irradiation at a distance of 40 inches from a quartz mercury arc sunlamp. The vehicles afforded no protection. Tanning was attractive. Unfortunately, the number of subjects was not given (ref. *1*).

A product containing 3.5 percent digalloyl trioleate in a vanishing cream base had 34 unsolicited mentions in the literature from 25 authors concerning its effectiveness as a sunscreen by 1973 (ref. *4*). For example, it was cited as an effective sunscreen for managing photosensitivity dermatitis (ref. *9*), discoid lupus erythematosus (ref. *10*), hydroa aestivale in children (ref. *11*), and for protection from sunlight (ref. *12*). In vivo, it protected better than glyceryl *p*-aminobenzoate and red petrolatum, but it did not protect as well as several other sunscreens (ref. *13*).

Digalloyl trioleate has been used over 40 years by patients and consumers and has been considered an effective sunscreen by authorities. Based on the available data, the Panel concludes that digalloyl trioleate is an effective sunscreen for OTC use in the dosage range specified below.

(3) *Dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 2 to 5 percent digalloyl trioleate: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 2 to 5 percent digalloyl trioleate: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

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

REFERENCES

(1) Hazelton, J. and E. P. Marsh, "Physical, Pharmacological and Dermatological Studies on a Sunscreen," *Proceedings of the Scientific Section, Toilet Goods Association,* 13:1-8, 1950.

(2) "Human Safety Data," Draft of unpublished paper in OTC Volume 060044.

(3) Sams, W. M., "Contact Photodermatitis," *Archives of Dermatology,* 73:142-148, 1956.

(4) OTC Volume 060044.

(5) Kern, A. B., "Solar Dermatitis in a Child," *Archives of Dermatology*, 73:92-93, 1956.
(6) OTC Volume 060004.
(7) Wells, F. V. and I. I. Lubowe, "Cosmetics and the Skin," Rheinhold Publishers, New York, p. 383, 1964.
(8) "Military Specifications; Sunburn-Preventive-Preparation, Cream Paste," Draft of unpublished paper in OTC Volume 060065.
(9) Fisher, A. A., "Dermatitis Medi-camentosa," *in* "Current Therapy," W. B. Saunders and Co., Philadelphia, p. 464, 1962.
(10) Haserick, J. R., "Lupus Erythematosus, *in* "Current Therapy," W. B. Saunders and Co., Philadelphia, p. 445, 1963.
(11) Perlman, H. H., "Hydroa Aestivale," *in* "Current Pediatric Therapy," 5th Ed., Edited by S. S. Gellis and B. M. Kagan, W. B. Saunders and Co., Philadelphia, 1971.
(12) Perry, H. O., "Discoid Lupus Erythematosus and Photosensitive Eruptions," *Modern Treatment*, pp. 909-915, Sept., 1965.
(13) Kahn, G. and G. Wilcox, "Comparison of In-vitro and In-vivo Sunscreen Testing Methods," *Journal of the Society of Cosmetic Chemists*, 20:807-824, 1968.

e. *Dioxybenzone.* The Panel concludes that dioxybenzone is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

Dioxybenzone is also know as 2,2'-dihydroxy-4-methoxybenzophenone. It is an organic benzophenone derivative designated as benzophenone-8 and exhibits a wider UV absorbance range than does padimate.

(1) *Safety.* Clinical use and marketing experience have confirmed that dioxybenzone is safe in the dosage range used as an OTC topical sunscreen.

Animal and human safety data have been obtained from studies evaluating a sunscreen lotion containing dioxybenzone in combination with another sunscreen agent, padimate A. On the basis of five animal toxicity studies the investigators concluded that: "Neither erythema nor edema was produced in any animal following the challenge dose" and "these results suggest that the sunscreen lotion formulation should not cause either skin sensitization or allergic contact dermatitis in man"; "these findings suggest that this sunscreen formulation should be safe for repeated dermal use in man"; the acute oral toxicity was determined to be 17.5 ml/kg for the rat and 14.7 ml/kg for the rabbit suggesting that accidental ingestion "should present little risk of serious toxicity in man"; and the likelihood of serious ocular damage following accidental ocular instillation would appear to be low but such contact may cause "slight to moderate redness of the conjunctivae" (ref. *1*).

Patch test involving 100 white females were performed to determine whether the ingredients contained in the combination product were capable of producing an immediate or primary irritation of the skin. It was reported that "there was no evidence of any inflammatory reaction on the site of application immediately, 15 minutes, and 24 hours after removal of the 48-hour patch test." From the above-described data it was concluded that the combination product is not a primary irritant (ref. *1*).

Based on the available data, the Panel concludes that dioxybenzone is a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are studies documenting the effectiveness of dioxybenzone as an OTC sunscreen.

Human efficacy data were obtained from three clinical studies comparing the effectiveness of a combination product (3 percent dioxybenzone and 2.5 percent padimate A) with one to three other marketed sunscreen preparations (ref. *1*). One product contained 5 percent *p*-aminobenzoate; another contained a 5 percent combination of padimate A and monoglycerol *p*-aminobenzoate; and the third contained 2.55 percent padimate A.

The reference contained the conclusions that:

(i) "It is felt that the total effect of these two sunblocking agents will provide greater effective absorption of ultra-violet rays than the effect of either agent used independently, in the range of 260-380 nm (2600-3800 Angstrom units)";

(ii) A double-blind, randomized study involving a total of 33 subjects and four different tests performed simultaneously (passive sunbathing; sweating and passive sunbathing; swimming and passive sunbathing; and passive sunbathing, sweating, swimming, and walk-around) and comparing the first three preparations listed above provided data indicating that the photoprotective potency of the dioxybenzone-padimate A lotion was equal to and in some respects greater than that for the *p*-aminobenzoate and padimate A-monoglycerol *p*-aminobenzoate products;

(iii) Stress, efficacy and protective index tests comparing the dioxybenzone-padimate A lotion with the padimate A-monoglycerol *p*-aminobenzoate product revealed that "there were no significant differences in stinging or burning sensations noted after application," but "there was an increasing incidence of both as additional stress was carried out." Both gave highly significant protection from erythemas as compared to untreated areas, and there were no significant differences regarding the MED, or the degree of pigmentation, and both increased the MED significantly compared to the untreated area;

(iv) A double-blind, randomized study comparing the four formulations listed above and using a solar simulator as the primary light source in the UV spectrum provided data indicating that the padimate A-monoglycerol *p*-aminobenzoate and *p*-aminobenzoate products were most effective in that order, followed by the dioxybenzone-padimate A lotion and the padimate A product last; and

(v) The dioxybenzone-padimate A lotion "is an effective agent to protect against ultraviolet radiation in the erythemogenic range, and has good substantivity."

Based on the available data, the Panel concludes that dioxybenzone is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) For products containing a minimum SPF value of 2 to under 4 containing 3 percent dioxybenzone: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 3 percent dioxybenzone: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.)

REFERENCE

(1) OTC Volume 060116.

f. *Ethyl 4-[bis(hydroxypropyl)] aminobenzoate.* The Panel concludes that ethyl 4-[bis(hydroxypropyl)] aminobenzoate is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

Ethyl 4-[bis(hydroxypropyl)] aminobenzoate is also known as the 2-mole propoxylate of aminoethylbenzoate and ethyldihydroxypropyl PABA.

The absorbance range of ethyl 4-[bis(hydroxypropyl)] aminobenzoate is between 280 and 330 nm, with the absorbance maximum at 308 to 311 nm. It is soluble in ethyl and isopropyl alcohol, propylene glycol, castor oil, and isopropyl myristate; but it is insoluble in water, mineral oil, and glycerin. Ethyl 4-[bis(hydroxypropyl)] aminobenzoate is usually formulated in an emulsion base.

(1) *Safety.* Clinical use and marketing experience have confirmed that ethyl 4-[bis(hydroxypropyl)] aminobenzoate is safe in the dosage range used as an OTC sunscreen.

Animal and human toxicological data attest to its safety for human

topical application. The oral LD_{50} is 20 ml/kg in rats while the intraperitoneal LD_{50} in rats was found to be 5.0 ml/kg (ref. *1*).

Animal safety data indicated that 5 percent ethyl 4-[bis(hydroxypropyl)] aminobenzoate in carbowax ointment, U.S.P. is not a primary irritant to the skin. It is not an ocular irritant, and will not induce comedones (blackheads) (ref. *1*).

Human safety data indicated that studies employing a 5 percent ethyl 4-[bis(hydroxypropyl)] aminobenzoate formulation demonstrated that normal and stripped skin sites on 10 healthy male volunteers showed no evidence of phototoxicity and a very low level of irritancy. Liberal application to the faces of 15 healthy male volunteers showed not instances of stinging or burning or irritation at 5, 10, and 30-minute intervals and 24 hours after application. A maximization test (ref. *2*) performed on 25 healthy male volunteers resulted in no instances of contact sensitization with the conclusion that it was unlikely that the formulation would present a danger of contact sensitization in normal, intended use. Topical application to the entire area of the chests, backs, shoulders and faces of 20 healthy male volunteers once daily for 21 days resulted in a very low level of irritancy with erythema being barely perceptible in some subjects with no repetition on successive days of the slight irritation in most cases (ref. *1*).

Based upon the available data the Panel concludes that ethyl 4-[bis(hydroxypropyl)] aminobenzoate is a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are studies documenting the effectiveness of ethyl 4-[bis(hydroxypropyl)] aminobenzoate as an OTC sunscreen.

Human efficacy data has been reported. The protective index of 2 to 5 percent ethyl 4-[bis(hydroxypropyl)] aminobenzoate in various vehicles ranged from 20 (2 percent formulation in alcohol/glycerine/water and 5 percent formulation in oil base) to 70 (5 percent formulation in carbowax base). Fifty mg of 1, 2.5 and 5 percent formulations were applied to 1-square inch patches of skin on six healthy male volunteers, who were then exposed using a xenon lamp to 20, 40 and 60 times the radiation necessary to produce mild erythema on untreated skin, with only barely perceptible erythema being observed at the highest radiation dose and minimal concentration. Fifty mg of 1, 2.5 and 5 percent formulations were applied to 1-square inch patches of skin on the forearms of six healthy male volunteers. Their forearms were then immersed in an agitated water bath thermostatically controlled at 37° C. After 10 minutes immersion, the subjects were exposed to 6 MED's. Barely perceptible erythema was noted on the test areas treated with the 2.5 and 5 percent formulations whereas erythema was easily recognized on test areas treated with the 1 percent formulation. Skin treated with an unspecified commercial lotion showed deep redness and swelling after a waterbath immersion test. It was concluded that the ethyl 4-[bis(hydroxypropyl)] aminobenzoate formulations "showed excellent promise of retaining sunburn protection after bathing."

Based on the available data, the Panel concludes that ethyl 4-[bis(hydroxypropyl)] aminobenzoate is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 1 to 5 percent ethyl 4-[bis(hydroxypropyl)] aminobenzoate: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 1 to 5 percent ethyl 4-[bis(hydroxypropyl)] aminobenzoate: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.)

REFERENCES

(1) OTC Volume 060084.

(2) Kligman, A. M., "The Identification of Contact Allergens by Human Assay," *Journal of Investigative Dermatology*, 47:393-409, 1966.

g. *2-Ethylhexyl 2-cyano-3,3-diphenylacrylate.* The Panel concludes that 2-ethylhexyl 2-cyano-3,3-diphenylacrylate is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

2-Ethylhexyl 2-cyano-3,3-diphenylacrylate is also known as 2-Ethylhexyl-alpha - cyano - beta - phenylcinnamate and is listed in the CFTA Dictionary as UV Absorber 3. The chemical formula is $C_{24}H_{29}O_2N$. It is a nonstaining pale yellow liquid with a specific gravity of 1.0478 (25° C/25° C), a freezing point of −10° C, and a boiling point of 200° C at 0.1 mm. It is insoluble in water, but miscible in methanol, ethanol, ethyl acetate, methyl ethyl ketone, mineral oil, isopropyl myristate, methyl pyrrolidone, and n-vinyl pyrrolidone. It is incorporated in aerosols, alcohol-type solutions, creams, emulsions, and oil formulations.

(1) *Safety.* Clinical use and marketing experience have confirmed that 2-ethylhexyl 2-cyano-3,3-diphenylacrylate is safe in the dosage range used as an OTC sunscreen.

Animal and human toxicological data attest to its safety for human topical application at a concentration of 7 percent (ref. *1*). The oral LD_{50} in Sherman-Wister strain of rats is greater than 64 ml/kg (ref. *2*). The Draize rabbit eye irritancy test revealed no irritation when 0.1 ml of the undiluted material was instilled into the eyes of rabbits (ref. *1*). A primary skin irritation study in six albino rabbits produced minimal effects when the chemical was applied for 72 hours (ref. *1*).

A modified Draize-Shelanski human repeated insult patch test in 52 men and women from 18 to 65 years of age revealed 2-ethylhexyl 2-cyano-3,3-diphenylacrylate not to be a strong irritant or photosenitizer. After applying the chemical to the upper back of the subjects, patch strips were applied for 24 hours. The patches were removed and the test sites were read. No patches were in place for 24 hours, then another application was made to the same site and the patches applied. This was repeated until 10 insults had been applied to the same site. A 10- to 14-day rest period followed. At the end of the rest period a challenge dose and patch were applied to the original site and remained in place for 48 hours. No reactions occurred during the entire induction period. There were two reactions (1+, mild erythema) seen during the challenge. On repeated challenge to these two subjects, only one gave a repeated 1+ reaction. The reactions were considered to be nonspecific irritation, disappearing by 72 hours (ref. *1*). Twenty-five of the above subjects also had phototoxicity testing done simultaneously with the skin irritancy and sensitization testing. Patches were applied as before. At induction, patches 1, 4, 7, and 10, and at the first challenge patch, the treated sites were exposed to a Hanovia Kromeyer Lamp filtered through window glass for 30 seconds. All photopatch tests were negative.

Additional skin and eye irritation tests have been carried out but details were not supplied. Various concentrations of 2-ethylhexyl 2-cyano-3,3-diphenylacrylate (4, 8, and 16 percent) were incorporated in dimethylphthalate or petrolatum as vehicles. The Draize skin irritancy test in 6 rabbits, the Draize eye irritancy test in 6 rabbits, and skin patch tests (unspecified) in 14 humans revealed no effects observable in all cases (ref. *2*).

Marketing data involving 15,000 units sold over a 24-month period revealed no complaints of sensitivity or intolerance to 2-ethylhexyl 2-cyano-3,3-diphenylacrylate (ref. *1*). 2-Ethylhexyl 2-cyano-3,3-diphenylacrylate in lower dosage has been used by a least three cosmetic manufacturers for several years to protect ingredients in cosmetics against UV degradation (ref. *3*).

Based upon the available date, the Panel concludes that 2-ethylhexyl 2-cyano-3,3-diphenylacrylate is a safe sunscreen for OTC use.

(2) *Effectiveness.* There are studies documenting the effectiveness of 2-ethylhexyl 2-cyano-3,3-diphenylacrylate as an OTC sunscreen.

2-Ethylhexyl 2-cyano-3,3-diphenylacrylate in a 7 percent gel base was tested on the backs of 10 fair skin volunteers using a xenon lamp-solar simulator (ref. *1*). The subjects' MED was determined the day before the test. The test product and a 3 percent aminobenzoic acid in alcohol control solution were applied to separate circular sites 1.9 cm in diameter at a rate of 5 μl/cm^2. Irradiated sites were 1.2 cm in diameter. 2-Ethylhexyl 2-cyano-3,3-diphenylacrylate sites were exposed to 3, 4, and 5 MED's while the 3 percent aminobenzoic acid solution was exposed to 4 and 5 MED's. Test sites were read 24 hours later. The mean SPF for the 7 percent 2-ethylhexyl 2-cyano-3,3-diphenylacrylate was 4.2 (standard deviation=0.92). In the same test, 10 percent 2-ethylhexyl 2-cyano-3,3-diphenylacrylate in an oil in water lotion was tested simultaneously. Five μl/cm^2 of the material was applied. The mean SPF for the 10 subjects was 4.6 (standard deviation=0.85) for the 10 percent formulation.

Rossman, Knox, and Freeman (ref. *4*) compared 100 sunscreen products and formulations on the untanned backs of white men. Different test agents were arranged in six vertical strips extending from the waist to the upper scapular areas. Test sites were 36 one-inch squares arranged in six rows of six each. 2-Ethylhexyl 2-cyano-3,3-diphenylacrylate was tested in 10 and 20 percent concentration while 10 percent 3-benzoyl-4-hydroxy-6 methoxy benzenesulfonic acid in a vanishing cream base and 10 percent aminobenzoic acid in the same vanishing cream base were used as control standard sunscreens. The light source was a hot quartz mercury vapor lamp and the test sites were irradiated at a fixed 75 cm distance. The average MED for the light source was 15 seconds (range 10 to 25 seconds).

In 32 subjects, 20 percent 2-ethylhexyl 2-cyano-3,3-diphenylacrylate in a vanishing cream base protected for 9.1 minutes (36 times the average MED) while 10 percent 2-ethylhexyl 2-cyano-3,3-diphenylacrylate in the same vehicle protected 13 subjects for 2.2 minutes (9 MED's). The 10 percent benzophenone formulations on 34 subjects protected in excess of 12 minutes 48 MED's). The 10 percent aminobenzoic acid formulation protected 17 subjects for more than 12 minutes (48 MED's) and in 13 more subjects from 20 to 60 minutes. In general, the protection offered by commercially available products, available in the early 1960's was limited to 2 minutes or less (mean 1.5 minutes or 6 MED's) (ref. *4*).

The 7 percent 2-ethylhexyl 2-cyano-3,3-diphenylacrylate was field tested in Florida, California, Hawaii, the Indian Himalayas, Panama, the Gulf of Mexico, Mt. McKinley, Guadalupe, Israel, France, and England, but the data were not submitted to the Panel.

Based on the available data, the Panel concludes that 2-ethylhexyl 2-cyano-3,3-diphenylacrylate is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 7 to 10 percent 2-ethylhexyl 2-cyano-3,3-diphenylacrylate: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 7 to 10 percent 2-ethylhexyl 2-cyano-3,3-diphenylacrylate: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.)

REFERENCES

(1) OTC Volume 060171.

(2) Technical Report GAF Corporation, Draft of unpublished paper in OTC Volume 060150.

(3) Strobel, A. and J. J. Inserra, "The Use of UV Absorbers in Cosmetic Products," *American Perfumer and Cosmetics,* 83:25-30, 1968.

(4) Rossman, R. E., J. M. Knox and R. G. Freeman, "Acrylonitriles, A New Group of Ultraviolet Absorbing Compounds," *The Journal of Investigative Dermatology,* 39:449-453, 1962.

h. *Ethylhexyl p-methoxycinnamate.* The Panel concludes that ethylhexyl *p*-methoxycinnamate is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

Ethylhexyl *p*-methoxycinnamate is also known as 2-methoxycinnamic acid 2-ethylhexyl ester.

Ethylhexyl *p*-methoxycinnamate is a practically odorless, pale yellow, slightly oily liquid with a molecular weight of 290, a boiling point at 3 mm of 198-200° C, and a specific gravity of 1.01-1.02. The ingredient is miscible in alcohols, propylene glycol monomyristate, and various oils, but insoluble in water. It is "stable to light and remains essentially unchanged on exposure to moderate heat." It is often formulated with other sunscreens. Absorbance in pure ethanol is 84 percent at 2 percent, 94 percent at 3 percent, and 98.8 percent at 5 percent concentrations.

(1) *Safety.* Clinical use and marketing experience have confirmed that ethylhexyl *p*-methoxycinnamate is safe in the dosage range used as an OTC sunscreen.

Extensive animal toxicological testing and widespread use attest to its safety for application to humans.

Animal toxicity data for ethylhexyl *p*-methoxycinnamate indicated that the LD_{50} exceeds 8 g/kg in mice. The Draize rabbit eye irritancy test revealed little irritation when 0.1 ml of the pure chemical was instilled into the rabbit's eyes (ref. *1*). The chemical was considered practically nonirritating to the eye. To determine epicutaneous tolerance and possible sensitization in the guinea pig, four guinea pigs received either 0.05 ml of the undiluted chemical unjected intracutaneously on 5 subsequent days or 0.025 ml of a 50 percent acetone solution applied topically daily for 3 weeks to 2 cm^2 areas on their shaved sides. The amount injected intracutaneously or topically administered was approximately 500 mg/kg. There was no allergic sensitization by either topical or intradermal route (ref. *1*).

Human safety studies have been reported. Tests using a 5 percent concentration and performed on 50 subjects, approximately one-third of whom had extremely sensitive skin, including some with eczema and sensitization, demonstrated that the product is very well tolerated on the skin. Patch tests using an unspecified concentration on 27 men and 22 women, 18 to 60 years of age, produced no positive results after 24 and 48 hours, thereby leading to the conclusion that the product would not act as a primary irritant or would not act, under longer use, as an allergenic substance. Photosensitization tests "showed that the product did not provoke photosensitization" (ref. *1*).

In a line of products where the ingredient was combined with a benzophenone, over 8 million units were sold, 38 complaints of skin irritation were received by the manufacturer,

but not a single case of skin irritation could be clearly related to the use of the products. Over 209 tons of ethylhexyl *p*-methoxycinnamate were sold in 27 countries in 2 years (ref. *1*).

A human Draize test was performed in 54 men and women. Ethylhexyl *p*-methoxycinnamate 7.5 percent in petrolatum was applied to the deltoid area alternately under occlusion for 48 hours for 11 applications. Two weeks later the challege dose was reapplied. No reactions occurred to the ethylhexyl *p*-methoxycinnamate (ref. *2*). No adverse reports were found in the literature to the use of topical ethylhexyl *p*-methoxycinnamate.

Based on the available data, the Panel concludes that ethylhexyl *p*-methoxycinnamate is a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are studies documenting the effectiveness of ethylhexyl *p*-methoxycinnamate as an OTC sunscreen.

Efficacy data reviewed by the Panel included in vitro studies of the absorption, solubility, and stability properties of ethylhexyl *p*-methoxycinnamate (ref. *1*). Absorption at 308 nm is 84 to 90 percent for 2.0 to 2.5 percent concentrations.

The ingredient absorbs UV light in the 290 to 320 nm range, with the maxima at 308 to 310 nm. Like many sunscreens, the percent of absorption depends upon the concentration. As noted above, absorption in pure ethanol is 84 percent at 2 percent, 94 percent at 3 percent, and 98.8 percent at 5 percent concentrations. It is often formulated with other sunscreens (ref. *1*).

In a series of five well-designed, controlled, randomized, singleblind laboratory and field trials, ethylhexyl *p*-methoxycinnamate alone and in combination performed well. Each subject had his/her MED and skin reflectance measured. In outdoor tests the solar energy flux was measured. In the laboratory test, 2.5 to 5.0 percent ethylhexyl *p*-methoxycinnamate in combination with other sunscreens was applied to the back of 12 men and women. Each subject had four sites; each site had three rows; and each row had five (2.5 X 2.5 cm) windows. Each site had only one product applied to a row, an untreated control row, and a 5 percent PABA in ethanol control row. A hot-quartz mercury lamp delivered 3, 5, 9, 12, and 15 MED's to each subject. Readings were made about 24 hours later. All formulations containing ethylhexyl *p*-methoxycinnamate performed well (ref. *3*). An experiment in 8 men compared two products, an untreated control, and a 5 percent PABA in ethanol control on the back of each man. Three products containing ethylhexyl *p*-methoxycinnamate were tested. The men sunbathed passively from 11 a.m. to 1 p.m. in the April sun in Arizona. The formulations had as SPF value of 2.8 to 10.1 (ref. *1*). The next outdoor experiment involved testing 12 products, 10 containing 2.5 to 5 percent ethylhexyl *p*-methoxycinnamate on 11 men exposed to 30, 60, 90, and 120 minutes sunlight from 11 a.m. to 1 p.m. Each man had three formulations and an untreated control applied. All formulations performed well. One product containing 4 percent ethylhexyl *p*-methoxycinnamate alone had an SPF value of 2.1 after 120 minutes exposure, while an aerosol product containing 2.5 percent ethylhexyl *p*-methoxycinnamate had an SPF value of 2.9 after 120 minutes exposure. The third field experiment tested three products in six subjects after exercising 0.5 hour then exposed to the noon sun for 30, 60, 90, and 120 minutes. All formulations performed well. The fourth experiment tested three products under conditions simulating normal usage like exercise (30 minutes), walking (30 minutes), sunbathing passively (60 minutes), and two swims. Each product was tested in nine subjects along with the 5 percent PABA control. The mean SPF values were 9.1, 5.9, and 9.3. The last experiment in the series compared the same three formulations in six subjects after a 15-minute swim followed by sun exposure to 90 minutes. Each subject tested two products and had an untreated control site. The mean SPF values were 4.2, 1.04, and 4.4 or greater (ref. *3*). Evaluation of the tanning response to two products containing 4.0 and 2.5 percent ethylhexyl *p*-methoxycinnamate exhibited a pigmentary response on clinical and skin reflectometer evaluation, but it was less than the untreated control sites. Another similar series of outdoor testing was performed in Australia, with similar results (ref. *1*).

Several partially controlled studies of formulations containing ethylhexyl *p*-methoxycinnamate were submitted by the manufacturer (ref. *1*).

Based on the available data, the Panel concludes that ethylhexyl *p*-methoxycinnamate is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 2.0 to 7.5 percent ethylhexyl *p*-methoxycinnamate: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 2.0 to 7.5 percent ethylhexyl *p*-methoxycinnamate: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.)

REFERENCES

(1) OTC Volume 060083.
(2) OTC Volume 060110.
(3) Pathak, M. A., T. B. Fitzpatrick and J. A. Parrish, "Evaluation of Piz Buin (Greiter, AG) Sunscreen Formulations under Laboratory and Field Conditions," Draft of unpublished paper in OTC Volume 060083.

i. *2-Ethylhexyl salicylate.* The Panel concludes that 2-ethylhexyl salicylate is safe and effective for OTC use as a suncreen as specified in the dosage section discussed below.

2-Ethylhexyl salicylate is also known as octyl salicylate.

Its absorbance is between 280 and 320 nm with a maximum absorbance wide peak at about 300 nm. It is an odorless, clear, white-to-slightly yellowish liquid with a molecular weight of 250.33, a specific gravity of 1.013 to 1.022, and a boiling point of 144° C at 1mm. It is completely soluble in mineral oil and two parts of 95 percent ethanol. It has been used as a sunscreen since 1938 and is incorporated in emulsion, oil, ointment, and paste formulations.

(1) *Safety.* Clinical and marketing experience have confirmed that 2-ethylhexyl salicylate is safe in the dosage range used as an OTC sunscreen.

Animal and human toxicological data and long use attest to its safety for human topical application.

The Draize rabbit eye irritation test revealed it to be a nonirritant when 0.1 ml 2-ethylhexyl salicylate was instilled into the eyes of nine albino rabbits. In three rabbits the eyes were not washed, while the other rabbits and the eyes washed in 2 or 4 seconds with 20 ml of lukewarm water. Evaluations were made at 1 hour, 24 hours, and 7 days. No damage was observed of the cornea or iris, while the conjuctiva had a mild reaction (ref. *1*).

The oral LD_{50} in Sherman strain albino rats was found to be 4.8 ± 0.3 g/kg (ref. *2*). U.S. Army Military Specification MIL-S-11262E lists 2-ethylhexyl salicylate among the approved suncreening agents, with a maximum amount of 5 parts by weight approved for toxicity for use with the basic cream formulation specified therein (ref. *2*).

Patch tests were performed on 10 randomly selected human subjects. A 5 percent 2-ethylhexyl salicylate preparation in mineral oil was applied to the inner surface of the upper right

arm of each subject. The patches were removed after the test material had been in contact with the skin for 24 hours. No reactions were observed at that time or after 72 hours. After a 7-day test period the above-described procedure was repeated, and again no reactions were noted either upon removal of the patches or after 72 hours. It was concluded that the test material did not contain primary and/or secondary skin irritants (ref. *2*).

In a human Draize repeated-insult patch test, no primary irritation, "fatiguing," or sensitization reactions were observed when 0.5 ml of 2-ethylhexy salicylate was applied under occlusion to the intact skin of 25 subjects for 10 applications at 48-hour intervals, with the 11th application 2 weeks later (ref. *1*).

The phototoxicity potential of 5 percent 2-ethylhexyl salicylate in ethanol was tested in 10 subjects. The solution was applied to normal skin sites and to cellophane tape-stripped sites. The sites were irradiated after either a 1-hour contact (stripped sites) or 24-hour contact (normal skin). All subjects had a 3 percent demeclocycline hydrochloride solution positive control. The sites were irradiated from 322 to 410 nm with a xenon arc lamp system. All subjects had a positive phototoxicity response to the demeclocycline, but none responded to the 2-ethylhexyl salicylate (ref. *1*).

Over a 10-year period, about 55,000 pounds of 2-ethylhexyl salicylate were sold each year. Several companies market products containing it, but the only data were supplied to the Panel by the manufacturer of the basic chemical (ref. *2*). One product manufacturer indicated that it had produced over a million units in 6 years and had had no complaints or reports of dermatitis, skin irritation, allergies, or sensitivity to the two products containing 2-ethylhexyl salicylate (ref. *2*). Another product manufacturer wrote that before marketing its product in 1946, it had conducted patch tests on 50 persons, with favorable results (ref. *2*). The Panel found no adverse reports to the topical use of 2-ethylhexyl salicylate in the literature.

Based on the available data, the Panel concludes that 2-ethylhexyl salicylate is a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are no controlled studies documenting the effectiveness of 2-ethylhexyl salicylate as a sunscreen. However, it is the Panel's conclusion that clinical use and marketing experience have confirmed effectiveness.

The effectiveness of 2-ethylhexyl salicylate as a sunscreen is demonstrated by its in vitro UV light absorption characteristics. The ingredient absorbs UV radiation between 280 and 320 nm, with maximal absorbance at 305 nm. Changing the concentration and vehicle changes the percentage of absorption. For example (refs. *1* and *3*):

Cream concentration (percent)	Erythema transmission (percent)
	290 to 310 nm
3.0	0.3
4.0	0.4
	290 to 320 nm
9.5	4.0
7.0	8.0
5.2	15.0

To meet the special requirements of a sunscreen, a compound must be able to resonate between alternate ionic forms. This ionization change must require an energy quantum within the UV region. This corresponds to electronic transition (ionization) energies of 91.4 to 99.4 kilocalories per gram mole (kc al/g mol) for compounds with absorption maxima between 290 and 315 nm, the sunburn erythema range. Few classes of compounds satisfy this basic requirement. The salicylates, cinnamates, *p*-aminobenzoates, and *p*-dialkyl aminobenzoates are examples of aromatic compounds meeting this basic requirement, and they have performed as effective sunscreens in use (ref. *4*).

The Quartermaster Corps of the U.S. Army approved 5-percent-by-weight 2-ethylhexyl salicylate as a sunburn preventative (U.S. Specification MIL-S-11 262 E, 15 March 1972). It was first approved for military procurement in 1951 (ref. *1*). The efficacy data from the Army tests were not available to the Panel.

Testimonial letters from six cosmetic manufacturers stated that they found 2-ethylhexyl salicylate to be an effective sunscreen and that it was chosen for use in their products because of its efficacy and desirable characteristics (ref. *3*). No data were given. Being one of the older sunscreens, such record-keeping was not necessary.

Based on the available data, the Panel concludes that 2-ethylhexyl salicylate is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 3 to 5 percent 2-ethylhexyl salicylate: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 3 to 5 percent 2-ethylhexyl salicylate: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.)

REFERENCES

(1) OTC Volume 060151.
(2) OTC Volume 060088.
(3) OTC Volume 060006.
(4) Kreps, S. I., "The Structure, Function and Formulation of Topical Sunscreens. I. Theoretical Considerations," *Journal of the Society of Cosmetic Chemists*, 14:625-630, 1963.

J. *Glyceryl aminobenzoate.* The Panel concludes that glyceryl aminobenzoate is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

Glyceryl aminobenzoate is also known as glyceryl *p*-aminobenzoate.

Glyceryl aminobenzoate is soluble in ethyl and isopropyl alcohol and glycerine and propylene glycol; but it is insoluble in water, mineral oil, and peanut oil. Glyceryl aminobenzoate can be incorporated into aerosols, emulsions, hydroalcoholic solutions, and lipstick formulations. Its absorbance is between 264 and 315 nm, with maximum absorbance at 295 nm (ref. *1*.).

(1) *Safety.* Clinical use and marketing experience have confirmed that glyceryl aminobenzoate is safe in the dosage range used as an OTC sunscreen.

Animal and human toxicological data attest to its safety for human topical application in 3 percent concentration (refs. *2* and *3*). The oral LD_{50} is 17.3 ml/kg in rats (ref. *4*).

A 20-day acute toxicity test of a preparation containing 20 percent glyceryl aminobenzoate in a base solution was performed using New Zealand strain male rabbits with abraded and intact skin. A shaved area of skin approximately 10 percent of the body surface was inuncted daily with 1, 2, and 4 g/kg of body weight, with control animals receiving 4 g/kg of the solvent only. No toxic manifestations were observed in any of the test animals. There were no abnormal, irritative, deteriorative, or coagulative effects on the intact or abraded skin (ref. *1*).

Toxicological studies employing a marketed sunscreen lotion containing 3 percent glyceryl aminobenzoate and 3 percent amyl *p*-dimethyl- aminobenzoate indicated that the product was nontoxic to mice and rats when administered in a single oral dose of 50 ml/kg (ref. *2*). For 32 consecutive days, 0.2 ml of lotion was applied to the shaved intrascapular area of albino rats without any dermal toxicity being noted in

any of the eight animals so treated (ref. *2*).

Using two sunscreen lotions each containing 3.15 percent glyceryl- aminobenzoate and 3.15 percent amyl *p*-dimethylaminobenzoate, acute eye irritation studies were performed on 12 New Zealand albino rabbits. Two drops of one lotion were instilled into the left eye of each rabbit, while the contralateral eyes were treated with an equal amount of the other lotion. Two minutes after administration, both eyes of six rabbits were rinsed with 20 ml of lukewarm water. One hour later the rinsed eyes were stained with one drop of 2 percent fluorescein for observation under UV light. Twenty-four hours after instillation, the unrinsed eyes were treated in the same manner. The eyes were scored for toxicity (ref. *5*). No toxicity was noted in any of the rinsed and unrinsed eyes, although mild to moderate discomfort characterized by repeated blinking was observed to last from 15 to 30 seconds in both the rinsed and unrinsed eyes. Slight conjunctival irritation was observed immediately following instillation in both groups; the condition subsided within 1 hour following rinsing and after 24 hours postinstillation in the unrinsed group (ref. *2*).

An evaluation was made as to the primary irritation potential of the two lotions described in the previous paragraph by applying 0.5 ml of the preparations to abraded and intact (occluded and unoccluded) rabbit skin. Twenty-four hours prior to the onset of the study, the dorsal area of 12 adult female New Zealand albino rabbits was shaved free of hair. The following day the shaved area was divided into 4 quadrants of no less than 4 square inches each. Two of the test sites on each rabbit were abraded by making four epidermal incisions through the stratum corneum with a sterile needle in a "tic-tac-toe" pattern. The abraded and intact sites were diagonally located from one another. Each of the two lotions was applied to six rabbits by using a glass disposable syringe under to gauze patch secured by adhesive tape. The test sites for three rabbits in each group were occluded. After 24 hours contact time the patches were removed and the resulting reactions were graded through 72 hours in accordance with a described method (ref. *5*). Variations in the reactions noted for the two preparations were minimal. Essentially, there was slight erythema (value of 1 or less) noted at 24 hours in the rabbits of the abraded-occluded and intact-occluded groups. Little or no irritation was noted at 48 hours and was absent at 72 hours. Likewise, in rabbits of the abraded-unoccluded and intact-unoccluded groups slight erythema (value of 1 or less) was noted at 24 hours and was reduced to very slight at 48 hours, with none noted at 72 hours. There was no edema formation noted in any of the 12 test animals (ref. *2*).

Another evaluation was made as to the primary irritation potential of two preparations, each containing 3.15 percent glyceryl aminobenzoate and 3.15 percent amyl *p*-dimethyl- aminobenzoate. Twelve adult female New Zealand albino rabbits were prepared in the same manner as described above. In the case, 0.2 ml instead of 0.5 ml of the test preparation was applied to each test site. The results were essentially similar to those noted in the study discussed above (ref. *2*).

Each ingredient in the above-described sunscreen preparation was evaluated for potential dermal irritation by combining the ingredient with a suitable vehicle, i.e., petroleum, methanol, or distilled water and applying it topically to rabbit skin for 7 consecutive days. Twenty-four hours prior to the onset of the study, the dorsal region in each of 15 rabbits was shaved free of hair and divided into 4 quadrants of no less than 25 cm^2 each. Three times daily, 0.2 ml of each test material was placed onto a test quadrant in each of three rabbits by using a glass disposable syringe and then gently inuncted onto the skin with a clean stainless steel spatula. The test sites were observed regularly for irritation, physical appearance, and general behavior, with dermal reactions being graded (ref. *5*). Glyceryl aminobenzoate (3 percent) elicited no untoward dermal reactions, while amyl *p*-dimethylaminobenzoate (3 percent) elicited very slight erythema. Slight to moderate erythema was noted on test sites treated with several other ingredients (ref. *2*).

The above-described sunscreen was tested in the rabbit ear for comedogenicity, along with two other sunscreens, one containing 10 percent sulisobenzone and the other containing 3 percent dioxybenzone and 3 percent oxybenzone. It was reported that the preparation containing 3 percent glyceryl aminobenzoate and 3 percent amyl *p*-dimethylaminobenzoate showed marginal hyperkeratosis and produced small comedones, whereas the other two preparations produced huge comedones. No specifics were given as to the testing procedure (ref. *6*).

Controlled human studies of the ralative irritancy potential of eight preparations were performed using the method outlined by Phillips et al. (ref. *7*). The materials to be tested were applied daily for 21 days to Webril patches and attached to the skin with an occlusive tape. Each day the patches were removed, the sites examined and scored, and fresh patches reapplied. It was reported that none of the test materials were rated as significant irritants, with only a few readings indication erythema over the entire test site. All the remaining responses were equivocal, with erythema present over part, but not the entire, test site.

Fifty human subjects were selected on the basis of their general good health and absence of any skin diseases which might be confused with skin reactions form the test material and were treated with glyceryl aminobenzoate to determine whether this ingredient was capable or irritating human skin under controlled test conditions. Sites on the upper arm of each subject were designated to receive a series of 16 applications, each of 24 hours' duration, of the test material. A lintine pad treated with the test material was placed on its predesignated site, covered, and sealed with overlapping strips of an occlusive tape. At the end of 24 hours the seal was broken and the patch was removed. The test sites were examined, and any gross changes were graded on a scale of from 1 to 4, with the absence of any visible changes being assigned a 0 value. After the removal of the patch, the test sites were rested for 24 hours, except on weekends when the rest period was extended to 48 hours. Prior to reapplication the test sites were examined again to determine whether any changes had occured. The test material was reapplied to the same site if the contact site manifested no changes. If significant irritation (2+ or more) was observed, the investigator could at his option rest the subject or apply the test material to a new site for the next contact period. After the fifteenth application the subjects were rested for 2 weeks before being challenged by applying the test material under occlusion for 24 hours to the previously used sites. Following removal of the patch, the test sites were examined immediately and after 24 and 48 hours. In no instance were visible changes noted signifying reaction to injury. It was concluded by the investigator that "under the test conditions, glyceryl para-aminobenzoate was not capable of eliciting visible skin changes consistent with criteria being characteristic of a primary irritant, fatiguing agent or a sensitizer" (ref. *8*). On the basis of the test results for 50 subjects, the investigator predicted with 95 percent certainty that at least 92.89 percent of the general population will not be sensitized by this material.

Maximization tests (ref. *9*) to determine the contact-sensitizing potential of a sunscreen product containing 3 percent glyceryl aminobenzoate and 3 percent amyl *p*-dimethylaminobenzoate were performed on 25 healthy adults male volunteers. The test mate-

rial was applied under occlusion to the same sites on the volar forearms of all subjects for 5 alternate 48-hour periods. The test sites were pretested for 24 hours with 5 percent aqueous sodium lauryl sulfate under occlusion. After a 10-day rest period, challenge patches were applied under occlusion to new sites for 48 hours, but were preceded by 1-hour applications of 10 percent sodium lauryl sulfate under occlusion. It was indicated that the challenge sites were read immediately upon removal of the patch and 24 hours thereafter. However, individual subject data indicated that the challenge sites were read after 48 and 72 hours. It was reported that there were no instances of contact-sensitization and that it was unlikely that the test material would present a danger of contact-sensitization in normal, intended use (ref. *10*).

The phototoxicity and photocontact allergenicity potential of a sunscreen formulation containing 3 percent glyceryl aminobenzoate and 3 percent amyl *p*-dimethylaminobenzoate were evaluated in 35 healthy adult male volunteers (ref. *11*).

To test for phototoxicity, 0.2 ml of the test materials was applied occlusively to duplicate 2 cm^2 normal and stripped skin sites on the upper backs of the subjects. Each stripped site received 6 MED's of xenon solar simulating radiation filtered through window glass. The normal site was similarly exposed to the same dose of long-UV radiation after 24 hours of occlusion. Observations were made a 1, 3, and 24 hours after irradiation. To test for photocontact allergenicity , 0.2 ml of the test materials was applied to one 2-inch square of stripped skin on the upper backs of the subjects, and the sites were then exposed to 3 MED's of xenon solarsimulating radiation and occluded. This procedure was repeated five times at intervals of 48 hours. Ten days after the final induction exposure, the subjects were challenged by applying 0.2 ml of the test materials to both normal and stripped skin sites, followed by exposure to 3 MED's of xenon solarsimulating radiation filtered through window glass. The sites were occluded, and observations were make at 24, 48, and 72 hours after irradiation. The results of the tests revealed no instances of phototoxicity or photocontact allergenicity among any of the subjects (ref. *11*).

Test were performed using 10 adult subjects for the purpose of discriminating among four formulations reported to be equally effective in providing protection against sunburn in the immediate and post-immersion assays. One formulation contained 3 percent glyceryl aminobenzoate and 3 percent amyl *p*-dimethylaminobenzoate; the formulations for the three remaining products were not provided. One-inch square Webril patches were loaded with 25 percent liquor carbonis detergents (LCD) and occluded to four sites on the forearm skin of each patient for 1 hour, after which the site was cleaned with mineral oil before the application of thin film of the test formulation. Each site then received 6 minutes of long-UV radiation. A control LCD site was irradiated on each subject without the application of any test formulation. The test sites were examined 24 hours later, and any gross changes were graded on a scale of 1 to 4, with the absence of any visible changes being assigned a 0 value. The preparation containing 3 percent glyceryl aminobenzoate and 3 percent amyl *p*-dimethylaminobenzoate was one of two formulations found to almost completely block the phototoxic response. It was concluded that these two formulations provide excellent protection in the phototoxic model, permitting the inference to be made that they efficiently absorb long-UV radiation in the spectral range of 320 to 400 nm and that "these two formulations therefore may be regarded as broad-spectrum sunscreens, providing excellent protection against sunburning radiation as well as longer rays which activate photosensitization reactions" (ref. *12*).

The photosensitivity, irritancy, and allergic sensitization potential of a sunscreen formulation containing 3 percent glyceryl aminobenzoate and 3 percent amyl *p*-dimethylaminobenzoate was evaluated in 15 healthy female and 25 healthy male subjects. The test material was applied daily for 30 days to the face and upper trunk of each subject, after which the subjects were irradiated with 3 MED's from a bank of fluorescent lamps. Individual subject data were not provided, but it was reported that 12 subjects (4 females and 8 males) complained of very mild itching around the eyes but that there were no visible signs of irritation in these subjects. It was further reported that there were no instances of photosensitivity of allergenicity in this test (ref. *13*).

Based on the extensive animal and human toxicological data, the Panel concludes that glyceryl aminobenzoate is a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are studies documenting the effectiveness of glyceryl aminobenzoate as an OTC sunscreen.

Doubleblind studies were performed comparing nine formulations for sunscreening efficacy in 10 healthy adult white males. The fomulations were applied in random fashion to 2 cm^2 on the medial forearm skin surface at the rate of 60 ul/cm^2. A 1,600 watt xenon lamp was used to provide solar-simulating radiation. One study evaluated protection immediately after application and involved each site immediately after inunction receiving 10 MED's individually determined beforehand for each subject. The skin was evaluated 24 hours later, with any reactions being graded on a 4-point scale (0—negative, 1—mild response, 2—moderate redness, and 3—sharp redness). In the second study, postimmersion protection was evaluated. Previously irradiated sites were avoided. The subjects' forearms were immersed for 10 minutes in a water bath at room temperature 2 hours after application of the test formulations. Following the immersion, 10 MED's were administered, and the skin reactions were evaluated 24 hours later and graded using the above-described scale. In both studies, it was concluded that a sunscreen formulation containing 3 percent glyceryl aminobenzoate and 3 percent amyl *p*-dimethylamino- benzoate provided excellent protection immediately after application (0.45 average value) and postimmersion (0.55 average value). Moderate protection was provided by a formulation containing unspecified concentrations of glycerly aminobenzoate and amyl *p*-dimethyl- aminobenzoate immediately after application (1.30 average value) and postimmersion (1.55 average value). Poor protection was provided by preparations containing unspecified concentrations of the single active ingredients glycerly aminobenzoate and amyl *p*-dimethylaminobenzoate immediately after application (1.90 and 2.50 average values, respectively) and postimmersion (2.20 and 2.50 average values, respectively) (ref. *14*).

Double-blind studies were performed on a series of single active ingredient and combination sunscreen preparations in a water-resistant emollient cream base using natural sunlight and ocean swimming. For the purposes of the present review, the Panel only considered the results for those formulations containing 3 percent glyceryl aminobenzoate and 3 percent amyl *p*-dimethylaminobenzoate alone and in combination and for a marketed sunscreen containing 5 percent aminobenzoate. Opaque white tape was used to mark out a series of 7.5 cm x 7.5 cm approximately 6 cm below the base of the neck and centered between the shoulder blades on the backs of 30 untanned light-skinned Caucasian volunteers. Using a randomized medication schedule, each test site was treated with 0.05 ml of a test formulation. The subjects were simultaneously exposed to 2 hours of sunlight (10 am. to noon on a clear day in Miami, Fla., in August 1971). Following this exposure, the subjects swam for 10 minutes while totally immersed in the ocean. Immediately thereafter they were

again exposed for 2 more hours until the 2 p.m. conclusion. At this point the tape was removed, the test sites photographed, and instructions were given to the subjects not to apply anything other than water to the test sites. Evaluations were made and photographs were taken of the test sites 24 and 72 hours following exposure. At each point the reactions were graded (0—no change, 1—mild erythema, 2—moderate erythema, 3—marked erythema, and 4—marked erythema with edema). Complete data for only 22 subjects were considered in the statistical evaluation, as 3 subjects failed to return for the final evaluation and 5 subjects had an uneven suntanning response. The results for the formulations under consideration in this review were as follows:

Means and standard deviations of severity gradings

	24-hour evaluation		72-hour evaluation	
	Mean value	Standard deviation	Mean value	Standard deviation
1. 3 pct glyceryl aminobenzoate	2.1727	0.0917	1.6818	0.1169
2. 3 pct amyl *p*-dimethylaminobenzoate	2.3545	.0789	1.8728	.0893
3. 3 pct glyceryl aminobenzoate, 3 pct amyl *p*-dimethylaminobenzoate	2.0227	.0696	1.7818	.1084
4. 3 pct glyceryl aminobenzoate, 3 pct amyl *p*-dimethylaminobenzoate	2.2045	.0710	1.8000	.1509
5. 5 pct aminobenzoate	3.0727	.0838	2.4955	.0862

The two combination formulations listed above differed only in a single base ingredient. Both of these formulations and the preparation containing glyceryl aminobenzoate of the formulations tested were found to provide the maximum absorption in the critical erythema range (290 to 320 nm) and maximum resistance to water wash-off if one excludes a similar formulation which also contained 2.5 percent 2-hydroxy-4-methoxy-benzophenone and which provided the lowest mean values at both the 24- and 72-hour evaluation periods. The latter formulation, however, produced sensitivity reactions traced and attributed to the benzophenone component in followup human irritation studies (ref. *15*).

Based on the extensive data, the Panel concludes that glyceryl aminobenzoate is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 2 to 3 percent glyceryl aminobenzoate: Adult and children over 2 years of age topical dosage is liberal application before sunexposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 2 to 3 percent glyceryl aminobenzoate: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.)

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(2) OTC Volume 060103.
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(14) "Clinical Studies, Protection Immediately After Application and Post Immersion," Draft of unpublished paper in OTC Volume 060104.
(15) "Efficacy—Clinical Studies," Draft of unpublished paper in OTC Volume 060104.

k. *Homosalate.* The Panel concludes that homosalate is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

Homosalate is also known as 3,3,5-trimethylcyclohexyl salicylate, and was formerly called homomenthyl salicylate.

Homosalate is an oily, colorless-to-faint-yellow liquid which does not precipitate when cooled at 15° C for 12 hours (ref. *1*).

(1) *Safety.* Clinical use and marketing experience have confirmed that homosalate is safe in the dosage range used as an OTC sunscreen.

Animal and human toxicological data attest to its safety for human topical use.

The acute oral LD_{50} in rats for homosalate has been determined to be greater than 8.0 ml/kg of body weight (ref. *2*). The acute oral LD_{50} in rats for a sunscreen lotion containing 8 percent homosalate was found to be greater than 10,000 μl/kg of body weight (ref. *3*). Two rabbit eye irritation studies of a sunscreen lotion and oil containing 8 and 9 percent homosalate, respectively, demonstrated no deleterious effects when 0.1 ml of the undiluted test material was instilled into the conjunctival sac of the right eye of nine albino rabbits, with the left eye serving as a control (ref. *4*).

Homosalate was applied full-strength to the arms, abdomens, and faces of five subjects without any reported untoward effects. An ointment containing unspecified amounts of the sunscreens homosalate and ethyl aminobenzoate was applied to 22 subjects without any reported cases of sensitivity (ref. *5*).

In 1964, the military approved, on the basis of toxicolgical considerations, a maximum of 8 percent homosalate for sunburn preventative preparations in a cream paste formulation (ref. *6*).

Patch tests of 25 human subjects (9 males and 16 females) treated with a 6 percent homosalate sunscreen oil for 48 hours demonstrated that the test material was not a primary irritant, as no reactions were noted at 30 and 60 minutes and at 24 hours following removal of the patches from the inner aspect of each subject's upper left arm (ref. *4*). Thereafter, these 25 subjects applied the preparation to an area approximately 1 inch in diameter on the skin of the dorsal surface or outer aspect of the left forearm daily for 3 weeks, with subsequent exposure to sunlight. Weekly evaluations of the application site for each patient revealed no evidence of reaction. Following a 2-week rest period after cessation of use, challenge patches saturated with the test material were applied to the upper left arm of each patient.

After 48 hours of skin contact the challenge patches were removed. Readings recorded at 30 and 60 minutes and at 24 hours afterwards showed no evidence of reaction. It was concluded that the test material was not a primary irritant or skin sensitizer (ref. 7).

Two Shelanski Repeated Insult Patch Tests were performed on each of 50 human volunteers. In one test each subject received 15 applications of a sunscreen lotion containing 8 percent homosalate, while in the other [illegible]st each subject received 15 applica[illegible]s of an aerosol spray preparation [illegible]ning 4 percent homosalate. In [illegible]ts no reactions were observed, [illegible]it was concluded that the test materials were not a primary irritant, sensitizing agent, or a fatiguing agent and may be considered safe for contact with human skin (ref. 8).

The safety of a sunscreen lotion containing 8 percent homosalate was evaluated by the Draize patch test method in a study involving 200 male and female subjects. A patch containing the test material was applied to the skin of the arm or back of each subject. After 24 hours of contact the patch was removed, and any reactions were graded and recorded. Following a 24-hour rest period a second patch application was made. This procedure was repeated until each subject experienced 10 exposures. A challenge dose was applied thereafter following a 14-day rest period. Among the 200 subjects one isolated reaction occurred in one subject at the ninth primary application. This reaction consisted of a well-defined erythema, but did not recur. It was concluded (ref. 9) that the product was not a primary irritant, a fatiguing agent, or a sensitizing agent.

The safety of a sunscreen cream containing 4 percent homosalate was evaluated by the Draize patch test method in 200 male and female subjects. Six of the 200 subjects experienced slight to moderate erythema on 1 to 3 occasions between the third and ninth primary applications. It was concluded (ref. 10) that the product possessed a mild fatiguing action, but was neither a primary irritant nor a sensitizing agent.

The safety of a sunscreen oil containing 9 percent homosalate was evaluated by the Draize patch test method in 200 male and female subjects. Two of the 200 subjects experienced slight to moderate erythema on two occasions between the fourth and tenth primary applications. It was (ref. 11) concluded that the product possesses a mild fatiguing effect, but is neither a primary irritant nor a sensitizing agent.

Salicylate excretion tests were performed in six subjects to determine whether homosalate as contained in a sunscreen lotion is absorbed through the unbroken skin. Five g of the test material (8 percent homosalate) were applied by inunction to each arm, including fingers and forearm to elbow, and rubbed in for a period of 5 minutes. Urinary salicylate excreted by each patient during the following 24 hours ranged from 4.3 to 17.7 mg. The testing laboratory reported, however that experience has shown the "values of less than 20 milligrams salicylate in 24 hours can be obtained with control urines in subjects who are in no manner exposed to salicylate" (ref. 1). It was concluded that the product is not absorbed through the unbroken skin (ref. 12).

Marketing experience for seven marketed sunscreen products containing between 4 and 9 percent homosalate indicated the ratio of minor untoward effect complaints to the number of units distributed between 1963 and 1972 ranged from 1:294,814 to 4:919,892. No complaints of serious untoward effects were reported, that is, complaints alleging serious illness or injury, prolonged illness or injury, or hospitalization. Of the 316 total complaints of minor untoward effects three had been confirmed; that is, the complaint had been verified by appropriate medical procedures (ref. 13).

Based upon the available data, the Panel concludes that homosalate is safe for use as an OTC sunscreen.

(2) *Effectiveness.* There are studies documenting the effectiveness of homosalate as a sunscreen.

Absorbance occurs from 295 to 315 nm, with a maximum at 306 nm (ref. 14). Depending upon the vehicle, 4 to 15 percent homosalate is effective. An 8 percent (W/V) lotion acts as a permits-suntanning sunscreen agent, while a 15 percent lotion will prevent suntanning and acts as a prevents-sunburn sunscreen agent. Homosalate can be formulated as an aerosol spray, oil, emulsified cream, ointment, and foam.

Homosalate demonstrates very high absorption at 297 nm, the maximum of the erythema action spectrum. The extinction coefficient as determined by the Lambert-Beer Law at 297 nm includes the density readying from the Beckman spectrophotometer, the concentration, and the thickness of the absorbing medium as variables, and was found by Geise to be 6,720 at a concentration of 2.5×10^{-4} mol/liter, whereas that for aminobenzoate was 21,750 at a concentration of 2×10^{-4} mol/liter (ref. 15).

A sunburn curve was determined and plotted by Kumler and Daniels by multiplying the ordinates of the erythema curve by those of the sunlight distribution curve. Such a curve shows graphically the wavelengths which should be screened out to prevent sunburn. The peak of this sunburn curve is at 308 nm. The greater the extinction coefficient at this wavelength the greater will be the effectiveness of the compound as a sunburn preventive. Aminobenzoate was found to have approximately four times the screening power of homosalate (ref. 16).

Sunburn and suntan curves were established and plotted by Vicklund by multiplying the intensity of radiation of each wavelength by its effectiveness in producing sunburn and suntan, with the height of the curve at any wavelength indicating the ability of such radiation to cause erythema or tan. The development of a deep, bronze, long-lasting tan requires the formation of melanin pigmentation stimulated by the erythema-producing rays of the energy range 290 to 320 nm and the thickening of the stratum corneum of the skin effected by the erythema-producing shorter wavelengths. Longer wavelengths only darken the preformed melanin, and the thickening of the stratum corneum provides natural protection from sunburn, not tanning. A comparison of the UV sunscreen curve of homosalate with the sunburn and suntan curves indicates that homosalate protects against, but does not provide total absorption of, the erythema-producing rays of the UV spectrum (ref. 17).

Kreps found that a 2 percent glyceryl aminobenzoate lotion and an 8 percent homosalate lotion transmit 7.0 and 7.5 percent incident E-viton units (unit of erythema flux), respectively, which in both cases will prevent a minimum perceptible erythema (MPE). Exposing skin patches to a standarized UV lamp for 3.5 minutes each hour over a 4-hour period (a total of 14 minutes of radiation which is equivalent to 4 hours of midday midsummer sunlight) produced a vivid erythema without any sensitivity in the case of the skin patch treated with the 2 percent glyceryl aminobenzoate lotion, whereas an extremely painful sunburn resulted in the skin patch treated with the 8 percent homosalate lotion. Kreps concluded that the 2 percent glyceryl aminobenzoate lotion was the more effective of the two, as it did not disappear by absorption into the skin as rapidly as did the 8 percent homosalate lotion. He further concluded that when the rate of percutaneous absorption of the sunscreen compound is marked, the concentration required to provide a desired degree of protection is greater than that indicated by in vitro spectrophotometric measurements (ref. 18).

Yankell at al. evaluated a 7.7 percent homosalate lotion for sunscreen efficacy using a xenon solar simulator and applying 1 ml of the test material over a 2 X 7 cm area on four sites of male

albino guinea pigs (ref. *19*). Reactions were read 18 hours after irradiating these sites at multiples of the previously determined minimum erythema dose (MED). For the unwashed test sites, the percent protection from erythema was calculated to be 100 percent at 1 MED, 100 percent at 2 MED's and 38 percent at 3 MED's. For the test sites which were washed to simulate swimming and sweating conditions, the percent protection from erythema at 1 MED was 38 percent, with no protection at 2 and 3 MED's.

Willis and Kligman reported that the protective index offered by homosalate was reduced from 4.75 to 1.75 at 4 hours postsweating. They further determined that the penetration of homosalate is limited to the loose, noncoherent upper zone of the stratum corneum, based on their observation that the sun-screening effects of homosalate were almost completely eliminated after 4 strippings with cellophane tape.

Human studies reported by Giese and Wells indicated that "Of some 100 formulations tried, a bentonite clay ointment, a stearate mixture base ointment, a vanishing cream, and an ethocel lotion, nearly all containing homomenthyl salicylate and in some cases also ethyl *p*-aminobenzoate as sunscreens and titanium dioxide as the pigment proved most satisfactory. The value of the ointments in sunburn protection was tested by comparing the ratio of the dosage required in the control patch of skin. Sweating and washing with water decrease the protective value of the ointments but not as much as in the case of commercial ointments tried" (ref. *20*).

Controlled human studies of marketed homosalate preparations demonstrated the significance of the way in which a homosalate preparation is formulated on sunburn protection. Oil formulations produced the thinnest films on the skin and accumulated the least after repeated applications under normal use application. Oil formulations provided approximately one-half the protection of cream formulations of the same concentration. Oil-less lotions and creams were found to produce thicker films and to accumulate to a greater extent, thereby producing a reduction in tanning but facilitating the adjustment of the formulation to a wide range of skin sensitivities. A cream formulation containing 4 percent homosalate provided greater sunburn protection than did a lotion formulation containing 8 percent homosalate based upon protective factor determinations, that is, the ratio of MED of protected skin to that of unprotected skin (ref. *21*).

Based on the available data, the Panel concludes that homosalate is an effective sunscreen for OTC use. It recommends that homosalate be used as an internal control standard for in vivo efficacy testing in man.

(3) *Dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 4 to 15 percent homosalate: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 4 to 15 percent homosalate: Adult and children over 6 months af age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

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

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1. *Lawsone with dihydroxyacetone.* The Panel concludes that lawsone in conjunction with dihydroxyacetone is safe and effective for OTC use as a sun screen as specified in the dosage section discussed below.

Lawsone is also known as 2-hydroxy-1,4-naphthoquinone. Lawsone is the principal dye component of henna, which has been used since antiquity to dye skin and hair (ref. *1*). Lawsone has a low vitamin K activity by means of its chemical relationship to 2-methyl-1,4-naphthoquinone (menadione) (ref. *2*).

Dihydroxyacetone (DHA) is also known as 1,3-dihydroxy-2-propanone. DHA is also a dye used as a skin browning agent. DHA is discussed earlier in this document. (See part II. paragraph I. above—Sunscreen Products Containing Dihydroxyacetone.)

DHA is produced from glycerol by *Aerobacter sp.* under aerobic conditions. It is a fairly hygroscopic, crystalline powder and has a characteristic odor and a sweet and cooling taste. It normally occurs as a dimer, in which form it is slowly soluble in 1 part water and 15 parts alcohol. When freshly prepared, DHA reverts rapidly to a monomer in solution, in which form it is very soluble in water, alcohol, ether, and acetone (ref. *3*).

The Panel received one submission for a marketed product composed of two lotions which are packaged together and labeled to be applied separately and in sequence. The first lotion to be applied contains 3 percent DHA, to be followed by application of a second lotion containing 0.25 percent

lawsone. The manufacturer claims that the product is effective, when applied as directed, in preventing sunburn and photosensitivity reactions caused by sunlight. The dual product is claimed to have an action spectrum that spans both short-UV (290 to 320 nm) and long-UV (320 to 400 nm) wavelengths.

The manufacturer claims "the product is unique in that it gains its effectiveness not from forming a film on the surface of the skin, but rather [illegible] its active ingredients fixed to the [illegible]in layer to form a permanent, [illegible]shable barrier. How this occurs [illegible]ly understood. It is postulat[illegible] dihydroxyacetone (DHA) [illegible] certain amino acids of ker[illegible]rees moieties for further re[illegible]h lawsone. One theory is [illegible] splits the disulfide bonds [illegible]e then reacts with the free [illegible] groups by 1,4 addition."

[illegible]iel has evaluated the submit[illegible]and concludes that when the [illegible]redients are used separately [illegible]quentially, the combination is [illegible]ed as Category I. Each ingredient when used alone cannot be classified as a Category I sunscreen. The submitted data indicate that the two solution product provides sunscreen protection which varies considerably among individuals, depending on such factors as susceptibility of the skin to fixing of the active ingredients, thickness of the keratin layer where the sunscreen resides, number of daily applications, degree of the individual photosensitivity, and amount of UV radiation received.

(1) *Safety.* The Panel concluded on the basis of toxicity studies that lawsone in conjunction with DHA is safe in the dosage range used as an OTC sunscreen.

Data were submitted for subacute dermal toxicity and irritation studies in which 20 healthy young adult albino rabbits were divided into 5 groups of 4 rabbits per group, including a control group (lotion base). Four concentrations (0.29, 0.58, 1.16, and 2.32 ml/kg) of a lotion containing 0.125 percent lawsone and 3.0 percent DHA were applied to the shaved abdominal skin area for 6-hour periods, 5 days a week for 13 weeks for a total of 65 applications. The application of 0.29 ml/kg of the lotion was considered to be equal to the normal human single dose. The shaved area in a male and female rabbit of each group was abraded initially and at the beginning of each subsequent week by using a hyperdermic needle to make a series of parallel minor epidermal incisions. The test materials were held in place by an occlusive bandage with an initial layer of plastic film. Twice daily each animal was examined for signs of dermal of systemic toxicity. Each rabbit was weighed weekly. Hematology, urinalysis, and blood chemistries were performed prior to the initial application of the test materials and just prior to the sacrificing of the animals at the end of 13 weeks. Hematology was also performed at 7 weeks. Following sacrifice, gross necropsies and histopathology of all organ systems were performed. The investigators concluded from the data that "No significant differences were noted among the groups with respect to body weight gains, gross appearance and behavior, mortalities, hematological findings, blood chemistry findings, urine findings or gross or microscopic pathological findings. The control animals showed mild to marked spotty erythema and mild to moderate desquamation during the study. The animals in the remaining groups showed occasional mild desquamation only" (ref. *4*).

Hanke and Talaat (ref. *1*) reported a study in which 3 g ground whole henna leaf equivalent to 30 mg of lawsone were orally administered daily to 90 patients with intestinal amoebiasis for periods of from 4 to 6 or 8 weeks. Seven patients, who relapsed during the 6-week followup period, were given a second course of treatment. One patient experienced severe diarrhea, and treatment was discontinued after 3 days. Transient diarrhea was experienced by five other patients whose treatment was continued full course. These were the only observed side effects.

Fusaro, Runge, and Johnson reported their experiences with 77 patients with various forms of recalcitrant sunlight sensitivity, who received topical applications of mixtures of 0.13 percent lawsone and 3.0 percent DHA in vanishing cream and 50 percent isopropyl alcohol/distilled water vehicles. They reported that "During these clinical trials, not a single incident of cutaneous sensitization was observed" (ref. *5*).

The Panel reviewed several other published studies by Fusaro et al., representing 10 years experience in the use of dihydroxyacetone/lawsone preparations in more than 350 patients with various types of photosensitivities. No adverse reactions attributable to these two active components were reported (refs. *6* through *13*).

The primary irritant and sensitization effects of a 0.125 percent lawsone lotion, the lotion base, a 3.0 percent DHA lotion, the lotion base, and a 0.125 percent lawsone and 3.0 percent DHA lotion were evaluated in a controlled study using an adaptation of the repeated-insult patch test procedure of Draize (ref. *14*). Webril patches affixed to the center of elastic adhesive bandages were moistened with 0.5 ml of the respective test material just prior to the application to the arms of each of 103 male and female subjects. The patches were applied on Mondays, Wednesdays, and Fridays for 3 consecutive weeks. Duplicate challenge applications of each test material were made after a 2-week rest period, with one set of patches being placed on the original test sites and the other set being placed on adjacent sites. The patch sites were scored on the second through tenth visits and at 48 and 96 hours following the challenge applications. Very slight irritation was observed following repeated applications of the 0.125 percent lawsone lotion and its lotion base. The 0.125 percent lawsone and 3.0 percent DHA lotion was found to be essentially nonirritating. None of the above-noted test materials showed evidence of sensitization.

A total of 9 patients received complete blood counts, SMA-12 profiles, and urinalyses at baseline and after 3 to 6 months of continuous administration of a sunscreen preparation in a lotion formulation containing 0.25 percent lawsone and 3.0 percent DHA. All of the above values remained in the normal range throughout the studies. One patient experienced what appeared to be acne vulgaris, which coincided with the initiation of oral contraceptive therapy. Another patient experienced transient irritation of the cheek during the initial 2 weeks, but responded to topical steroid therapy and continued in the study (refs. *14* and *15*).

A total of 56 photosensitive patients were treated with a sunscreen preparation in a lotion formulation containing 0.25 percent lawsone and 3.0 percent DHA. Adverse reactions consisted of one case of an aggravation of a previous dermatitis condition and a case of a burning sensation on application which was tolerated upon continued use (refs. *14, 15,* and *16*).

Based on the available data, the panel concludes that lawsone with DHA are safe sunscreen ingredients for OTC use.

(2) *Effectiveness.* There are controlled studies documenting the effectiveness of lawsone in conjunction with DHA as an OTC sunscreen.

The use of lawsone in conjuction with DHA as a topical sunscreen is reported to be effective against both short-UV (290 to 320 nm) and long-UV (320 to 400 nm) wavelengths, to alter the keratin layer and strengthen its inherent light-screening characteristics, to be permanently affixed to the skin thereby resisting bathing, sweating and swimming, and to be especially recommended for light-sensitive individuals (ref. *17*).

Fusaro et al. evaluated the protective effects of 50 percent isopropanol solutions of 3.0 percent DHA in combi-

nation with 0.035 and 0.13 percent lawsone on normal skin using natural sunlight under controlled conditions (ref. *6*). The DHA and lawsone solutions were not mixed until shortly before application. Six consecutive applications of the test materials were made at 1-hour intervals and then were allowed to remain on the skin from 10 to 12 hours prior to washing the test sites with soap and water. Sunlight exposure was started 2 hours afterwards. From 2½ to 3 MED's protection was provided the 18 subjects treated with the combination of the 3.0 percent DHA and 0.035 percent lawsone preparations. The four subjects treated with the mixture of the 3.0 percent DHA and 0.13 percent lawsone preparations received greater than 5 MED protection, as did the subject who increased the number of applications of the 0.035 percent lawsone preparation. Results obtained for five subjects indicated that neither the 3.0 percent DHA solution nor the 0.13 percent lawsone solution provided significant protection when applied alone as compared with the application of the mixture of these two solutions. The protective barrier provided by the application of DHA and lawsone solutions is resistant to washing with soap and water on the basis of the above-described results.

Fusaro et at. evaluated 77 patients with various forms of recalcitrant sunlight sensitivity, who received topical applications of mixtures of 0.13 percent lawsone and 3.0 percent DHA in vanishing cream and isopropyl alcohol/water vehicles. The degree of protection received by each patient was determined by the change in the patient's tolerance to sunlight exposure during use of the test materials. The median tolerance time prior to the application of the test materials was less than 1 hour, which was increased to 3 hours following use of the sunscreen. Of the 77 subjects, 51 (66 percent) obtained 3 or more hours of protection, 8 (10 percent) received less than 1 hour of protection, and 9 (12 percent) failed to obtain any benefit. Fusaro et al. reported that because DHA and lawsone will react and deteriorate when mixed together, the active ingredients should be given in separate vehicles, with the DHA preparation being applied first (ref. *5*).

Fusaro and Runge reported 9 years experience with a total of 267 mental patients with photosensitivity caused by chlorpromazine therapy, who received topical applications of equal amounts of 6.0 percent DHA and 0.25 percent lawsone both in 50 percent isopropyl alcohol/distilled water vehicles which were not mixed until just prior to application. Approximately 10 percent of the patients received the sunscreen for more than one season. The sunscreen mixture was applied by spraying five times daily for 3 days prior to the first exposure and once or twice daily thereafter, depending on the individual patient's degree of photosensitivity. It was reported that 84 percent of the patients experienced good (unlimited protection) or fair (mild erythema after several hours exposure to sunlight) results. Among the explanations offered for treatment failures were improper application of the sunscreen by the staff and uncooperative patients who refused to be sprayed regularly and/or washed the treated area immediately following spraying (ref. *12*).

Fusaro and Runge reported studies involving seven patients with erythropoietic protoporphyria wherein 3.0 percent DHA and 0.13 percent lawsone preparations in both a vanishing cream base and a 50 percent isopropyl alcohol/distilled water solution were applied after the patients' cutaneous eruption had cleared by means of topical steroid therapy and avoidance of sufficient light exposure to cause symptoms. The topical preparations were applied six to eight times daily for the first 2 days and thereafter three times daily for the next 5 days. At the end of the first week each patient was allowed to be exposed to sunlight for a period of time which was equivalent to the time based upon past experience when there would be an outbreak of cutaneous symptoms or eruption. Following the first exposure, each patient, depending on his/her degree of light sensitivity would apply the preparations one to four times daily. Only two patients applied the preparation in the alcohol/water vehicle, and upon receiving virtually no protection they were restarted on the preparation in the cream base. Fusaro and Runge reported that after protection with the above-described preparation in the cream base, all seven patients "were able to change their daily lives from one of predominantly 'indoors' to that of 'outdoors'" and that the five children among the patients were able for the first time to go swimming and participate in outdoor sports. For the seven patients the time necessary to produce symptoms or lesions from sunlight exposure was from less than 10 minutes to 2 hours at baseline and ranged from more than 3 hours to more than 8 hours after receiving protection from the DHA preparation in the vanishing cream base. Fusaro and Runge pointed out, however, that the total amount of electromagnetic radiation available in Minneapolis, where the study was conducted, is much less than in other areas of the country and that the Minnesota area has fewer sunny days than elsewhere (ref. *18*).

Three fair-skinned female volunteers participated in a controlled study wherein application schedules for 3.0 percent DHA and 0.125 percent lawsone creams and 6.0 percent DHA and 0.25 percent lawsone lotions were compared. Five test sites, including one control, were marked on the midthigh area of each leg, and the light source was a xenon-mercury lamp equipped with a filter which excluded all radiation below 260 nm and whose output between 280 and 320 nm was about 6.5 percent of the total energy. The MF[illegible] was determined for each subject. [illegible] of the two preparations tested c[illegible] ed of equal amounts of 6 perce[illegible] and 0.25 percent lawsone [illegible] prior to application. The other co[illegible] ed of two single preparations in which a 3.0 percent DHA cream was applied 15 minutes before the application of a 0.125 percent lawsone cream. One of the two application schedules tested involved making three applications of both preparations at 30-minute intervals on days 1 and 2, while the other consisted of three applications of both preparations at 30 minute intervals on day 2 only. On day 3, the treated and control sites on one leg of each patient were exposed to 3 MED's radiation, while the test sites on the other leg were exposed to 6 MED's. On days 4 and 5, the test sites were scored on a 0 (no perceptible erythema) to 4 (marked erythema and blisters) scale. Minimal protection was afforded by three or six applications of DHA and lawsone when applied as freshly prepared mixtures, as the scores mostly fell into the 2 (moderate erythema) to 4 (marked erythema and blisters) range. Scores ranged generally between 0 (no perceptible erythema) and 2 (moderate erythema) when the DHA cream was applied 15 minutes prior to the lawsone cream, with the application shedule involving three applications on both days 1 and 2 providing significantly more protection than that in which the applications were only made 24 hours prior to exposure. The control sites generally showed marked erythema with and without blisters (ref. *19*).

Fusaro treated 16 patients with severe photosensitivities of varied etiologies. The test preparations consisted of a 3.0 percent DHA lotion and a 0.25 percent lawsone lotion applied during spring, summer, and fall prior to exposure to potentially damaging light. Each application was made in the evening prior to retiring with the treated areas being bathed in the morning and throughout the day as required. The DHA lotion was applied 15 minutes before the application of the lawsone lotion. Initially, two or three applications were made each evening, with 15 minutes elapsing from the time the lawsone lotion was

applied prior to the reapplication of the DHA lotion. Either three applications each night for 2 nights or two applications each night for 3 nights were made. Thereafter, the protection was maintained by making one or two daily applications. The tolerance of the subjects to sunlight prior to the use of the test materials ranged from 5 minutes to 3 hours, with a median time of 10 minutes. Following the above applications, the median time increased to 2 hours, with the tolerance ranging from 25 minutes to more than 8 hours for these subjects considered to have benefited from the use of the sunscreens. In the opinion of the investigator, 13 or 80 percent of the 16 subjects exhibited excellent to good response (ref. *16*).

O'Quinn treated 14 patients of whom 12 had allergic contact photodermatitis, and all but 2 were Blacks. A 3.0 percent DHA lotion and a 0.25 percent lawsone lotion were applied in the same manner as described above except that two or three daily applications were in most cases made following the initial exposure to sunlight to maintain protection. O'Quinn reported that excellent or good protection was achieved in eight patients (57 percent), fair protection in one, poor protection in three, and no protection in two. Four of the eight patients with good to excellent protection had previously used various proprietary sunscreens, including those containing aminobenzoate (PABA). The investigator experienced difficulty clearing the dermatitis in several patients and was of the opinion that increased protection would have been obtained had the treated areas been normal throughout the study (Ref. 14).

Rice treated 26 photosensitive patients. A 3.0 percent DHA lotion and a 0.25 percent lawsone lotion were applied in the same manner as in the preceding two studies, with one application daily following the initial exposure to light. In addition, a part of the test area was treated with 3.0 percent DHA lotion in three cases, with 0.25 percent lawsone lotion in two cases, and with the lotion vehicle in two cases. At baseline, three patients tolerated from 1 to 2 hours. Rice reported that all 26 patients achieved good to excellent protection as 11 patients tolerated 6 to 8 hours of sunlight exposure, 5 tolerated 4 to 6 hours and 10 tolerated 2 to 4 hours. Median tolerance time increased from less than 1 hour prior to treatment to about 5 hours during treatment before the patients experienced eruptions or burning. Before the study, 12 patients had used commercial sunscreens containing aminobenzoate (PABA) without obtaining adequate protection. Rice also reported that those test sites were considered unprotected which were only treated with the single ingredient lotions or the lotion vehicle (Ref. 15).

Based on the available data, the Panel concludes that lawsone with DHA are effective sunscreen ingredients for OTC use.

(3) Dosage. (i) For products composed of two separate formulations (Solution 1: containing 3 percent dihydroxyacetone. Solution 2: containing 0.25 percent lawsone) providing a minimum SPF value of 2 to under 4: Adult and children over 2 years of age topical dosage is liberal application before sun exposure as follows: First application. The evening prior to sun exposure: Apply Solution 1. Wait 15 minutes; then apply Solution 2 to the same areas of skin. Wait until dried. Then repeat application of solutions alternately as before until a total of three applications of both lotions has been applied. Leave on skin without washing. Repeated application. After first day, apply one application of each lotion. Reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products composed of two separate formulations (Solution 1 containing 3 percent dihydroxyacetone. Solution 2: containing 0.25 percent lawsone) providing a minimum SPF value of 4: Adult and children over 6 months of age topical dosage is liberal application before sun exposure as follows: First application. The evening prior to sun exposure: Apply Solution 1. Wait 15 minutes; then apply Solution 2 to the same areas of skin. Wait until dried. Then repeat application of solutions alternately as before until a total of three applications of both lotions has been applied. Leave on skin without washing. Repeated application. After first day, apply one application of each lotion. Reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) Labeling. The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.) In addition, based upon the discussion above, the Panel recommends the following warnings: (i) "This is a two lotion product. Do not mix the contents of the two solutions. Use both solutions, for use of one alone will not provide protection."

(ii) "Use only on skin free of rash and abrasions."

(iii) "May stain clothing when freshly applied."

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m. *Menthyl anthranilate.* The Panel concludes that menthyl anthranilate is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

Menthyl anthranilate is the menthyl ester of anthranilic acid. It belongs to the group of ortho-aminobenzoate compounds which are much weaker sensitizers than are the para-amino-

benzoate compounds. Menthyl anthranilate is insoluble in water, and is soluble in 7 parts of 80 percent ethanol.

(1) *Safety.* Clinical use and marketing experience have confirmed that menthyl anthranilate is safe in the dosage range used as an OTC sunscreen.

Animal and human toxicological data and wide use attest to its safety for human topical application. The oral LD_{50} is 8.39 g/kg in rats (ref. *1*).

An in vivo percutaneous absorption study was performed in which 50 mg of a sunscreen cream containing 5 percent menthyl anthranilate and 4 percent ethylhexyl *p*-methoxycinnamate was applied to the inner surface of each arm of six healthy adult subjects. It was reported that 98 percent of the menthyl anthranilate was recovered after 4 hours' contact with the skin (ref. *2*).

Sams reported a study in which a 1:100 alcoholic solution of a perfume was streaked on the undersurface of the right forearm of a subject and allowed to dry. A 5 percent menthyl anthranilate in alcohol solution was then applied across this streak, and the arm was exposed to the midday sun for 1 hour on a bright day. It had previously been demonstrated that the perfume solution under such exposure would provoke a sensitivity reaction with erythema and mild vesiculation. It was reported that the 5 percent menthyl anthranilate solution adequately blocked the erythema from sun exposure (ref. *3*).

The erythema response with equimolar (3×10^{-4} M) solutions of various topical sunscreens was evaluated in 10 subjects and scored on a scale of 0 to 4 following exposure to UV radiation from an artifical light source. The average value for the preparations was tannic acid—0.25, aminobenzoate—0.95, glyceryl aminobenzoate—1.7, menthyl anthranilate—2.2, phenyl salicylate—2.8, and ethyl alcohol control (common vehicle)—3.5 (ref. *4*).

On the subject of the ortho-aminobenzoates, Fisher reported that "The 'ortho' compounds are essentially the anthranilates—methyl, phenyl, menthyl and benzyl—which are much less commonly sensitizers than are the 'para' compounds" (ref. *5*).

Repeat-insult patch tests were performed on 11 healthy Caucasian males to study the relative irritancy of six topical preparations among which were a marketed sunscreen cream containing 5 percent menthyl anthranilate and 5 percent titanium dioxide and another sunscreen cream containing 5 percent menthyl anthranilate and 4 percent ethylhexyl *p*-methoxycinnamate. Each test material was applied to a 1-inch square nonwoven cloth patch which was then placed in contact with the skin of the back of each patient by means of an occlusive, impermeable plastic tape. The patches were replaced daily for 10 days or until redness appeared, after which no further applications were made at that test site. In the case of the menthyl anthranilate/titanium dioxide cream, all but three subjects completed the study, with the tests being concluded on the fourth, seventh, and ninth days for these subjects. As for the menthyl anthranilate/ethylhexyl *p*-methoxycinnamate cream, all subjects completed the study, except for one patient who was terminated on the seventh day when redness appeared at the test sites for both of the above-named creams. On the basis of a 0 to 4 scale, the average index was 1.3 for the former preparation and 0.4 for the latter. The investigator concluded that these preparations were virtually nonirritating (ref. *6*).

The incidence of complaints for a sunscreen containing 5 percent menthyl anthranilate and 5 percent titanium dioxide was reported to be slightly less than one complaint per 100,000 units distributed. Approximately 13 percent of the complaints involved reports of contact dermatitis and possible photocontact dermatitis, but in the latter case photopatch tests were negative or photosensitivity from systemic medication was suspected (ref. *7*).

Based on the available data, the Panel concludes that menthyl anthranilate is a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are studies documenting the effectiveness of menthyl anthranilate as an OTC sunscreen.

Insoluble in water, but soluble in ethanol, menthyl anthranilate can be incorporated into emulsion, oil, and paste formulations. It is often used in combinations with other sunscreens. At higher concentrations it does offer 290 to 320 nm range absorption, with peak UV absorption at approximately 340 nm (ref. 8).

Harber evaluated the protection from light provided by five compounds containing the benzoic acid nucleus with various substituted side chains. Each ingredient was dissolved in 95 percent ethyl alcohol, as this solvent was found to have no significant UV absorption. Fifty volunteers (32 females and 18 males) with no skin lesions on their backs were involved in the study. In the first experiment, the test materials were placed in cylindrical quartz cups and were not in contact with the skin. UV radiation was provided by a D.C. Hanovia lamp at 30 inches for 60 seconds which approximated 1½ times the empirical minimal erythema dose. All test materials at a 3×10^{-2}M concentration were effective in preventing erythema, with no significant differences among them being discernible at 3×10^{-4}M and 3×10^{-5}M concentrations. Tannic acid and aminobenzoate were decidedly superior to the remaining compounds which in decreasing order were glyceryl aminobenzoate, menthyl anthranilate, and phenyl salicylate. In the second aspect of the investigation, 2 drops or approximately 0.4 ml of 5 percent solutions of each test material were placed on the backs of the subjects. The source of irradiation was again the D.C. Hanovia lamp at 30 inches for 60 seconds. The investigator reported that phenyl salicylate and menthyl anthranilate provided protection only minimally different from that of the 95 percent ethyl alcohol control; whereas when compared to the control, both tannic acid and aminobenzoate provided excellent protection, and glyceryl aminobenzoate protection was rated as good. In the third part of the experiment, approximately 0.4 ml of each test material was applied to the test sites on the subjects' backs, which were then exposed to 2 hours of midday natural sunlight. The investigator reported that both tannic acid and aminobenzoate were excellent in preventing erythema. Glyceryl aminobenzoate and phenyl salicylate had fair sun-screening ability, and the protection provided by menthyl anthranilate was poor. Harber stated, however, that "Under rigid statistical analysis, no significant differences could be established in the sunscreening properties of phenyl salicylate, menthyl anthranilate, or glyceryl para-aminobenzoate. It is the author's belief that further studies may demonstrate that menthyl anthranilate is the poorest erythema-protecting agent of all compounds tested in this study" (ref. *9*).

Seven Caucasian males were involved in a study comparing the protection to graded dose of UV irradiation by a sunscreen containing 5 percent menthyl anthranilate and 4 percent ethylhexyl *p*-methoxycinnamate and a 5 percent menthyl anthranilate cream. The radiation provided by a hot quartz UV lamp at 30 inches for 15 seconds was calibrated to be equivalent to 1 MED. The test materials were applied to different sides of the subjects' backs. Three patients who had ingested aspirin both before and after as much as 10 MED's irradiation showed no reaction on either side and were retested at different sites on their backs several days later because of the suppressive effects of aspirin. The final test results showed that the menthyl anthranilate/ethylhexyl *p*-methoxycinnamate cream provided complete protection up to and including 14 MED's, whereas the 5 percent menthyl anthranilate cream provided

protection from erythema up to at least 4 MED's in all cases (ref. *10*).

The protective ability of menthyl anthranilate against long-wave ultraviolet (UV-A) radiation constituting the spectrum between 320 and 400 nm was determined using 8 sensitized albino guinea pigs. Seven hours prior to exposure the abdominal skin was shaved and depilatorized. One hour prior to exposure the test animals were sensitized to UV-A by intraperitoneal injections of 88 mg/kg of 8-methoxypsoralen. The UV-A light source was a Black-Ray UVL-56 which was placed 3½ inches from the animals. A 5 percent menthyl anthranilate in alcohol solution and a placebo solution were applied to test sites on the first animal, and the test sites were irradiated at 5-minute increments from 5 to 20 minutes. A 5 percent menthyl anthranilate preparation in its cream base, but without its other active sunscreen component (titanium dioxide), was applied to test sites on the remaining seven animals and exposed at 3-minute increments from 3 to 15 minutes. The test sites were read at 24 and 72 hours following exposure and were scored on a scale from 0 (no erythema) to 4+ (necrotic erythema). In the case of the first test animal, the readings after 20 minutes' exposure at 24 and 72 hours were 2+ (medium erythema) at the menthyl anthranilate-treated site and 3+ (maximum erythema) and 4+ (necrotic erythema) at the placebo-treated and untreated sites, respectively. After 15 minutes exposure the readings for the menthyl anthranilate-treated site in the seven remaining animals were 0 (no erythema) at 72 hours following exposure, whereas five of these animals demonstrated slight erythema (1+) at 24 hours following exposure. For the placebo-treated test sites the latter seven animals had 3+ (maximum erythema) readings at 24 hours and 4+ (necrotic erythema) readings at 72 hours after exposure. The investigators concluded that "The uniqueness of menthyl anthranilate as an UV absorber has been demonstrated in this study. Although menthyl anthranilate showed some absorption in the mid-UV region, as manifested by reduced erythema compared with placebo and untreated sites, it absorbs preferentially in the near UV as demonstrated by its protective effect on psoralensensitized albino guinea pigs" (ref. *11*).

Based on the available data, the Panel concludes that menthyl anthranilate is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 3.5 to 5 percent menthyl anthranilate: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 3.5 to 5 percent menthyl anthranilate: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

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

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n. *Oxybenzone.* The Panel concludes that oxybenzone is safe and effective for OTC use a sunscreen as specified in the dosage section discussed below.

Oxybenzone is also known as 2-hydroxy-4-methoxybenzophenone and benzophenone-3.

Its absorbance is between 270 and 350 nm, with the maximum absorbance at 290 nm. It is soluble in ethyl and isopropyl alcohol and in mineral oil and linseed oil, but it is virtually insoluble in water. Oxybenzone is incorporated in emulsion, oil, and lipstick formulations. It is frequently used in combination with other sunscreens.

(1) *Safety.* Clinical use and marketing experience have confirmed that oxybenzone is safe in the dosage range used as an OTC sunscreen.

Extensive animal and human toxicological data and wide use attest to its safety for human topical application. The LD_{50} is over 12.8 g/kg in rats treated orally and in excess of 1.6 g/kg in mice treated intraperitoneally (refs. *1, 2,* and *3*).

Pads, each 4 cm^2 and containing 0.5 g oxybenzone moistened in distilled water, were applied to shaved areas on the backs and flanks of six New Zealand white rabbits. The test sites in one-half of the rabbits had been previously abraded with a skin scraper. After 24 hours, the pads were removed, and the test sites were rinsed with water to remove residues of the substance. Daily examinations were made the next week for signs of systemic poisoning and skin changes in the test site areas. It was reported that both the intact and abraded sites remained free of irritation throughout the 7-day observation period. The investigators instilled 0.1 g oxybenzone into the conjunctival sac of the left eye of each of three New Zealand white rabbits, with the right eye serving as a control. Daily examinations during the following week revealed that the eyes remained completely free of irritation (refs. *2* and *3*).

The subchronic dermal toxicity of a sunscreen containing 6 percent oxybenzone and 12 percent homosalate was evaluated by applying 0.5 g or 2 g/kg of the test material to the shaved intact or shaved abraded skin of albino rabbits daily, five times weekly, for 3 weeks (15 applications), with 2 g/kg of 0.6 percent methycellulose being applied to the controls. All test animals remained healthy and vigorous throughout the study. Hematology, clinical biochemistry, necropsy reports, histopathology, weight gain, and food consumption of all test animals were within normal limits. During the early stages the intact and abraded skin of all test animals, including the controls, exhibited mild erythema, which appeared to be dose related and disappeared early, thereby suggesting some degree ot dermal hardening. From the second week, the abraded skins of all test animals, including the controls, exhibited drying and scaling of the skin, but this condition was considered to be of no major consequence (ref. *4*).

A sunscreen containing 6 percent oxybenzone and 12 percent homosalate was evaluated by instilling 0.1 ml of the product into the conjunctival sac of one eye of each of six New Zealand white rabbits, with the the opposite eye serving as a control. Following instillation, no erythema or edema was observed, and no subsequent irritation

was detected. Detailed visual and ophthalmoscopic examinations were performed 24, 48, and 72 hours after instillation and did not reveal any positive overt ocular abnormalities (ref. *5*). In a similar study, 0.1 ml of the above-named sunscreen product was instilled into the left eye of each of 12 albino rabbits, with the right eye serving as the control. Six test animals received no further treatment, while the treated eyes of the remaining six rabbits were irrigated with 20 ml of lukewarm tap water approximately 4 seconds after instillation of the test material. One hour after instillation and once daily thereafter until any observed eye irritation subsided completely, or for a maximum of 14 days, the eyes were observed both for irritation and gross signs of systemic toxicity from mucous membrane absorption of the test material. The irritative effects in both the irrigated and nonirrigated eyes were limited to mild conjunctivitis, which was observed at the 1-hour reading only. No evidence of systemic toxicity resulting from mucous membrane absorption was observed, nor was corneal opacity or iritis noted (ref. *6*).

Photosensitization studies were conducted in which the hair of the saddle area of each of nine albino rabbits was removed with electric clippers, and 0.4 ml of a sunscreen containing 6 percent oxybenzone and 12 percent homosalate was applied to 2-inch square test sites on six of the rabbits, with the remaining three rabbits being untreated and serving as controls. These applications were made daily, five times weekly, for 2 weeks (10 applications). Following each application the control and test animals were irradiated with UV light for 15 minutes using a sunlamp at a distance of 12 to 14 inches. Readings were made 24 hours after each application and were graded on a scale from 0 (no erythema) to 3 (erythema and trauma, or marked edema or desquamation). No significant increases in the severity of the reaction during the course of the study were noted between the control and test animals. Mild erythema and edema were generally observed in all test animals throughout the study. Desquamation was noted after the fifth application to the test animals and after the eighth application in the controls. It was reported that the reactions were not considered manifestations of photosensitization, but represented a normal response to repeated dermal insult (ref. *6*).

One ml (approximately 0.5 g) of a sunscreen lotion containing 6 percent oxybenzone and 12 percent homosalate was applied to a 1½ X 3 inch area on the posterior forearm of each of 14 subjects. After 4 hours, the lotion was removed. It was calculated that an average of 95.41 and 96.51 percent of the homosalate and oxybenzone, respectively, was recovered from the skin. Within the technical limits of the above-described percutaneous absorption study, essentially complete recovery of the test material was indicated by the data (ref. *7*).

Patch tests of a sunscreen formulation containing 3 percent oxybenzone, 3 percent padimate A, and 4 percent padimate 0 on 100 female volunteers showed no evidence of any inflammatory reaction at the test sites on the upper back of the subjects immediately, 15 minutes, and 24 hours following the removal of the 48-hour patch tests (ref. *8*). Further patch tests of the above-described preparation on 203 female volunteers, who were subjected to ten 48-hour repeated patch tests and a challenge dose 14 days later, confirmed that the preparation is not a primary irritant and also demonstrated that any "sensitizing potential, if existent at all, is exceedingly low" (ref. *9*). The photosensitization potential of the above-described formulation was evaluated by subjecting 25 female volunteers to repeated-insult patch tests with an UV light source. The light source was used to determine the MED for each subject. Comparison of the light-protected control site and the test site treated with the test material and irradiated with the MED established for the subject revealed no change in skin character 24 and 48 hours later. It was concluded that the photosensitization potential of the formulation, if existent at all, is exceedingly low (ref. *10*).

In another study by Kantor, a product containing 7 percent padimate 0 and 3 percent oxybenzone was tested on 150 subjects according to a modified Draize-Shelanski repeated-insult patch procedure. Several non-specific irritation reactions were observed under occlusive conditions, but none showing signs of being a primary irritant. The same test material was applied to the backs of 26 subjects for photpatch testing. Ultraviolet light, from a Hanovia Tanette Mark I lamp, was directed on the subjects' backs for a period of 1 minute, from a distance of 12 inches. Results following 48 hours from initial testing showed no adverse reactions observed in the 26 subjects tested (ref. *11*).

Jordan evaluated a product containing 7 percent padimate 0 and 3 percent oxybenzone applied to the backs of 150 healthy adult patients. The test material was evaluated according to a modified Draize repeated-insult patch test. The material tested was applied to the scapular back under occlusive patches three times a week for 10 applications. Two consecutive occlusive challenge tests were applied to different areas on the scapular back after a 2-week rest period from initial testing. Results from observations taken immediately after removal of the patches showed mild irritational responses from the challenge tests, but no allergic response (ref. *11*).

Based on the available data, the Panel concludes that oxybenzone is a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are studies documenting the effectiveness of oxybenzone as an OTC sunscreen.

By means of a solar simulator, the protective indices (P.I.) of a lotion vehicle, 3 percent oxybenzone in the lotion vehicle, 3 percent padimate A in the lotion vehicle, and 4 percent padimate 0 in the lotion vehicle were determined to be 1.31 ± 0.3, 2.37 ± 0.82, 6.03 ± 1.03, and 7.06 ± 1.25, respectively. The tests were performed by applying 100 ml of the test material to a 5×10 cm^2 area on each subject's back. The number of subjects varied from 9 to 17 for each test material. Fifteen minutes after application, each subject had areas of 1 cm^2 exposed to UV light from a solar simulator with a graded series of exposures being administered to both the test sites and adjacent untreated control sites. Twenty-four hours later, the minimal delayed erythemic responses were evaluated, and the protective indices were then calculated. The above-stated values reflect the mean protective index and standard deviation for the respective test material (ref. *12*). In a similarly conducted solar simulator test of a preparation in which the above-stated three ingredients had been combined in the lotion vehicle in the same concentrations as stated above, the mean protective index was determined to be 20.4 ± 5.8 based on the data for 18 subjects (ref. *13*).

Katz evaluated the relative effectiveness of four sunscreen preparations, i.e., 3 percent oxybenzone and 3 percent dioxybenzone in a cream base, 2.5 percent padimate A in 65 percent ethanol with emollients, 5 percent aminobenzoate in 70 percent ethanol with emollients, and 5 percent aminobenzoate in 70 percent ethanol (ref. *14*). Previously unexposed skin of the buttocks or cleanly shaven suprapubic areas of nine male subjects was divided into six to eight equal 2- or 3-inch square patches with adhesive tape. The four sunscreens were liberally applied to randomized areas on one side of each subject and allowed to dry for 15 minutes. After swimming in a fresh water pool for 10 minutes, the previously untreated side of each subject was thoroughly dried and the same test materials were applied to randomized areas. The test sites were then exposed to the maximum possible natural sunlight for 1 hour. Erythema was evaluated by three independent observers 24 hours later and graded on a

scale from 0 (no reaction) to 4 (bright and fiery red). Except for the 2.5 percent padimate A preparation, all sunscreens were considered to have provided good protection from the erythematogenic rays of the sun on the side treated following swimming, as the scores ranged from 0 (no reaction) to 2 (pink) for these three preparations. However, none of the preparations was considered to have provided consistently satisfactory protection when applied to the test sites after swimming, but slightly more protection was provided than when the preparations were applied prior to swimming. In the latter instance, it was thought that the failure of the aminobenzoate preparations to provide satisfactory protection when the subjects swam after application may be due to the short interval between application and swimming (i.e., 15 minutes) which lessened the penetration of the aminobenzoate molecules into the stratum corneum.

Based on the available data, the Panel concludes that oxybenzone is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 2 to 6 percent oxybenzone: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 2 to 6 percent oxybenzone: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.)

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o. *Padimate A.* The Panel concludes that padimate A is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

Padimate A is also known as amyl *p*-dimethylaminobenzoate, isoamyl *p*-*N,N*-dimethylaminobenzoate, and pentyl 4-(dimethylamino) benzoate.

Padimate A is a yellow, mobile liquid, with a faint aromatic odor. It has a molecular weight of 277. It is soluble in isopropyl alcohol, mineral oil, and ethyl alcohol. It is insoluble in water, glycerin, and propylene glycol (ref. *1*).

(1) *Safety.* Clinical use and marketing experience have confirmed that padimate A is safe in the dosage range used as an OTC sunscreen.

Extensive animal and human toxicological data attest to its safety for topical application to human skin. Acute oral toxicity studies determined that the LD_{50} of padimate A in mice was 4.5 ml/kg, whereas it was 13.0 ml/kg in rats, indicating that the ingredient is approximately three times more toxic in mice than in rats (ref. *2*).

Primary skin irritation and eye irritation tests conducted on six female albino rabbits demonstrated that padimate A produced no erythema or edema 24 and 72 hours after the application of 0.5 g (0.5 cc) on intact and abraded skin and that very slight conjunctival redness was observed 24, 48, and 72 hours following the instillation of 0.1 ml padimate A into the conjunctival sac (ref. *2*).

Similar animal (albino rabbit) studies of sunscreen formulations containing 3 and 5 percent padimate A demonstrated that the preparations are mild skin irritants (generally very slight erythema and edema) and are definitely eye irritants (corneal opacity, conjuntival redness, chemosis, and iritis) probably due to the alcoholic nature of the vehicle (ref. *2*).

Draize eye irritation tests of a sunblocking lotion containing 3 percent padimate A, 4 percent padimate 0 and 3 percent oxybenzone were performed on nine New Zealand white rabbits by instilling 0.1 ml of the test material into the conjunctival sac of one eye of each rabbit, with the remaining eye serving as a control. Three animals received no further treatment. Three animals had their eyes gently flushed with 20 ml of lukewarm physiological saline 2 seconds after treatment, and the remaining 3 animals had their eyes flushed in the above-described manner 4 seconds after instillation. Observations were made at 24, 48, and 72 hours later and at 4 and 7 days later. Except for one test animal in the untreated group, which experienced a very mild erythematous response in the palpebral conjunctiva which cleared prior to the 72 hour observation, none of the test animals showed any evidence of eye irritation. The investigator concluded that the preparation was not an eye irritant (ref. *3*).

Willis and Kligman (ref. *4*). reported on their study of the records of several hundred test subjects and their finding that some subjects have complained of burning and itching of the face during hot weather following applications of 2.5 and 5 percent padimate A in alcohol solutions and that this reaction has been reported by up to 20 percent of the subjects using the 5 percent solution. No eye or skin irritation has been observed by them in patients using 5 percent aminobenzoate in alcohol solutions applied to the face and trunk while fishing or sunbathing.

Wilson et al. (ref. *5*) reported that 3 percent of their patients have complained of a stinging or burning sensation when a 5 percent padimate A preparation was applied to the face, especially around the eyes. It was indicated, however, that this reaction was not observed until the beginning of hot summer weather. In some patients the reaction was noticeable only when the face perspired. Some patients experienced the reaction following each application; others experienced a stinging sensation initially which did not recur upon continued use.

A primary irritation test was performed on 100 white female subjects to determine the degree of irritation to the intact skin of the upper back from a sunscreen lotion containing 2.5 percent padimate A and 3.0 percent dioxybenzone. One-half inch square patches impregnated with the test material were applied to the test sites and held in place with plaster. Following

removal of the patches 48 hours later, the test sites were observed immediately and after 15 minutes and 24 hours. The erythema intensity was scored on a scale from 0 (no erythema) to 3+ (vesiculation with edema). It was concluded by the investigator that the preparation was not a primary irritant, as all readings showed no evidence of erythema (ref. *6*).

An irritation test of a sunblock lotion containing 3 percent padimate A, 3 percent oxybenzone, and 4 percent padimate O was conducted on the upper backs of 100 female subjects following the same procedures as described for the previous study. Based on data which showed no evidence of any inflammatory reaction immediately, 15 minutes, and 24 hours following the removal of the 48-hour patch tests, the investigator concluded that the test material was not a primary irritant (ref. *7*).

Irritation tests have indicated that the irritation effect of padimate A is apparently dose related. Various lotions were applied to areas below the eyes, and after 5 to 10 minutes, determination was made as to whether there was any irritation or burning. Lotions containing 5 percent homosalate in combination with 0.5 or 1.2 percent padimate A produced slight facial irritation in 2 of 57 and 1 of 51 subjects, respectively. A lotion containing 5 percent padimate A when applied to the faces of 31 subjects produced moderate irritation in one case and slight irritation in 9 others, whereas an 8 percent homosalate lotion produced slight facial irritation in 2 of 53 subjects tested (ref. *8*).

Repeated insult patch tests of a gel containing 3 percent padimate A were performed on the upper arms of 55 adult human subjects (ref. *9*). The test material was applied to approximately 0.5 square inch lintine discs, which were then applied to the test sites and held in place with occlusive patches. Each 24-hour period the patches were removed, and the reactions were graded on a scale from 0 (no erythema) to 4+ (marked erythema, edma, with vesicles and oozing). After a 24-hour rest period, repeat applications of the test material were made. This sequence was repeated 10 times, after which there was a 2-week rest period before a challenge dose was applied. Of the 55 subjects tested, three patients exhibited slight erythema (1+ reading) following the tenth application. One of these subjects also experienced slight erythema following the seventh application. Otherwise, all other readings for the repeat insult and challenge dose applications showed no evidence of erythema. It was concluded by the investigator that the test material was neither a primary irritant nor a sensitizing agent and that it can be predicated with 95 percent certainty based on the number of test subjects that at least 94 percent or more of the general population will not be sensitized by the test material.

Repeat insult patch tests of an ointment containing 4 percent padimate A in white petrolatum USP were performed on the upper arms of 50 human volunteers (ref. *10*). The repeat insult and challenge dose applications were made in the sequence described above except that there were 15 repeat insult applications and 48-hour rest periods on weekends. None of the 50 subjects exhibited visible skin changes at any time throughout the study. It was concluded that the test material did not demonstrate characteristics of a primary irritant, fatiguing agent, or sensitizer.

A report indicated that adverse reaction complaints for millions of units of padimate A-containing sunscreens used during the 1967–1972 period averaged less than one complaint per 100,000 units sold (ref. *11*).

Based on the available data, the Panel concludes that padimate A is a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are studies documenting the effectiveness of padimate A as an OTC sunscreen.

Padimate A absorbance is between 290 and 315 nm, with the peak absorbance at 310 nm. Soluble in isopropyl and ethyl alcohol, mineral oil, and peanut oil, but insoluble in water, glycerine, and propylene glycol, padimate A is formulated in anhydrous emulsion, hydroalcoholic solutions, oil, and ointment preparations (ref. *12*).

Yankell et al. (ref. *13*) determined by tape stripping, combined with spectrophotometric analysis, the recovery of various sunscreens from the stratum corneum of Mexican hairless dogs. The sunscreens tested consisted of 3 and 5 percent concentrations of padimate A and aminobenzoate in 75 percent ethanol and 75 percent isopropanol vehicles. The solutions were applied on 1.5 cm^2 sites on the animals' flanks. One hour after application the test sites were stripped 13 times by repeatedly applying and removing 2 cm^2 cellulose tape squares. This procedure was repeated on other test sites, except that 1 hour after application the test sites were swabbed with damp absorbent cotton squares prior to being tape stripped in the above-described man- ner. The swabs were assayed along with the tapes as part of the determination of ingredient recovery. In the case of the unwashed test sites, 70 to 90 percent padimate A and 40 to 48 percent aminobenzoate were recovered, whereas 24 to 32 percent padimate A and 2 to 7 percent aminobenzoate were recovered from the tapes for the washed test sites. Recovery from the ethanol and isopropanol vehicles was comparable. Additional test sites were treated with 3 percent aminobenzoate in a hydroalcoholic vehicle and commercial sunscreen creams, i.e., 2.5 percent padimate A in the same hydroalcoholic vehicle, 2.5 percent padimate A, 4.4 percent homosalate, and a 3 percent oxybenzone and 3 percent dioxybenzone combination. One hour after application the treated sites were rinsed for 1 minute with a moderate stream of warm (37° C) water to simulate exercise, swimming, etc. and allowed to air dry before being tape stripped 13 times. In the case of the two ingredients in hydroalcoholic vehicles, 30.8 percent padimate A and 2.9 percent aminobenzoate were recovered. The remaining data indicated that 5.9 percent padimate A in the other formulation, 13.1 percent of homosalate, and less than 1 percent oxybenzone and dioxybenzone were recovered. The investigators reported that the data demonstrated that "sunscreens in alcoholic vehicles provide more protection than many available preparations in lotion or cream vehicles."

Yankell et al. (ref. *14*), using a solar simulator to produce erythema, evaluated eight sunscreens on male albino guinea pigs both with and without washing after application. The minimum erythemal dose (MED) for the shaved and depilated test areas was determined to be 2 seconds of solar simulator exposure time. One-tenth ml (0.1 ml) of each test material was applied over a 2 × 7 cm area on four sites on each side of dorsal surfaces. Two different test materials were tested in at least four guinea pigs. The unwashed sites 1 hour after application of the test materials were exposed to UV irradiation from the solar simulator at 1, 2, and 3 MED levels. Control areas were exposed to 1 MED irradiation. Other test sites 1 hour after application of the test materials were rinsed for 1 minute under a stream of warm (35° C) water, dried with a soft cloth, and then exposed to 1, 2, and 3 MED irradiation with control areas receiving 1 MED irradiation. The test materials consisted of a sunscreen containing 2.5 percent padimate A in a water-repellent cream base with opaque constituents (I), a sunscreen containing 2 percent padimate A in 75 percent ethyl alcohol (II), a sunscreen containing 2.5 percent padimate A in a hydroalcoholic lotion with emollients (III), a sunscreen containing 1.1 percent padimate A in oils (IV), a sunscreen lotion containing 2 percent glyceryl aminobenzoate (V), a sunscreen lotion containing 7.7 percent homosalate (VI), a sunscreen lotion containing 3 percent oxybenzone and 3 percent dioxybenzone (VII), and a sunscreen containing 5 percent aminobenzoate in 75 percent ethyl alcohol

(VIII). For the unwashed sites all test materials provided complete protection at 1 MED, but at 3 MED's only preparation I was fully effective; preparations II (50 percent), III (63 percent), VII (50 percent) and VIII (87 percent) were less effective; preparations V (25 percent) and VI (38 percent) were marginally effective; and preparation IV (0 percent) exhibited no effect. In the case of the washed test sites only preparations II and VIII, the only sunscreens prepared in 75 percent ethyl alcohol vehicles, provided protection above 1 MED. Preparation IV, which contained the lowest concentration of padimate A of the four padimate A-containing test materials and the lowest level of active ingredient among all test materials, provided the least protection to both the washed and unwashed sites.

Pathak et al. (ref. *15*) reported their 3-year study (1965–68) of the protective value of 24 sunscreens of various chemical agents known to absorb UV light. They indicated that 5 percent aminobenzoate in 70 to 90 percent ethyl alcohol and 2.5 percent padimate A in 65 to 95 percent alcohol "are by far the best sunscreen preparations" and that these preparations, after a single application, "can protect fair-skinned persons undergoing long exposure (over 4 hours) under natural sunlight, and are more effective than 24 of the commercially available products tested" and "afford excellent protection when subjects undergo exercise accompanied by profuse sweating, and tend to remain on the skin after bathing or swimming and exert a partial yet very satisfactory protection." Pathak et al. further found that these preparations provided very effective protection against sunburn "under intensely bright sun with hot, dry climatic conditions (in the Arizona desert), under warm and humid conditions (during the months of July and August in the Northern Hemisphere, 40° N. latitude) and on snow-covered mountains at high altitudes that reflect UV radiation causing sunburn of the exposed parts of the skiers." In addition, it was determined by Pathak et al. that these preparations "only partially inhibit tanning and allow immediate pigment darkening, as well as melanogenesis by long-wave UV and visible radiation" and "are cosmetically acceptable, being invisible and without odor or color on the skin."

Armati and Johnson (ref. *16*) evaluated the efficacy of two sunscreen creams containing 2.5 percent padimate A, one in a hydrophilic base and the other in a petrolatum and propylene glycol base, in nine human subjects with varying degrees of skin pigmentation. Fluorescent lights situated 25 cm from the skin surface were used to produce UV light in the 290 to 340 nm wavelength range. The minimum erythemal dose (MED) was determined for each subject. The test materials were applied to 1-inch square test sites on the subjects' backs, which were then exposed to 3 MED's irradiation with the results being assessed 24 hours afterwards. Padimate A in the petrolatum and propylene glycol base provided absolute protection (no erythema), whereas just detectable to moderate erythema was observed in test sites treated with padimate A in a hydrophilic base. It was noted, however, that test areas treated with the hydrophilic base only showed erythema which in the case of four subjects was worse than that for untreated sites exposed to the above-specified light source. A hydroxybenzoate derivative used as a preservative in the hydrophilic base was considered to be a possible source of the above-described phototoxic reaction.

From 9 to 17 human subjects were treated with one of four test materials to determine their protective indices using a solar simulator, i.e., 3 percent padimate A in the lotion vehicle, 4 percent padimate O in the lotion vehicle, 3 percent oxybenzone in the lotion vehicle, and the lotion vehicle. The mean protective indices and their respective standard deviation were 6.03 ± 1.03, 7.06 ± 1.25, 2.37 ± 0.82, and 1.31 ± 0.3, respectively (ref. *17*).

Kreps (ref. *18*) reported that padimate A transmits 10 percent of the incident erythemal flux at a 1 percent concentration and is a total sunblock at a 2 percent concentration. Based on determinations of percent erythemal (290 to 320 nm) and tanning (320 to 375 nm) transmission, a 1.4 percent concentration would provide a protective suntan for sensitive skin. A 1.1 percent concentration would provide a regular suntan for average skin, and a 0.8 percent concentration would be suitable for a minimum-protection quick-tanning preparation.

Based on the available data, the Panel concludes that padimate A is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 1 to 5.0 percent padimate A: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 1.0 to 5.0 percent padimate A: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.)

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(17) Sayre, R., "Sunscreen Evaluations, Human Testing," Draft of unpublished paper in OTC Volume 060131.

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p. *Padimate O.* The Panel concludes that padimate O is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

Padimate O is also known as 2-ethylhexyl *p*-dimethylaminobenzoate, 2-ethylhexyl 4-(dimethylamino)ben-

zoate, octyl dimethyl PABA and 2-ethylhexyl PABA.

Padimate O is a yellow mobile liquid, with a faint aromatic odor. It has a molecular weight of 235. It is soluble in isopropyl alcohol, mineral oil and ethyl alcohol. It is insoluble in water, blycerin and propylene glycol (ref. *1*).

(1) *Safety.* Clinical use and marketing experience have confirmed that padimate O is safe in the dosage range used as an OTC sunscreen.

Animal and human toxicological data attest to its safety at 4 percent concentration for human topical applications.

The oral LD_{50} in rats of a 5 percent concentration in corn oil is over 64 ml/kg (refs. *2, 3,* and *4*).

A primary irritation and sensitization study of a 5 percent padimate O sunscreen was conducted on the shaved backs of 10 male albino guinea pigs. A 0.1 percent solution of the test material in sterile, pyrogen-free physiological saline was injected intracutaneously three times weekly until a total of 10 injections was reached, after which there was a 12-week rest period before a challenge dose was injected just below the region of the 10 sensitizing injections. Each injection consisted of a 0.1 ml dose except for the initial and challenge doses, which were 0.05 ml each. Distilled water was used as a control. Except for one test animal who exhibited barely perceptible erythema throughout the study following injections of the test material and distilled water, readings made 24 hours following each injection showed no evidence of erythema or edema. It was concluded by the investigator that the test material was neither a primary irritant nor a sensitizer (refs. *2, 5,* and *6*).

The intact and abraded skin on the clipped backs of three albino rabbits was used for a primary irritation study of 5 percent padimate O in mineral oil (refs. *2, 7,* and *8*). Double-layered, light gauze patches, 2.5 cm^2, were secured by thin bands of adhesive tape to four areas approximately 10 cm apart on each test animal's back. One-half ml (0.5 ml) of the test material was introduced beneath each patch before wrapping the animals' trunks in clear plastic trunk bands to hold the patches in place and prevent the evaporation of volatile substances during the 24-hour exposure period. Following exposure the patches were removed, and readings were made immediately and 72 hours later. None of the readings showed any evidence of erythema or edema. The investigator concluded that the test material was not a primary irritant.

A Draize eye irritation study of 2.0 percent padimate O in mineral oil was performed on the unwashed eyes of three rabbits. The data indicated that the test material was not a primary irritant to the cornea and iris of the test animals, but was at the upper limit of the mild primary irritant range in regard to its effect on the conjunctivae, as hyperemia was observed (ref. *2*).

Eye irritation studies with 5 percent padimate O in mineral oil were conducted on the unwashed eyes of three rabbits (refs. *9* and *10*). A dose of 0.1 ml was instilled into the conjunctival sacs, and evaluations were made after 1 hour, 24 hours, and daily thereafter until 7 days had elapsed. The test material was determined not to be an irritant to the cornea or iris of the test animals. Slight redness (1 on a scale of 0 to 3) of the palpebral and bulbar conjunctivae of each test animal was noted on the first and second days following treatment, but not during the remaining 5 days of the study.

Repeated insult patch tests of 4 percent padimate O in which petrolatum, U.S.P., were conducted on 50 human volunteers (refs. *11,* and *12*). Lintine pads moistened with the test material were placed on predesignated sites on the upper arm of each subject and were then covered and seated with overlapping strips of tape. After 24 hours the patches were removed. The test sites were evaluated on a scale of 0 (no erythema) to 4+ (marked erythema, edema, with vesicles and oozing). The test material was reapplied to the same sites after a 24-hour rest period if less than marked erythema (less than 2+ value) was observed. The above-described cycle was repeated 15 times, except rest periods lasted 48 hours on weekends. Following the fifteenth application, there was a 2-week rest period before a challenge dose was applied to each of the previous test sites. After 24 hours the challenge doses were removed, and readings were made immediately and 24 and 48 hours afterwards. Throughout the study none of the 50 subjects exhibited any evidence of erythema at the test sites. The investigator concluded that the test material was not a primary irritant, a fatiguing agent, or a sensitizer. Based on the data for the above-described 50 subjects, the investigator predicted with 95 percent certainty that at least 92.89 percent of a general population would not be sensitized by the test material.

In another study by Kantor, a product containing 7 percent padimate O and 3 percent oxybenzone was tested on 150 subjects according to a modified Draize-Shelanski repeated insult patch procedure. Several non-specific irritation reactions were observed under occlusive conditions, but none showed signs of being a primary irritant. The same test material was applied to the backs of 26 subjects for photopatch testing. Ultraviolet light from a Hanovia Tanette Mark I lamp was directed on the subjects' backs for a period of 1 minute, from a distance of 12 inches. Results following 48 hours from initial testing showed no adverse reactions observed in the 26 subjects tested (ref. *13*).

Jordan evaluated a product containing 7 percent padimate O and 3 percent oxybenzone applied to the backs of 150 healthy adult patients. The test material was evaluated according to a modified Draize repeated insult patch test. The material tested was applied to the scapular back under occlusive patches three times a week for 10 applications. Two consecutive occlusive challenge tests were applied to different areas on the scapular back after a 2-week rest period from initial testing. Results from observations taken immediately after removal of the patches showed mild irritational responses from the challenge test, but no allergic response (ref. *13*).

Based on the available data, the Panel concludes that padimate O is a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are controlled studies documenting the effectiveness of padimate O as an OTC sunscreen.

Its absorbance is between 290 to 315 nm, with a maximum absorbance at 310 nm. Soluble in ethyl and isopropyl alcohol, mineral oil, and peanut oil, but insoluble in water, glycerine, and propylene glycol, padimate O can be incorporated in emulsions, hydroalcoholic solutions, and anhydrous formulations (refs. *1, 14,* and *15*).

Cumpelik (ref. *16*) evaluated the relative substantivity or retention by the skin of 2 percent padimate A in isopropanol compared with isopropanol solutions containing 2 percent padimate O, aminobenzoate, homosalate, cinoxate, sulisobenzone, or ethyl 4-[bis- (hydroxypropyl)] aminobenzoate. After the hands and the arms of the five subjects were washed up to the elbows in isopropanol at 30° C, their left arms were dipped into the 2 percent padimate A solution for 1 minute. Each subject's right arm was then dipped for 1 minute into a 2 percent solution of one of the other sunscreen ingredients listed above. The amount of each solution deposited on the subject's arm was determined by weighing the amount of test solution remaining and by spectrophotometric analysis of the residual solution. Following air drying, the subjects' hands were submerged in 2 gallons of tap water at 25° C for 30 minutes, during which time the hands and fingers were moved constantly without touching any surface of the container. After air drying, the hands were exposed to irradiation by a Hanovia UV lamp with a Corex D filter for 7 minutes, which was equivalent to 2 hours of midsummer midday sun expo-

sure. Following the water insult and irradiation, the residual sunscreen on the subjects' hands was extracted by immersing the hands in isopropanol at 50° C for 2 minutes. The volumes of the solutions were then equalized and spectro-analyzed. The percent substantivity was then determined by multiplying the amount of ingredient recovered after exposure by 100 and dividing this figure by the amount of the ingredient initially deposited. The percent substantivity of padimate A compared with that of each of the other test solutions was 42.2 vs. 58.6 for padimate O; 48.3 vs. 0.3 for aminobenzoate; 46.8 vs. 11.4 for homosalate; 40.6 vs. 7.6 for cinoxate; 40.6 vs. 2.3 for sulisobenzone; and 37.3 vs. 0.4 for ethyl 4-[bis- (hydroxypropyl)] aminobenzoate. The data above correlated very well with the relative differences in the degree of reddening on the subjects' hands and lower forearms 24 hours following irradiation. Because sunscreens containing aminobenzoate and homosalate contain concentrations above 2 percent, the above-described test using 5 percent aminobenzoate and a 10 percent homosalate was performed on another subject. The hand treated with aminobenzoate was allowed to air dry 30 minutes and to permit the material to attach itself to the stratum corneum before the 30-minute water insult. As before, these preparations demonstrated poor resistance to washoff. The data above did demonstrate, however, that in terms of percent substantivity or degree of skin retention under conditions involving perspiration and/or swimming, padimate O was superior to padimate A, and both were decidedly superior to aminobenzoate, homosalate, cinoxate, sulisobenzone, and ethyl 4-[bis- (hydroxypropyl)] aminobenzoate.

A comparative substantivity study of six sunscreen lotions was conducted on six untanned human subjects with fair complexions. The lotions were a combination of 4 percent padimate O, 3 percent padimate A, and 3 percent oxybenzone; a combination of 3 percent padimate A and 3 percent glyceryl aminobenzoate, 10 percent sulisobenzone; a combination of 3 percent oxybenzone and 3 percent dixoybenzone; and 5 percent aminobenzoate (ref. *17*). Each test material was applied to two sites on each subject's back at the rate of 2 ul/cm² (20 ul applied to a 10 cm² area) and allowed to dry for 1 hour without sunlight exposure. Following a 10-minute swim in an indoor swimming pool, the treated areas and untreated control areas were delineated with Dermical and masking tape before applying a 5 percent aminobenzoate lotion other than the one being tested and toweling to the remainder of the body. Sunlight exposure measured at 1,200 counts on the Berger-Robertson Meter and equivalent to a total exposure of 4 to 6 MED's was then administered. Twenty-four hours after this exposure the test sites were photographed and graded on a scale from 0 (no burn) to 4 (severe erythema, i.e., bright red, vesiculation, edema, and painful to touch). Both the photographs and scores demonstrate that the padimate O/padimate A/oxybenzone lotion provided the greatest degree of protection among the preparations tested because little if any sunburn resulted under the above-described test conditions (mean protective value of 0.292±0.396). In the order of decreasing protective value, the results for the remaining preparations were 3 percent padimate A and 3 percent glyceryl aminobenzoate (1.250±0.866), 3 percent oxybenzone and 3 percent dixoybenzone (2.833±0.937), 5 percent aminobenzoate (3.500±0.674), 10 percent sulisobenzone (3.583±0.515), and control (3.667±0.651). From the data above, it would appear that the 5 percent aminobenzoate and 10 percent sulisobenzone preparations were almost completely removed during swimming, as the resulting burns in the test sites treated with these preparations were as severe as in the untreated control sites. The investigator concluded that the padimate O/padimate A/oxybenzone preparation showed statistically significant protection and even after swimming should provide at least one-half day of protection without reapplication for most users.

Using a solar simulator, the mean protective indexes and their respective standard deviations were determined for the components of a sunblock lotion consisting of lotion vehicle (1.31±0.3), lotion vehicle plus 3 percent padimate A (6.03±1.03), lotion vehicle plus 4 percent padimate O (7.06±1.25), and lotion vehicle plus oxybenzone (2.37±0.82). Between 9 and 17 human subjects were used to test each component. A 5x10 cm² area on each subject's back was treated with 100 ul of the test material, and after 15 minutes the test areas and adjacent untreated control areas were administered a graded series of 1 cm² UV exposures from a solar simulator. Twenty-four hours after exposure the minimal delayed erythemic responses were evaluated and the protective indexes were then calculated (ref. *18*). In another solar simulator study, the mean protective index for the above-described sunblock lotion was determined to be 20.4±5.8 (ref. *19*).

In another solar simulator study of the above-described preparation (ref. *20*), the test material was applied to the forearm of 14 human volunteers at the rate of 2 ul/cm² (100 mg applied to a 5x10 cm² area) and allowed to dry for 15 minutes. The treated areas were then rinsed in a stream of flowing tepid water for 1 minute and allowed to air dry before administering a graded series of UV exposures from a solar simulator to the treated and adjacent unprotected control areas. Twenty-four hours following this exposure, the minimal delayed erythemic responses were evaluated and the protective indexes were then calculated. A substantive protective index of 13.0±3.6 was determined by dividing the MED for the treated area by that for the control area.

The mean protective index of a sunscreen lotion containing 7 percent padimate O and 3 percent oxybenzone was found by a solar simulator study to be 18.6±4.3 (ref. *19*). For this and the previous study, however, there were no results given for any determination of the mean protective index of the lotion vehicle itself; thus, a determination as to the contribution of the lotion vehicle to the product's protective index was not feasible.

Based on the available data, the Panel concludes that padimate O is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 1.4 to 8 percent padimate O: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 1.4 to 8 percent padimate O: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.)

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q. *2-Phenylbenzimidazole-5-sulfonic acid.* The Panel concludes that 2-phenylbenzimidazole-5-sulfonic acid is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

2-Phenylbenzimidazole-5-sulfonic acid has a chemical formula of $C_{13}H_{10}N_2O_3S$ and a molecular weight of 274.30. It is a white, finely crystalline powder, almost odorless. It is practically insoluble in benzene, but it is soluble in water, ethanol, ether, and chloroform (ref. *1*).

(1) *Safety.* Clinical use and marketing experience have confirmed that 2-phenylbenzimidazole-5-sulfonic acid is safe in the dosage range used as an OTC sunscreen.

Extensive animal and human toxicological data attest to its safety for human topical application. The oral LD_{50} is more than 5 g/kg in mice (refs. *2* and *3*).

Tolerance tests of the sodium, monothanolamine, and triethanolamine salts of 2-phenylbenzimidazole-5-sulfonic acid and two unidentified preparations of the ingredient were performed on both the skin of the auricle and the mucous membrane of the conjunctiva of rabbits. Concentrations of the test materials ranged from 1 to 5 percent. The test materials were administered twice daily for 5 days by placing three drops on the conjunctiva and 0.5 ml on the auricle. In vitro tissue tolerance tests were also performed on growing chicken heart fibroplastic cultures. The results reportedly demonstrated that the salts and their preparations were well tolerated, with skin tolerance, in particular, being very good. The ingredient itself was found to have no irritating effect on the mucous membrane of the conjunctiva. There was no observable difference in tolerance between the three salts (ref. *2*).

The subacute skin tolerance and sensitizing effect of 5 and 10 percent solutions and a 5 percent cosmetic preparation of the sodium salt of 2-phenylbenzimidazole-5-sulfonic acid were evaluated by applying 4 ml of each test material to the shaved backs of five rabbits for a total of 30 times during a 43-day period. Blood counts were performed at the beginning, midpoint, and end of the test period. In addition, 1.5 ml of each test material was applied to the shaved backs of five guinea pigs for a total of 3 times during a 40-day period. A second group of five guinea pigs received a total of 20 such treatments during a 25-day period. After a 14-day rest period there were concurrent injections of 0.2 ml of the test material intramuscularly into the popliteal fossa and 0.1 ml of the test material intracutaneously into the skin of the neck. It was reported that no irritating effects were observed on the backs of any of the rabbits or guinea pigs and that the sensitization test was absolutely negative. Blood counts remained normal throughout the study, and the animals did not experience any weight loss or behavioral changes (refs. *2* and *3*).

Oil/water emulsions of 3 percent 2-phenylbenzimidazole-5-sulfonic acid were applied daily for a period of 3 weeks to 21 human subjects of different sex and ages, some of whom suffered from skin disorders (refs. *2* and *3*). It was reported that the preparations were well-tolerated and did not give any indication that they might cause undesired skin reactions, particularly toxic acne, or might led to sensitization of the skin.

Eye irritation tests of two sunscreen lotions containing 1.5 and 2 percent 2-phenylbenzimidazole-5-sulfonic acid and 2.5 and 4.5 percent ethylexyl *p*-methoxy cinnamate, respectively, were performed on two rabbits and one human subject (ref. *4*). In the case of the rabbits, a drop of one preparation was instilled in the conjunctival sac of one eye, and a week later a drop of the other preparation was instilled into the conjunctival sac of the previously untreated eye. In each case the untreated eye was used as the control. Evaluations were performed 1, 2, 3, 24, and 48 hours following instillation. Both animals reacted similarly to both preparations; that is, immediately after instillation the rim of the eyelid and the conjunctiva reddened slightly and the cornea showed "slight freckles" for 1 to 2 hours. All these changes disappeared within 24 hours. The investigator rubbed a small quantity of each preparation into a conjunctival sac and reported that he experienced a slight reddening of the conjunctiva and a slight burning sensation, both of which disappeared within 1 hour. It was concluded by the investigator that these sunscreen preparations when used as directed present no danger to the eyes (ref. *4*).

A manufacturer of 2-phenylbenzimidazole-5-sulfonic acid reported that in the preceding 10 years more than 50 tons of the compound were marketed worldwide and that the suppliers have received no reports of adverse reactions from the use of the ingredient in sunscreen preparations (ref. *5*).

Based on the available data, the Panel conludes that 2-phenylbenzimidazole-5-sulfonic acid is a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are controlled studies documenting the effectiveness of 2-phenylbenzimidazole-5-sulfonic acid as an OTC sunscreen.

Its absorbance is between 290 and 320 nm, with the maximum absorbance at 302 nm. This ingredient is used in the form of its sodium, monoethanolamine, and triethanolamine salts. Aqueous solutions of these salts are miscible with ethanol and ispropanol in almost any proportion. The ingredient is practically insoluble in alkali solutions, and at a pH below 6.3, the free acid is precipitated as insoluble matter. It is recommended for hydrous formulations, including emulsions and transparent gels, and is frequently used in combination with other sunscreens (ref. *6*).

Twelve subjects (8 females and 4 males) participated in a laboratory study to determine the protective indexes of a sunscreen containing 5 percent aminobenzoate and 7 sunscreen preparations containing 2-phenylbenzimidazole-5-sulfonic acid in combination with ethylhexyl *p*-methoxy cinnamate with and without 2-hydroxy-4-methoxy benzophenone (ref. *7*). The test materials were applied to the subjects' backs 60 minutes prior to UV exposures equivalent to 3, 6, 9, 12, and 15 times the minimal erythemal dose (MED) of the subject. A hot quartz

mercury arc lamp was used as the light source. Twenty-four hours after exposure the test sites were evaluated as to the degree of erythema by visual gradations which were used to determine the protective index of each of the test materials. All test materials were found to provide significant protection against erythemnogenic radiation. Three formulations were considered to have provided excellent protection, as their maximum protective indexes always exceeded 10. They were a cream containing 2.75 percent 2-phenylbenzimidazole-5-sulfonic acid, 4 percent ethylhexyl *p*-methoxycinnamate, and 3 percent 2-hydroxy-4-methoxy benzophenone (preparation 1); a lotion containing 3 percent 2-phenyl-benzimidazole-5-sulfonic acid and 4.5 percent ethylhexyl *p*-methoxy cinnamate (preparation 2); and a cream containing 2.75 percent 2-phenylbenzimidazole-5-sulfonic acid, 5 percent ethylhexyl *p*-methoxy cinnamate, and 4 percent 2-hydroxy-4-methoxy benzophenone (preparation 3). These preparations provided greater protection than a sunscreen containing 5 percent aminobenzoate, but this was explained as resulting from the latter preparation not exerting its maximum photoprotective effect at higher doses of UV radiation (12 and 15 times the MED) because of it being less protective against the erythemogenic effects of 254 nm radiation emitted by the light source. The least protection (mean minimum protective index of 6.7) was provided by a cream preparation containing 1.5 percent 2-phenylbenzimidazole-5-sulfonic acid and 2.5 percent ethylhexyl *p*-methoxycinnamate.

A total of 39 untanned fair-skinned male subjects participated in studies conducted in Arizona in the early spring to determine the photoprotective properties of the above-described and other sunscreen preparations under conditions of passive sunbathing, swimming and/or sweating induced by exercise. The MED for each subject was determined by exposing appropriate sites to 5, 10, 20, 25, and 30 minutes of midday sun on the day of the test (ref. *8*).

In one study, 80 subjects participated in a passive sunbathing study to evaluate the photoprotective properties of the three formulations described above, a sunscreen containing 5 percent aminobenzoate, and a lotion contining 10 percent *p*-methoxy cinnamic acid diethanolamine salt. Sixty minutes prior to exposure, two of the above-described preparations were applied to test sites on the back of each subject. Each test material was then exposed to 1- or 2-hour periods of midday sunlight without the subject engaging in any physical activity. Preparation 3 (cream containing 2.75 percent 2-phenylbenzimidazole-5-sulfonic acid, 5 percent ethylhexyl *p*-methoxy cinnamate, and 4 percent 2-hydroxy-4-methoxy benzophenone) provided the best and most consistent protection. The protection afforded by the sunscreen containing 5 percent aminobenzoate only exceeded that provided by the 10 percent *p*-methoxy cinnamic acid diethanolamine salt preparation, which itself was considered to provide a good degree of protection under the above-described conditions.

Eleven subjects participated in another passive sunbathing study to evaluate the photoprotective properties of the above-described and other sunscreen preparations except that the sunscreen containing 5 percent aminobenzoate was not included. Sixty minutes prior to exposure, three preparations were applied to test sites on the back of each subject and were then exposed to 30-, 60-, 90-, or 120-minute periods of midday sunlight without the subjects engaging in any physical activity. Preparation 3 described above again provided the best and most consistent protection. Substantial protection was also provided by preparation 1 and 2 discussed above. A preparation containing 3 percent 2-phenylbenzimidazole-5-sulfonic acid, even though one of the least protective of the 12 preparations tested, had a mean protective index of 5.0 after 120 minutes of exposure, which compared favorably with protective indexes of 6.6 and 7.0 for preparations 1 and 2, respectively, after similar exposure.

Six patients participated in a study to evaluate the photoprotective properties of preparations 1, 2, and 3 described above under conditions of sweating induced by exercise. Sixty minutes prior to 30 minutes of strenuous calisthenics two preparations were applied to the back of each subject. Following the exercise period the test sites were exposed to 30-, 60-, 90-, or 120-minute periods of midday sunlight. All three preparations were considered to have provided excellent protection, as it was concluded that they could protect normal skin against sunburn reaction for a period of 2 hours.

Nine patients participated in a study to evaluate the photoprotective properties of the five preparations involved in the first study in this series under conditions of normal beach activities. Sixty minutes following the application of two test materials to different sides of each subject's back, the subjects performed 60 minutes of passive sunbathing, 10 minutes of swimming, 30 minutes of passive sunbathing, 15 minutes of exercise to induce sweating, and 30 minutes of walking. Total sun exposure was 150 minutes. Again, preparation 3 described above provided the best protection, whereas the 10 percent *p*-methoxycinnamic acid diethanolamine salt lotion was easily removed from the skin during swimming and sweating and gave only partial protection. In terms of decreasing degree of protection under the above-described conditions as determined by their mean protective indexes, the ranking of the test materials was preparation 3 (9.3), preparation 1 (9.1), a sunscreen containing 5 percent aminobenzoate (6.8), preparation 2 (5.9), and a lotion containing 10 percent *p*-methoxy cinnamic acid diethanolamine salt (4.6).

Six subjects participated in a study to evaluate the photoprotective properties of preparations 1, 2, and 3 described above, wherein 60 minutes after two test materials were applied to test sites on each subject's back there was a 15-minute swimming period followed by the exposure of the test sites to 30-, 45-, 60-, or 90-minute periods of midday sunlight. It was determined that preparations 1 and 3 were not removed by swimming and afforded fairly good protection, as no test sites treated with these preparations showed evidence of erythema even after 90 minutes of midday sunlight exposure. Preparation 2, however, was readily removed as the result of swimming, and the test sites treated with this material showed evidence of a sunburn reaction. The mean protective indexes were as follows: preparation 3 (greater than 4.4), preparation 1 (greater than 4.2), and preparation 2 (1.04).

In the latter two studies described above, the substantivity of preparation 2 was decidedly less than that for either preparation 1 or 3. The formulations for the three preparations are quite similar, except that preparation 2 does not contain 2-hydroxy-4-methoxy benzophenone. In regard to 2-phenylbenzimidazole-5-sulfonic acid, the second study cited above demonstrated that a lotion containing a 3 percent concentration of this compound provided adequate protection after 120 minutes of midday sunlight exposure, but the last two studies would appear to demonstrate that the substantivity of this compound is questionable.

A total of 41 fair-skinned male subjects participated in a series of four studies under conditions similar to those for the five studies described above to evaluate the photoprotective properties of several preparations which were 1.5 percent 2-phenylbenzimidazole-5-sulfonic acid and 3 percent ethylhexyl *p*-methoxycinnamate cream; 2.75 percent 2-phenylbenzimidazole-5-sulfonic acid, 4 percent ethylhexyl *p*-methoxy-cinnamate and 3 percent 2-hydroxy-4-methoxy benzophenone cream; 2.75 percent 2-phenylbenzimidazole-5-sulfonic acid, 5 percent eth-

ylhexyl *p*-methoxycinnamate and 4 percent 2-hydroxy-4-methoxy benzophenone cream; 7 percent ethylhexyl *p*-methoxycinnamate and 3 percent 2-hydroxy-4-methoxy benzophenone oil; 5 percent aminobenzoate in 55 percent ethanol lotion; and 2.55 percent padimate A in 70 percent ethanol lotion (ref. 9). The latter two preparations were commercial sunscreens. The studies were conducted in Australia under bright sunlight and high humidity (over 90 percent) in mid-November. The MED for each subject was determined by exposing the appropriate sites to 5, 10, 15, 20, 25, and 30 minutes of midday sun on the day of the study.

In one study (study 1), 11 male subjects were used to evaluate the photoprotective properties of the above-described preparations against the stress of prolonged sunbathing without seating and swimming. Sixty minutes after applying two test materials and one of the two commercial sunscreen lotions to designated test sites on the back of each subject, each test site received 45, 90, 135, or 180 minutes of midday sunlight exposure. Erythema response was evaluated immediately and 24 hours later; 5 days following exposure an evaluation was made as to pigment response and evidence of any delayed phototoxic or photoallergic reactions. Preparations 1, 2, 3, and 5 (a lotion containing 5 percent aminobenzoate) were found to protect the skin against an immedate erythema reaction and to provide good protection against a sunburn reaction 24 hours following exposure. Preparations 4 (lacking 2-phenylbenzimidazole-5-sulfonic acid found in preparations 1, 2, and 3) and 6 (a lotion containing 2.55 percent padimate A) did not block an immediate erythema reaction and exhibited unsatisfactory protection 24 hours following exposure. All the above-described preparations neither stimulated nor inhibited a tanning reaction. A greater tanning response was obtained with the least protective formulations, namely, preparations 4 and 6 described above. None of the 11 subjects showed evidence of immediate or delayed phototoxicity or evidence of any cell-mediated delayed hypersensitivity reactions.

Nine male subjects (study 2) were involved in a substantivity study to evaluate the photoprotective properties of the above-described formulations under the combined stress of sweating and prolonged sunbathing. Sixty minutes after the application of two test materials and one of the two commercial lotions to designated test sites on the back of each subject, the subjects performed 30 minutes of calisthenics, running, and walking before the test sites were exposed to 90 or 180 minutes of midday sunlight exposure. Evaluations of the pigment darkening and erythema reactions were made immediately and 24 hours after exposure. Preparations 1, 2, 3, and 5 (commercial lotion containing 5 percent aminobenzoate) were again found to protect the skin against the immediate erythema reaction and to provide good protection against a sunburn reaction 24 hours after exposure. Preparation 2 was found to be especially substantive. Test sites treated with preparations 4 and 6 showed evidence of immediate vasodilation following sun exposure. These latter two preparations did not prevent an immediate erythema reaction and demonstrated unsatisfactory protection 24 hours following exposure. Evaluations performed 5 days after exposure found no evidence that any of the formulations caused phototoxic or photoallergic reactions or that they stimulated or inhibited the tanning response.

Eleven male subjects (study 3) participated in a substantivity study to evaluate the photoprotective properties of the six formulations under the combined stress of swimming and prolonged sunbathing. Sixty minutes following the application of two test materials and one of the two lotions to designated test sites on the back of each subject, the subjects swam in a chlorinated pool for 15 minutes prior to exposing the test sites to 60 or 120 minutes of midday sun. In terms of the immediate response, preparations 4, 5, and 6 showed definite presence of erythema, whereas the remaining three formulations rarely showed any immediate sunburn response. Erythema response 24 hours following exposure indicated that preparations 1, 2, and 3 were significantly more protective than preparation 4 and the two sunscreen lotions. Most of the test sites treated with the least protective formulation (the commercial lotion containing 5 percent aminobenzoate) showed a fair degree of sunburn reaction 24 hours after exposure. The protection provided by preparations 1, 2, and 3 was rated as good to excellent for a 120-minute sun exposure period. None of the formulations tested were found to be phototoxic or photosensitizing.

Ten male subjects (study 4) participated in a substantivity study to evaluate the photoprotective properties of the six formulations under the combined stress of sweating, swimming, and prolonged sunbathing. Sixty minutes after aplying three test materials and one of the two sunscreen lotions to designated test sites on the back of each subject, the volunteers engaged in 75 minutes of passive sunbathing before swimming in a chlorinated pool for 15 minutes. This was followed by 60 minutes of passive sunbathing, 10 minutes of calisthenics, 10 minutes of jogging and running, 10 minutes of walking, and 30 minutes of sunbathing while walking or in the sitting position. Total sun exposure for each subject was 195 minutes. The results were identical to those described above for the previous study.

The four studies described above revealed that preparations 1, 2, and 3 are significantly more protective and substantive than preparation 4. Preparation 4 differed from preparations 1, 2, and 3 in that it lacked 2-phenylbenzimidazole-5-sulfonic acid and was formulated with an oil rather than a cream base.

Based on the available data, the Panel concludes that 2-phenylbenzimidazole-5-sulfonic acid is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 1 to 4 percent 2-phenylbenzimidazole-5-sulfonic acid: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 1 to 4 percent 2-phenylbenzimidazole-5-sulfonic acid: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.)

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r. *Red petrolatum.* The Panel concludes that red petrolatum is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

Red petrolatum is also known as red veterinary petrolatum. Red petrola-

tum is a product of oil refineries, as are the other petrolatums. It is the product of minimal filtration, which accounts for its red color. Specifications, other than color, are similar to those of the liquid, white or yellow petrolatum.

(1) *Safety.* Clinical use and marketing experience have confirmed that red petrolatum is safe in the dosage range used as an OTC sunscreen.

Long use by millions of people attest to the safety of petrolatum. The petrolatums (liquid petrolatum, white petrolatum, yellow petrolatum, and red petrolatum) are products of oil refineries. A parafinic base crude oil is subjected to distillation at the refinery to remove the lighter hydrocarbons like gasoline and home fuel oil. The residue is a complex mixture containing heavy lubricating oil and petrolatum. This residue is mixed with a solvent (usually methyl ethyl ketone) and chilled to precipitate the petrolatum. The petrolatum is removed by special canvas filters. The petrolatum remains on the canvas, is distilled to remove the solvent, and is filtered through fuller's earth to the desired color. The red color passes through the filter as part of the petrolatum and is not an additive. Red petrolatum is the product of minimal filtration of the petrolatums (ref. *1*).

The physical properties of the petrolatums are vague in the "United States Pharmacopeia XV," where white and yellow petrolatum are mentioned, but red petrolatum is not. Penetrometer tests for consistency for both white and yellow petrolatum can vary from 100 to 275. Melting points vary from 38° to 60° C. Red petrolatum conforms to these tests. Red petrolatum contains the intrinsic red pigment from crude oil and some paraffin wax. Because it is the heaviest of the petrolatums (industrial petrolatum number zero), it contains more wax than the other petrolatums; but red petrolatum spreads to a smooth, almost invisible film on the skin, and leaves no visible greasy film that can be felt, as do the other petrolatums (ref. *1*).

The petrolatums are considered to be inert when applied to the skin. They serve as vehicles for many drugs and cosmetics for topical application. The product manufacturer reports one complaint per 120,000 units sold (ref. *2*).

The Panel concludes that the long and extensive use of the substance with no adverse effects being reported in the medical literature attests to the safety of red petrolatum as a sunscreen for OTC use.

(2) *Effectiveness.* There are well-controlled studies documenting the effectiveness of red petrolatum as an OTC sunscreen.

A 0.03 mm film of red petrolatum absorbs UV-light below 320 nm. About 16 percent is transmitted at 334 nm and 58 percent at 365 nm (ref. *3*). Why red petrolatum is also called red veterinary petrolatum is not clear because veterinarians do not use it. Currently, the red pigment is thought to be the single ingredient responsible for its sun-protective effect. Red petrolatum fluoresces brilliantly under Wood's light (365 nm).

In December 1942, the Army Air Corps requested the most effective protective substance against sunburn for men marooned on life rafts or in the desert following airplane crashes. The substance was required to have maximum protection per unit weight and volume so as to fit into life rafts and emergency equipment, maximum skin coverage per unit weight and volume, stability and freedom from rancidity, and should not burst on freezing. Red petrolatum was found to be the most effective (ref. *3*). Red petrolatum completely protected a subject against erythema at a dose of 20 minutes' exposure from an S-1 type of sunlamp, the equivalent to 20 hours of the strongest sunlight in Cleveland, Ohio.

A controlled clinical trial performed in Houston, Tex., on 30 light-complexion white subjects compared red petrolatum, a benzophenone, amyl *p*-dimethylaminobenzoic acid and 7 percent para-aminobenzoic acid, simultaneously, for protection against exposure to the summer sun. Testing began at noon and continued for periods of 5 to 60 minutes. Red petrolatum gave the following cumulative percent protection for duration of exposure in minutes: 100 percent for 20 minutes, 92 percent for 30 minutes, 92 percent for 40 minutes, 84 percent for 50 minutes, and 65 percent for 60 minutes. The end point was the minimal time necessary to produce erythema. In this test, red petrolatum performed second best (ref. *4*).

Jillson and Baughman (ref. *5*) recommended red petrolatum as an effective sunscreen following their study of eight patients with photo-allergic dermatitis to bithionol, an antiseptic. They found it more effective than para-aminobenzoic acid for these patients (ref. *5*). Other dermatologists have recommended red petrolatum for patients and other consumers (refs. *6* and *7*).

Based on the available data, the Panel concludes that red petrolatum is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) for products providing a minimum SPF value of 2 to under 4 containing 30 to 100 percent red petrolatum: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 30 to 100 percent red petrolatum: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.)

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s. *Sulisobenzone.* The Panel concludes that sulisobenzone is safe and effective for OTC use as a sunscreen as specified in the dosage sectin discussed below.

Sulisobenzone is also known as 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid and is a sulfonic acid derivative of oxybenzone (ref. *1*). It has an approximate melting point of 145° C and is soluble in water, methanol, and ethanol (ref. *2*).

(1) *Safety.* Clinical use and marketing experience have confirmed that sulisobenzone is safe in the dosage range used as an OTC sunscreen.

The oral LD_{50} of sulisobenzone in rats is greater than 6.4 g/kg (ref. *3*). In a rabbit eye irritation study patterned after the Draize method, 0.1 ml of a 5 percent aqueous solution of sulisobenzone was instilled in the conjunctival sac of the right eye of each of nine albino rabbits. Four seconds after instillation the treated eye of three test animals was washed with 20 ml of lukewarm water. The left eye of each rabbit served as a control. Every 24 hours for the following 7 days, the cornea, iris, and conjunctiva of each rabbit were examined for signs of irritation and were graded according to

the standard Draize scoring system. It was reported that none of the washed or unwashed eyes treated with the test material showed any involvement of the cornea, iris, or conjunctiva fat any time during the 7-day period following instillation. It was thus concluded that the test material was not an ocular irritant (ref. *3*).

A repeated insult patch study was performed by applying 1-square inch gauze pads wetted with 0.5 ml of a 5 percent aqueous solution of sulisobenzone to the skin of 50 human subjects for 24 hours. Following the removal of the patches the test sites were evaluated. After a 24-hour rest the patches were reapplied. This process was repeated until there had been 15 applications of the treated patches after which there was a 2-week rest period before challenge doses were applied for 24 hours to the previous test sites. It was reported that the above-described test material was determined not to be a primary irritant, a fatiguing agent, or a sensitizer in any of the 50 subjects tested (ref. *3*).

Based on the available data, the Panel concludes that sulisobenzone is a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are studies documenting the effectiveness of sulisobenzone as an OTC sunscreen.

Sulisobenzone is soluble in water, ethanol, and methanol. It absorbs throughout the UV range, with its maximum absorbance at 285 nm (ref. *2*).

Using a solar simulator with a filter to eliminate wavelengths below 295 nm, 10 human subjects (8 females and 2 males) participated in a study to determine the protective factors of 1 and 3 percent aqueous solutions of sulisobenzone and similar concentrations of aminobenzoate preparations (ref. *4*). Once the MED for each subject was determined, 3.6 ul of each test material was applied to each cm^2 of test site area. Each sulisobenzone-treated area was exposed to 1.5, 2, 2.5, and 3 times MED. The 1 percent aminobenzoate-treated areas were exposed to 2.5, 3, 3.5, and 4 times MED. Twenty-four hours after exposure, the test areas were graded for erythemal response on a scale from 0 (no perceptible erythema) to 4 (severe erythema with blistering). The protection factor was determined by dividing a test material's MED for protected skin by its MED for unprotected skin. the mean protection factors were 1.9 for 1 percent sulisobenzone, 2.5 for 3 percent sulisobenzone, 3.35 for 1 percent aminobenzoate, and 4.6 for 3 percent aminobenzoate.

A substantivity study of five sunscreens, including one containing 10 percent sulisobenzone, found that the mean protective value exhibited by the 10 percent sulisobenzone preparation was only slightly less than that for the untreated control sites when the subjects, 1 hour after applying the test materials, swam in an indoor pool for 10 minutes before the test sites were exposed to 4 to 6 MED's of sunlight. This study was discussed elsewhere in this document. (See part III. paragraph B.1.p. above—Padimate O.) The data would indicate that sulisobenzone was for all practical purposes completely removed during the swimming period (ref. *5*).

Knox et al. (ref. *6*) evaluated the comparative ability of sulisobenzone and aminobenzoate to prevent the development of ultraviolate-induced skin cancers in albino mice. In a series of studies, 5 and 10 percent solutions of sulisobenzone in alcohol and a 5 percent solution of aminobenzoate in alcohol were employed. Both ingredients were reported to decrease markedly the erythematous and carcinogenic effect of UV light, with sulisobenzone being superior to aminobenzoate under certain conditions because of its wider absorption spectrum.

Based on the available data, the Panel concludes that sulisobenzone is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 5 to 10 percent sulisobenzone: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 5 to 10 percent sulisobenzone: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.)

REFERENCES

(1) Remington's Pharmaceutical Sciences, 15th Ed., Mack Publishing Co., Easton, Pa., p. 729, 1975.

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(4) "Efficacy Data," Draft of unpublished paper in OTC volume 060128.

(5) Sayre, R. E., "PSL Formula RB 292-240A, Lot No. 352206, Outdoor testing of PSL versus Comparative Products: Eclipse, PreSun, Sol-Bar, Super Shade and Uval," Draft of unpublished paper in OTC volume 060131.

(6) Knox, J. H., A. C. Griffen and R. E. Hakim, "Protection from Ultraviolet Carcinogenesis," *Journal of Investigative Dermatology*, 34:51-58, 1960.

t. *Titanium dioxide.* The Panel concludes that titanium dioxide is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

Titanium dioxide is employed as a physical sunscreen. It reflects and scatters UV and visible light rays providing a barrier for sun-sensitive individuals, against the effects of the sun. It is used to prevent sunburn and suntan.

Titanium dioxide is found in nature as the minerals rutile, ilmenite, perovskite, anatase or octahedrite and brookite. It is a white powder, with a melting point of 1,855° C, insoluble in water, hydrochloric acid, nitric acid, and diluted sulfuric acid. It is used as a mordant in dyeing, as a pigment in the rubber industry, and in the manufacture of synthetic resins and oil cloth. It is also used in preparations of face powders and beauty creams (ref. *1*).

Titanium dioxide scatters both UV and visible light radiation (290 to 700 nm) rather than absorbing the rays. It may occasionally be so occlusive as to produce miliaria (ref. *2*).

(1) *Safety.* Clinical use and marketing experience have confirmed that titanium dioxide is safe in the dosage range used as an OTC sunscreen.

Because titanium dioxide is chemically inert, no meaningful oral LD_{50} can be obtained in animals. For all practical purposes, titanium dioxide is inert, devoid of toxicity, and is not a sensitizer or primary irritant. Being a brilliant white powder, it is formulated with cosmetic pigments for consumer acceptance. Often other sunscreens are incorporated with titanium dioxide in emulsion bases, lipsticks, and ointments.

In a single dose, acute oral toxicity study in which a cream containing 5 percent titanium dioxide in combination with 5 percent menthyl anthranilate was given in a dose of 5 g/kg to 10 Sherman albino rats, no fatalities were reported during a 14-day observation period. Histopathological examination revealed no gross organ abnormalities (ref. *3*).

No reports of irritation have been attributed to titanium dioxide (ref. *4*). The probable lethal dose in humans is reported to be above 15 g/kg, or more than 1 qt for a 70 kg man. A pound (16 oz) has been ingested without apparent harm or distress. It was eliminated in about 24 hours (ref. *5*).

Fisher proposed the inclusion of titanium dioxide, "an effective non-sensitizing sun-screen for all wavelengths of UV light," with other effective sunscreens to possibly prevent photosensi-

tizing reactions caused by the latter (ref. *2*).

Between 1949 and 1972 almost 3.5 million units of a sunscreen containing 5 percent menthyl anthranilate and 5 percent titanium dioxide were distributed with less than one complaint received per 100,000 units marketed. None of the complaints could be attributed to the inclusion of titanium dioxide in the formulation (ref. *6*).

Based on the available data, the Panel concludes that titanium dioxide is a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are studies documenting the effectiveness of titanium dioxide as an OTC sunscreen.

Titanium dioxide is a white, amorphous, odorless powder which is insoluble in water. It is used in ointments and lotions at a concentration of 15 to 25 percent as a protective against sunburn. It is also used in other protective preparations and in dusting powders and face powders (ref. *12*). It is physiologically and pharmacologically an inert substance (ref. *7*).

Titanium dioxide was found to be an effective mechanical screen in humans exposed to artificial UV light (ref. *8*). It is effective in preventing or reducing the passage of UV radiation to the skin. Titanium dioxide is "perhaps the most suitable and widely used" light-scattering ingredient in sunburn preventives (ref. *9*).

Titanium dioxide is recognized as an effective opaque chemical for use as a physical sunscreen because it scatters UV rays, thereby preventing sunburn.

Giese and Wells investigated the use of various pigments such as titanium dioxide, zinc oxide, magnesium oxide, magnesium carbonate, magnesium stearate, etc. as fillers in vehicles for sunscreen preparations. Titanium dioxide was found to surpass the other ingredients tested in terms of overcoming the after-sticky or greasy feel and improving the water resistance, covering power and screening power in a mechanical way (ref. *10*). They further concluded that "As a pigment, titanium dioxide was found more satisfactory than magnesium oxide. The pigment gives covering power and mechanical screening."

Schwartz and Peck reported that "Heavily pigmented preparations (liquids, creams or powders) will prevent or reduce the passage of the UV radiation" but, "while preventing sunburn, such preparations will prevent also suntan. Zinc oxide, calamine, and titanium dioxide are most effective in this regard" (ref. *11*).

Based on the available data, the Panel concludes that titanium dioxide is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 2 to 25 percent titanium dioxide: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 2 to 25 percent titanium dioxide: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.)

REFERENCES

(1) OTC Volume 060001.

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(4) "Human Safety Data," Draft of unpublished paper in OTC Volume 060001.

(5) Gleason, M. N., R. E. Gosselin, H. C. Hodge and R. P. Smith, "Clinical Toxicology of Commercial Products," 3d Ed., The Williams and Wilkins Co., Baltimore, p. 144, 1969.

(6) "Human Safety Data," Draft of unpublished paper in OTC Volmue 060001.

(7) "Animal Safety Data," Draft of unpublished paper in OTC Volume 060001.

(8) "Efficacy Data," Draft of unpublished paper in OTC Volume 060001.

(9) Kesten, B. M. and M. Slatkin, "Diseases Related to Light Sensitivity," *Archives of Dermatology and Syphilology*, 67:284-301, 1953.

(10) Giese, A. C. and J. M. Wells, "Sweat and Water Resistant Sunburn Preparations," *Journal of the American Pharmaceutical Association*, (SAci. Ed.), 35:208-212, 1946.

(11) Schwartz, L. and S. M. Peck, "Cosmetics and Dermatitis," Paul B. Hoeber, Inc., New York, p. 145, 1947.

(12) "The United States Dispensatory," 27th Ed., Edited by A. Osol and R. Pratt, J. B. Lippincott and Co., Philadelphia, P. 1198, 1973.

u. *Triethanolamine salicylate.* The Panel concludes that triethanolamine salicylate is safe and effective for OTC use as a sunscreen as specified in the dosage section discussed below.

Triethanolamine salicylate is miscible in all proportions in water, glycerin, propylene glycol, ethyl and isopropyl alcohol but it is insoluble in mineral or vegetable oil.

(1) *Safety.* Clinical use and marketing experience have confirmed that triethanolamine salicylate is safe in the dosage range used as an OTC sunscreen.

Animal and human toxicological data attest to its safety for human topical application. The oral LD_{50} is 2.8 g/kg in rats (ref. *1*).

Triethanolamine salicylate was applied to the intact and abraded skin of six albino rabbits. The intact skin sites showed no evidence of erythema or edema 24 and 72 hours following treatment except for two rabbits where very mild erythema was present after 24 hours, but disappeared by the time of the 72-hour evaluation. The abraded skin sites generally showed moderate erythema and mild edema 24 and 72 hours after application. A primary irritation index of 1.5 was obtained, but the compound was not considered to be a primary irritant to the skin (ref. *2*).

A rabbit eye irritation study patterned after the Draize method was conducted in which 0.1 ml of triethanolamine salicylate as instilled into the conjunctival sac of the right eye of each of nine albino rabbits, with the left eye serving as a control. Following the instillation of the test material, the animals were divided into three groups with three rabbits having their treated eyes washed 2 seconds later, three rabbits having their treated eyes washed 4 seconds later, and three rabbits having their treated eyes remain unwashed. No corneal, iridial, or conjunctival irritation was observed after 1, 2, and 3 days in the treated eyes which were washed 2 and 4 seconds following instillation of the test material. The unwashed treated eyes of two rabbits showed very mild, transient conjunctival irritation which cleared by the second day. From the data above the investigator concluded that the test material was not a severe ocular irritant as defined by the Draize procedure (ref. *3*).

Repetitive intracutaneous injections of a 0.1 percent suspension of triethanolamine salicylate in physiological saline into the closely clipped back and flanks of 10 white male guinea pigs (Hartley strain) were performed every other day or three times weekly until each animal had received a total of 10 injections. Initially, 0.05 ml of the test material was injected, with 0.1 ml being administered during each of the nine remaining injections. After a 2-week rest period, a 0.05 ml challenge dose was administered. Twenty-four hours following each injection, readings of the diameter, height, and color of any reactions were made. As none of the animals showed evidence of any response to any of the repetitive or challenge intracutaneous injections, the investigator concluded that the test material was not a sensitizing agent as defined by the Draize procedure (ref. *4*).

The acute oral LD_{50} for a sunscreen gel containing 8.625 percent triethanolamine salicylate was greater than 21.5 ml/kg of body weight in albino rats.

The acute dermal LD_{50} of this preparation in albino rabbits was determined to be greater than 10.0 ml/kg of body weight (ref. *5*). A primary skin irritation study of this preparation involving the intact and abraded skin of six albino rabbits found that the irritative effects were confined to very slight erythema to two intact and three abraded skin sites at the 24-hour reading and had disappeared by the 72-hour reading. The primary irritation index was found to be 0.21 (ref. *5*). When 0.1 ml of this preparation was instilled into one eye of each of six albino rabbits, no irritative effects involving the cornea, iris, and conjuctiva were noted in any of the test animals 24, 48, and 72 hours following instillation (ref. *5*).

A double-blind skin irritation study comparing a 10 percent methyl salicylate cream, 10 and 20 percent triethanolamine creams, and a placebo control or vehicle were performed on seven female and three male human subjects wherein patches of each test material were applied to four different areas of each individual's back (ref. *6*). The patches were evaluated at 0 hour (preapplication) and at 4, 8, and 24 hours postapplication for evidence of skin reactions such as erythema, scaling, itching, dryness, and texture. None of the formulations produced dermographia, ulceration, hair loss, eruption, or burning. It was concluded by the investigator that both the 10 and 20 percent triethanolamine salicylate creams were well-tolerated by all 10 subjects and that the degree and frequency of erythema resulting from these two preparations were very similar and did not differ significantly from the degree and frequency resulting from the placebo. Significantly more erythema was caused by the 10 percent methyl salicylate cream, and there was a statistically significant increase in the erythema caused by this preparation from 4 to 24 hours postapplication, whereas the degree of any erythema caused by the other preparations generally remained constant throughout the evaluation period.

Repeated insult patch tests of a sunscreen gel containing 8.625 percent triethanolamine salicylate were performed on the upper arms of 11 human subjects using an adaptation of the Draize method (ref. *7*). For each application, five drops of the test material were placed on a patch which was then affixed to the designated test site and left in place for 24 hours. Applications were made every other day or three times weekly until each patient received a total of nine applications. Evaluations of any skin reactions were made just prior to reapplication of the test material. After an approximately 3-week rest period, challenge doses were applied and evaluations were made 24 and 72 hours after removal of the patches. None of the 11 subjects showed evidence that the test material was a sensitizing agent, and the test material was nonirritating to all but one subject. This subject experienced erythema and papules at the time of the seventh repeat application which did not reappear when subsequent applications were made to adjacent test sites. Because this subject reacted similarly to two of seven other test materials that were applied concurrently during this study, the investigator concluded that "the pattern of reactions observed indicates that these were probably due to cumulative irritation (skin fatigue)" (ref. *7*).

Similar repeated insult patch tests of a sunscreen lotion containing 8.5 percent triethanolamine salicylate were performed on the upper arms of 57 human subjects in which 0.2 to 0.3 ml of the test material was placed on a patch at the time of each application. Eight subjects showed evidence of slight erythema on one or more occasions during the repeated insult tests. Except for one subject who showed evidence of slight erythema from the first through the seventh application, this reaction was normally observed once but no more than three times during the series for the other seven patients. Another subject showed evidence of slight erythema following removal of the challenge dose. The investigator concluded that the above-described test material was only slightly more irritating than two other compounds tested concurrently in the same population which were considered essentially not irritating throughout the study (ref. *8*).

A percutaneous absorption study of a cream containing 10 percent triethanolamine salicylate was performed on 12 healthy male volunteers by applying the contents of a 0.5 oz tube (equivalent to 750 mg salicylic acid) to a 25 cm x 30 cm area on the back of each subject and determining the amount of salicylic acid and its metabolites excreted in in the urine during the next 24 hours (ref. *9*). In one group of six individuals the test material was layered on the test site with a wood applicator. In the second group of six individuals the test material was applied to the test site and massaged with gloved hands for 5 minutes. The empty tubes of the test material and the application materials were then reweighed to determine the amount of test material actually applied to each test site. The test sites were protected with a polyethylene sheet covering. The sheets were removed after 24 hours, and the test sites were observed then and 2 days later for any sign of irritation. Only one individual experienced any skin reaction, which consisted of very mild transient pruritis with blanching of the skin after slight pressure which cleared by the second day of the study. Total salicylate recovery, including metabolites, in terms of free salicylic acid, ranged from 4.3 to 26.8 (mean of 12.2) percent in those individuals on whom the test material was applied by a wood applicator. Total salicylate recovery for those subjects on whom the test material was massaged for 5 minutes ranged from 0.8 to 32.5 (mean of 14.8) percent. Mean salicylate recovery for all 12 individuals was 13.5 percent. No explanation was given for the little or no recovery (0.8 percent) of salicylate from one individual, but it is possible that additional salicylate would have been recovered from all individuals if urine collection had extended beyond 24 hours.

Percutaneous absorption studies of various salicylates in rabbits demonstrated that 15.6 percent of the salicylic acid contained in a triethanolamine salicylate preparation having a base of glyclo stearate, paraffin oil, and water was excreted in the urine over a 48-hour period (ref. *10*).

Based on available data, the Panel concludes that triethanolamine salicylate is a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are studies documenting the effectiveness of triethanolamine salicylate as an OTC sunscreen.

Its absorbance is between 260 and 320 nm, with its maximum absorbance at 298 nm. Miscible in all proportions in water, glycerine, propylene glycol, ethyl and isopropyl alcohol, but insoluble in mineral or vegetable oil, it has been incorporated into aqueous lotions and gels (ref. *11*).

The efficacy of a sunscreen lotion containing 8.5 percent triethanolamine salicylate was evaluated in 16 human subjects at a St. Petersburg, Fla. beach (ref. *12*). Except for a few patients who participated in the study on a mid-November day when the temperature was 67° F and the sky was partly cloudy, the tests were performed on sunny days at a temperature of 73° F. Approximately 0.1 ml of the test material was applied to four 1 x 1½ inch areas on the back of each subject, and each site received 45, 75, 120, or 180 minutes of sun exposure. The erythema response was graded on a scale from 1 (no perceptible erythema throughout the study except in some instances when evaluations of erythema response were made 1 day after sun exposure: The instances of erythema were just perceptible erythema in two cases with 45 minutes' exposure. Two subjects showed just perceptible erythema, and one subject showed moderate erythema with 75 minutes of sun exposure. One subject had just perceptible erythema, and two subjects had moderate erythema

with 120 minutes of exposure. Moderate erythema was seen in four cases with 180 minutes exposure. The percent protection based upon the erythema scores for treated sites and untreated control sites was determined to be 82, 75, and 76 percent after 75, 120, and 180 minutes of sun exposure, respectively. Based on a scale from 00 (no tanning) to 02 (marked tanning), it was determined that treated sites showed a slight tan (score of 01) or greater from the second to fifth day after 120 and 180 minutes of sun exposure and generally showed more of a tan than the untreated control sites during the same period following similar sun exposure.

Based on available data, the Panel concludes that triethanolamine salicylate is an effective sunscreen ingredient for OTC use.

(3) *Dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 5 to 12 percent triethanolamine salicylate: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 5 to 12 percent triethanolamine salicylate: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. below—category I labeling.)

REFERENCES

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(2) "Primary Skin Irritation—Triethanolamine Salicylate," Draft of unpublished paper in OTC Volume 060091.

(3) "Eye Irritation—Triethanolamine Salicylate," Draft of unpublished paper in OTC Volume 060091.

(4) "Intracutaneous Sensitization—Triethanolamine Salicylate," Draft of unpublished paper in OTC Volume 060091.

(5) "Acute Toxicity and Irritation Studies of Suretan Gel," Draft of unpublished paper in OTC Volume 060091.

(6) "Evaluation for Potential Skin Irritation of Mobisyl Cream," Draft of unpublished paper in OTC Volume 060156.

(7) "Pilot Repeated Insult Patch Test of Eight Samples," Draft of unpublished paper in OTC Volume 060091.

(8) "Repeated Insult Patch Test," Draft of unpublished paper in OTC Volume 060091.

(9) OTC Volume 060144.

(10) "Animal Safety Data," Part III.A.2.e., Draft of unpublished paper in OTC Volume 060024.

(11) OTC Volume 060091.

(12) "Sunscreening and Tanning Efficacy Study," Draft of unpublished paper in OTC Volume 060091.

CATEGORY I LABELING

The Panel recommends the following category I labeling for sunscreen active ingredients to be generally recognized as safe and effective and not misbranded as well as any specific labeling discussed in the individual ingredient statements.

a. *Indications.* The indications should be limited to one or more of the following phrases:

(1) *For all (minimal, moderate, extra, maximal and ultra) sunscreen products.* (i) "Sunscreen to help prevent sunburn."

(ii) "Filters (or screens) out the sun's burning rays to prevent sunburn."

(iii) "Screens out the sun's harsh and often harmful rays to prevent sunburn."

(iv) "Overexposure to the sun may lead to premature aging of the skin and skin cancer. The liberal and regular use over the years of this product may help reduce the chance of these harmful effects."

(v) "Overexposure to the sun may lead to premature aging of the skin and skin cancer. The liberal and regular use over the years of this product may help reduce the chance of premature aging of the skin and skin cancer."

(2) *Additional indications.* In addition to the indications provided above in item (1), the following may be used:

(i) *For minimal sunscreen products.* (*a*) "Affords minimal protection against sunburn."

(*b*) "Prolongs exposure time before sunburn occurs."

(*c*) "Permits tanning (or suntanning) and reduces chance of (or minimizes) sunburning."

(*d*) "Helps prevent sunburn on limited exposure of untanned skin."

(*e*) "Helps to protect the skin against sunburn while permitting tanning."

(*f*) "Allows you to stay in the sun 2 times longer than without sunscreen protection."

(*g*) "Provides 2 times your natural protection from sunburn."

(ii) *For moderate sunscreen products.* (*a*) "Affords moderate protection against sunburn."

(*b*) "Prolongs exposure time before sunburn occurs."

(*c*) "Permits tanning (or suntanning) and reduces chance of (or minimizes) sunburning."

(*d*) "Helps prevent sunburn on moderate exposure of untanned skin."

(*e*) "Allows you to stay in the sun 4 times longer than without sunscreen protection."

(*f*) "Provides 4 times your natural protection from sunburn."

(iii) *For extra sunscreen products.* (*a*) "Affords extra protection against sunburn."

(*b*) "Prolongs exposure time before sunburn occurs."

(*c*) "Permits limited tanning (or suntanning) and reduces chance of (or minimizes) sunburn."

(*d*) "Helps prevent sunburn."

(*e*) "For sun-sensitive skin."

(*f*) "Extra protection against sunburn for blondes, redheads and fair-skinned persons."

(*g*) "Allows you to stay in the sun 6 times longer than without sunscreen protection."

(*h*) "Provides 6 times your natural protection from sunburn."

(iv) *For maximal sunscreen products.* (*a*) "Affords maximal protection against suburn."

(*b*) "Prevents sunburn and limits tanning."

(*c*) "For sun-sensitive skin."

(*d*) "Maximal protection against sunburn for blondes, redheads, and fair-skined persons."

(*e*) "Allows you to stay in the sun 8 times longer than without sunscreen protection."

(*f*) "Provides 8 times your natural protection from sunburn."

(v) *For ultra sunscreen products.* (*a*) "Affords the most protection against sunburn."

(*b*) "Prevents tanning and sunburning."

(*c*) "For highly sun-sensitive skin."

(*d*) "Greatest protection against sunburn for blondes, readheads and fair-skinned persons."

(*e*) "Provides the highest degree of sunburn protection and permits no tanning."

(*f*) "Provides the highest degree of sunscreen protection and permits no tanning."

(3) *For all (maximal and ultra) sunscreen products that contain sunscreen opaque sunblock ingredients.* "Reflects the burning rays of the sun."

b. *Statement on product performance*—(1) *Product category designation (PCD).* The Panel concludes that improved, more informative labeling should be provided to the consumer to aid in selecting the most approriate sunscreen product. The Panel recommends that the following appropriate labeling statement(s) be prominently placed on the principal display panel of the products:

(i) Products containing active ingredient(s) that provide an SPF value of 2 to under 4: "Minimal sun protection product (SPF 2)—Stay in the sun twice as long as before without sunburning."

(ii) Products containing active ingredient(s) that provide an SPF

value of 4 to under 6: "Moderate sun protection product (SPF 4)—Stay in the sun 4 times as long as before without sunburning."

(iii) Products containing active ingredient(s) that provide an SPF value of 6 to under 8: "Extra sun protection product (SPF 6)—Stay in the sun 6 times as long as before without sunburning."

(iv) Products containing active ingredient(s) that provide an SPF value of 8 to under 15: "Maximal sun protection product (SPF 8)— Stay in the sun 8 times as long as before without sunburning."

(v) Products containing active ingredient(s) that provide an SPF value of 15 or greater: "Ultra sun protection product (SPF 15)—Stay in the sun 15 times as long as before without sunburning."

(2) *Labeling claims related to the PCD and SPF value.* The Panel recommends any of the following labeling claims for sunscreen products that satisfy the sunscreen product testing procedures described elsewhere in this document. (See part III. Paragraph D. below—Sunscreen products testing procedures for determination of the sun protection factor (SPF) value and related labeling claims.)

(i) *For all (minimal, moderate, extra, maximal, and ultra) sunscreen products—(a) That satisfy the water resistance testing procedures.* (*1*) "Water resistant."

(*2*) "Retains its sun protection for at least 40 minutes in the water."

(*3*) "Resists removal by sweating."

(*b*) *That satisfy the waterproof testing procedures.* (*1*) "Waterproof."

(*2*) "Retains its sun protection for at least 80 minutes in the water."

(*3*) "Resists removal by sweating."

(*c*) *That satisfy the sweat resistance testing procedures.* (*1*) "Retains its sun protection for at least 30 minutes of heavy sweating."

(*2* "Sweat resistant.")

(3) *Labeling guide for recommended sunscreen product use.* The Panel recommends the following compilation of skin types and PCD's be appropriately included in labeling as a guide:

RECOMMENDED SUNSCREEN PRODUCT GUIDE

Sunburn and Tanning History and Recommended Sun Protection Product

Always burns easily; never tans: Maximal, ultra.
Always burns easily; tans minimally: Extra.
Burns moderately; tans gradually: Moderate.
Burns minimally; always tans well: Minimal.
Rarely burns; tans profusely: Minimal.

c. *Warnings—For all (minimal, moderate, extra maximal, and ultra) sunscreen products.* The labeling of all sunscreen products should contain the following warnings:

(i) "For external use only, not to be swallowed."

(ii) "Avoid contact with the eyes."

(iii) "Discontinue use if signs of irritation or rash appear."

(2) *Specific warnings*—(i) *For sunscreen products providing an SPF value of 2 to under 4.* "Use on children under 2 years of age only with the advice of a physician."

(ii) *For sunscreen products providing an SPF value of 4 or greater.* "Use on children under 6 months of age only with the advice of a physician."

d. *Directions for use.* The Panel believes that many consumers use inadequate amounts of sunscreen. Offering more detailed guidelines would benefit the consumer.

Based upon a review of the available data, the Panel recommends that the directions for use state: "Apply liberally before sun exposure and reapply after swimming or after excessive sweating."

However, for sunscreen products that satisfy the water resistance, waterproof and sweat resistance testing procedures described elsewhere in this document, the directions for use in the labeling of these products may be modified in accordance with the results of the test. (See part III. paragraph D. below—Sunscreen product testing procedures for determination of the sun protection factor (SPF) value and related labeling claims.) The Panel recommends that for sunscreen products that satisfy these testing procedures the following modifications replace the directions-for-use labeling indicated above:

For all (minimal, moderate, extra, maximal and ultra) sunscreen products—(1) *That satisfy the water resistant testing procedures.* "Apply liberally before sun exposure and reapply after 40 minutes in the water or after excessive sweating."

(2) *That satisfy the waterproof testing procedures.* "Apply liberally before sun exposure and reapply after 80 minutes in the water or after excessive sweating."

(3) *That satisfy the sweat resistance testing procedures.* "Apply liberally before sun exposure and reapply after 30 minutes of excessive sweating."

2. *Category II conditions under which sunscreen ingredients are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the category II conditions be eliminated from OTC sunscreen drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER.

CATEGORY II ACTIVE INGREDIENTS

The Panel has classified the following sunscreen ingredients not generally recognized as safe and effective or as misbranded:

2-Ethylhexyl 4-phenylbenzophenone-2'-carboxylic acid,
3-(4-Methylbenzylidene)-camphor,
Sodium 3,4-dimethylphenyl-glyoxylate.

a. *2-Ethylhexyl 4-phenylbenzophenone-2'-carboxylic acid.* The Panel concludes that 2-ethylhexyl 4-phenylbenzophenone-2'carboxylic acid is not safe and not effective for OTC use as a sunscreen.

The ingredient 2-ethylhexyl 4-phenylbenzophenone-2'carboxylic acid is a clear, faintly brownish-yellow, highly viscous oil with a faint characteristic odor. It is miscible in all proportions with methanol, ethanol, ether, chloroform and benzene, but is immiscible with water. It has a molecular weight of approximately 414 (ref *1*).

(1) *Safety.* Clinical use and marketing experience are insufficient to confirm that 2-ethylhexyl 4-phenylbenzophenone-2'carboxylic acid is safe for use as an OTC sunscreen.

2-Ethylhexyl 4-phenylbenzophenone-2'-carboxylic acid was tested for acute toxicity using 40 rats of the Wistar strain. A dosage ranging from 8,000 mg/kg to 16,000 mg/kg was given to the rats in the form of a 20 percent solution of 2-ethylhexyl 4-phenylbenzophenone-2'carboxylic acid in peanut oil. The test material was administered by means of a gastric tube. Readings on days 1, 7, and 14 showed an approximate LD_{50} in excess of 16,000 mg/kg (ref. *2*).

In another test the approximate LD_{50} of 2-ethylhexyl 4-phenylbenzophenone-2'carboxylic acid was determined by means of topical application. One hour before the start of the test, 10 rats, with an average weight of 152 g, had the hair of the back and stomach removed with an electric clipper. 2-Ethylhexyl 4-phenylbenzophenone-2-carboxylic acid was then applied undiluted onto the shorn skin area. The test material was left on the skin area for 24 hours and then rinsed with water. Observations of the area tested gave an approximate LD_{50} reading in excess of 10,000 mg/kg (ref. *2*).

Skin irritation was studied using six white New Zealand rabbits. Twenty-four hours prior to the test, the backs and flanks of the animals were shorn with an electric clipper. In three of the animals the skin was scarified with razor blade cuts. 2-Ethylhexyl 4-phenyl - benzophenone - 2' - carboxylic acid, undiluted and in the amount of 0.5 ml, was applied to the left side of the test animals. An equal amount of peanut oil was applied to the right side. The 2-ethylhexyl 4-phenylbenzophenone-2'-carboxylic acid was rinsed away 24 hours after initial testing. All the rabbits were observed daily for any skin changes or toxicity. In all rabbits tested, none showed any sign

of behavioral changes, altered general condition, or any sign of skin irritation in either 2-ethylhexyl 4-phenylbenzophenone-2'-carboxylic acid or in peanut oil (ref. *2*).

2-Ethylhexyl 4-phenylbenzophenone-2'-carboxylic acid was also tested for primary mucosal irritation in rabbit's eyes. Three male white New Zealand rabbits with an average weight of 2 kg were used in the test. All animals were preexamined to ensure no pathological states existed in the eye before actual testing. A 0.1 ml volume of 2-ethylhexyl 4-phenylbenzophenone-2'-carboxylic acid was then instilled into the conjunctival sac of the left eye. The untreated right eye served as a control. There was no rinsing of the eye after instillation of the test substance. The eyes were examined for 6 days by evaluation methods proposed by Draize. No eye irritation was observed in any of the rabbits tested (ref. *2*).

Based on the lack of human clinical and marketing data, the Panel concludes that 2-ethylhexyl 4-phenylbenzophenone-2'-carboxylic acid is not a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are no studies documenting the effectiveness of 2-ethylhexyl 4-phenylbenzophenone-2'-carboxylic acid as an OTC sunscreen.

One manufacturer submitted a booklet suggesting the ingredient as a UV filter for cosmetics. It was recommended that a 2 to 4 percent concentration be used in the sunscreen products.

2-Ethylhexyl 4-phenylbenzophenone-2'-carboxylic acid absorbs UV light mainly in the range of 290 to 340 nm. Testing has shown that the UV permeability of 2-ethylhexyl 4-phenylbenzophenone-2'-carboxylic acid dissolved in methanol at a concentration of 0.001 g/100 ml and at a thickness layer of 1 cm, ranges from 98 percent at 340 nm to 27 percent at 290 nm (ref. *1*).

Based on the lack of sufficient data, the Panel concludes that 2-ethylhexyl 4 - phenylbenzophenone - 2' - carboxylic acid is not an effective sunscreen ingredient for OTC use.

(3) *Evaluation.* Based on the lack of clinical and marketing data, the Panel concludes that 2-ethylhexyl 4-phenylbenzophenone-2'-carboxylic acid is not safe and effective for OTC use.

REFERENCES

(1) OTC Volume 060090.
(2) OTC Volume 060093.

b. *3-(4-Methylbenzylidene)-camphor.* The Panel concludes that 3-(4-methylbenzylidene)-camphor is not safe and not effective for OTC use as a sunscreen.

3-(4-Methylbenzylidene)-camphor is a white crystalline powder, having a faint characteristic odor not resembling camphor. It is soluble in ethanol, chloroform, and vegetable oils, though practically insoluble in water. It has a melting point of 65° to 67° C. It absorbs UV radiation primarily at 280 to 315 nm (ref. *1*).

(1) *Safety.* Clinical use and marketing experience are insufficient to confirm that 3-(4-methylbenzylidene)-camphor is safe for use as an OTC sunscreen.

3 - (4 - Methylbenzylidene) - camphor was studied in 30 rats of the Wistar strain. An aqueous suspension of 3-(4-methylbenzylidene)-camphor was administered orally by means of an esophageal tube to the rats, in dosages ranging from 10,000 mg/kg to 16,000 mg/kg. Observations recorded on days 1, 7, and 14 of the study showed the approximate LD_{50} to be in excess of 16,000 mg/kg (ref. *1*).

In another study, the approximate LD_{50} of 3-(4-methylbenzylidene)-camphor was determined by means of topical applications. Ten Wistar rats had the hair of the back and stomach removed with an electric clipper. The 3-(4-methylbenzylidene)-camphor was moistened with an equal amount of desalinated water and applied to the shorn skin area. The dosage applied to the skin was 10 g/kg. Twenty-four hours following initial application the test area was rinsed with water and observed for 2 weeks. any changes in the test area were recorded according to the method of Draize. Readings on days 1, 7, and 14 of the study showed an approximate LD_{50} in excess of 10,000 mg/kg. Rats autopsied at the end of the 14 days showed no evidence of abnormality (ref. *1*).

Skin irritation was studied in six white New Zealand rabbits. The rabbits were prepared 24 hours prior to the start of the study by shaving the back and upper flanks with an electric clipper. Three of the six rabbits had the test area scarified by means of a skin scraper consisting of 10 razor blades spaced 1 mm apart. Each blade had an exposed blade area of 0.5 mm. All of the rabbits received, on the left half of the test area, 5 g of 3-(4-methylbenzylidene)-camphor moistened with water and spread on pads 4 centimeters square. The right half of the back received an equal amount of talcum powder applied by the same method. An occlusive bandage was then applied to the area. After 24 hours of skin contact, the test material was removed and rinsed with water. The rabbits were then observed daily for 6 days. No sign of any skin irritation was found in any of the animals tested (ref. *1*).

Another test studied 3-(4-methylbenzylidene)-camphor for primary mucosal irritation on the rabbit eye. Six white New Zealand rabbits, preexamined to exclude any eye abnormalities, were used for the test. The left eye of three of the rabbits was subjected to 0.1 g of 3-(4-methylbenzylidene)-camphor suspended in 0.1 ml peanut oil. the right eye, untreated, served as a control. The other three rabbits had 0.1 ml peanut oil placed in the conjunctival sac of the left eye. The right eye again was left untreated. The rabbits were examined daily for 6 days, and changes were recorded according to the Draize test evaluation. Observations showed no eye reaction or irritation in any of the rabbits tested (ref. *1*).

Based on the lack of human clinical and marketing data, the Panel concludes that 3-(4-methylbenzylidene)-camphor is not a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are no studies documenting the effectiveness of 3-(4-methylbenzylidene)-camphor as an OTC sunscreen.

One manufacturer submitted a booklet suggesting use of the ingredient as a UV filter for cosmetics. The booklet contained in vitro absorption data indicating an absorption maximum at 300 nm. It was recommended that a 1 to 2.5 percent concentration be used in sunscreen products.

3 - (4 - Methylbenzylidene) - camphor absorbs UV light mainly in the range of 280 to 315 nm. Testing has shown that the UV permeability of 3-(4-methylbenzylidene)-camphor dissolved in chloroform at a concentration of .0005 g/100 ml and at a thickness layer of 1 cm, ranges from 53 percent at 280 nm to 39 percent at 310 nm (ref. *2*).

Based on the lack of sufficient data, the Panel concludes that 3-(4-methylbenzylidene)-camphor is not an effective sunscreen ingredient for OTC use.

(3) *Evaluation.* Based on the lack of clinical and marketing experience, the Panel concludes that 3-(4-methylbenzylidene)-camphor is not safe and not effective for OTC use.

REFERENCES

(1) OTC Volume 060090.
(2) OTC Volume 060083.

c. *Sodium 3,4-dimethylphenyl-glyoxylate.* The Panel concludes that sodium 3,4-dimethylphenyl-glyoxylate is not safe and not effective for OTC use as a sunscreen.

Sodium 3,4-dimethylphenly-glyoxylate is also known as 3,4-dimethylphenyl-glyoxylic acid sodium salt.

It is a white powder with no discernible odor. It is very soluble in water but practically insoluble in ethanol, ether, chloroform and benzene. It has a molecular weight of approximately 232 with no sharp melting point (ref. *1*).

(1) *Safety.* Clinical use and marketing experience are insufficient to confirm that sodium 3,4-dimethylphenyl-glyoxylate is safe for use as an OTC sunscreen.

Safety data included a study in mice which showed the oral toxic dose to be 8.0 g/kg (tachypnea) and the intravenous toxic dose to be 2.0 to 4.0 g/kg (giddiness, dyspnea, etc.). It was reported that 0.3 ml of a 10 percent aqueous solution was tolerated without any adverse reaction.

Based on the lack of sufficient animal data and lack of human clinical and marketing data, the Panel concludes that sodium 3,4-dimethylphenyl-glyoxylate is not a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are no studies documenting the effectiveness of sodium 3,4-dimethylphenyl-glyoxylate as an OTC sunscreen.

Based on the lack of any data, the Panel concludes that sodium 3,4-dimethylphenyl-glyoxylate is not an effective sunscreen ingredient for OTC use.

(3) *Evaluation.* Based on the lack of clinical and marketing experience, the Panel concludes that sodium 3,4-dimethylphenyl-glyoxylate is not safe and not effective for OTC use.

REFERENCE

(1) OTC Volume 060086.

CATEGORY II LABELING

The Panel has examined the submitted labeling claims for sunscreens and for combination products with nonsunscreen ingredients and has placed certain claims into category II.

The Panel found no evidence for labeling claims for sunscreen products such as "promote suntanning," "accelerate suntanning," "fast tanning," "rapid tanning," "give a deeper suntan," "give a longer lasting suntan," "give a deeper, darker suntan," "permits even tanning," "increases your ability to achieve a rich satisfying tan." The Panel concludes that a prudent person can obtain natural tanning without the use of these substances. Suntanning results from sun exposure, but these substances lessen the likelihood of painful sunburn from a consumer's carelessness or ignorance of sun exposure. Therefore, claims such as the above are classified as category II.

3. *Category III conditions for which available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of category III conditions to category I.

CATEGORY III ACTIVE INGREDIENTS

The Panel concludes that the available data are insufficient to permit final classification of the following claimed sunscreen active ingredients:

Allantoin combined with aminobenzoic acid,
5-(3,3-Dimethyl-2-norbornyliden-3-penten-2-one,
Dipropylene glycol salicylate.

a. *Allantoin combined with aminobenzoic acid.* The Panel concludes that allantoin combined with aminobenzoic acid is safe, but there are insufficient data to determine effectiveness as an OTC sunscreen. Other names used for allantoin-aminobenzoic acid are allantoin-*p*-aminobenzoic acid and ALPABA.

Allantoin-aminobenzoic acid is a tannish-white powder having a 1 percent solubility in water.

Information sumbitted to the Panel refers to allantoin-aminobenzoic acid as a complex (refs. *1* and *2*). No data were supplied by the manufacturer to show that there was complexation involved between allantoin and aminobenzoic acid, or that any modification had resulted which would alter in any way the individual characteristics of the two parent compounds. The panel recognizes that allantoin-aminobenzoic acid in combination has shown sun-screening activity equivalent to aminobenzoic acid. However, studies do not show that addition of allantoin to aminobenzoic acid, forming a combination, in any way contributes to the activity of the molecule, insomuch as to influence sunscreen potential or skin protection. It is to be noted that allantoin, used as a single entity and not in the combination form, has been shown to have protectant properties. The Panel has reviewed the data submitted and concludes that further testing is required to show the rationale of combining allantoin with aminobenzoic acid.

(1) *Safety.* Clinical use and marketing experience have confirmed that allantoin combined with aminobenzoic acid is safe in the dosage range used as an OTC sunscreen.

Studies demonstrating the safety of aminobenzoic acid as a single ingredient are discussed elsewhere. (See part III. paragraph B.1.a. above—Aminobenzoic acid.)

A toxicity test using allantoin combined with aminobenzoic acid was performed on five mature rats of the Casworth strain. The weights of the rats ranged from 200 to 240 g. The allantoin-aminobenzoic acid was ground and suspended in a physiological saline solution to form a concentration of 10 mg/0.5 ml. Subcutaneous doses of the test material were injected once daily for 5 days under the loose skin of the back, and observations were made for any signs of toxic symptoms. The rats were autopsied on the 7th day from the start of the testing. No deaths or any signs of toxic symptoms or reactions were observed in any of the rats tested (refs. *1* and *2*).

In another study, a patch test using a 5 percent solution of allantoin-aminobenzoic acid was applied to the backs of 200 white females, and observed for any irritation. The allantoin-aminobenzoic acid solution was placed on a 0.5 inch square of white blotting paper, applied to the back and then covered. An equal square using dry, white blotting paper served as a control. The patches remained on the skin for 48 hours. Observations were recorded immediately and 20 minutes after removal of the patch. Readings were based on a scale ranging from no reaction to vesiculation with edema. Results from both time observations showed that all 200 subjects in the irritation test showed no reaction to allantoin-aminobenzoic acid (refs. *1* and *2*).

Based on the available data, the Panel concludes that allantoin combined with aminobenzoic acid is safe for OTC sunscreen use.

(2) *Effectiveness.* There are no well-controlled studies docmenting the effectiveness of allantoin combined with aminobenzoic acid as an OTC sunscreen.

One study using three females tested allanatoin-aminobenzoic acid for its sun-screening ability. Allantoin-aminobenzoic acid was applied by inunction into a 3 inch by 4 inch area and exposed to UV light by means of a Hanovia sun lamp. An equal skin area served as a control. Both areas were exposed to the UV light daily until slight hypermia was induced in the untreated area. After 5 continuous days of treatment, none of the subjects tested showed any signs of edema in the areas treated with allantoin-aminobenzoic acid. Two of the three untreated patients tested showed evidence of hypermia (refs. *1* and *2*).

Another study compared the effectiveness of aminobenzoic acid with allantoin-aminobenzoic acid. Ten subjects, eight women and two men, were exposed to the midday sun for a period of 2 hours. Each subject was prepared by taping to the back a template consisting of three rows of four 1-inch square holes. Four of the holes were covered with a thin film of 5 percent allantoin-aminobenzoic acid cream. A second group of four holes was covered by a thin film of 5 percent aminobenzoic acid in 60 percent alcohol. The last four holes were used to determine the minimum erythema dose. The holes containing aminobenzoic acid and allantoin-aminobenzoic acid were closed at 30-minute intervals after initial exposure, and the holes testing minimum erythema dosage were closed at 5-minute intervals. Two hours following start of exposure, the test area was dried and checked for tape burns and allergies. Subjects took a warm shower 6 hours later, following which the results were recorded. A subsequent observation was made 24

hours after initial exposure for any further untoward effects.

Readings from the test were varied, mainly due to difficulty in matching erythema produced with tanning observed in both products tested. Both the allantoin-aminobenzoic acid and the aminobenzoic acid showed equivalent sun screening protection (refs. *1* and *2*).

Based on the available data, the Panel concludes that there are insufficient data to determine the effectiveness of allantoin combined with aminobenzoic acid as a sunscreen for OTC use.

(3) *Proposed dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 2 to 5 percent allantoin-aminobenzoic acid: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 2 to 5 percent allantoin-aminobenzoic acid: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. above—category I labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for sunscreen active ingredients. (See part III. paragraph C. below—Data required for evaluation.)

REFERENCES

(1) OTC Volume 060117.
(2) OTC Volume 060147.

b. *5-(3,3-Dimethyl-2-norbornyliden)-3-penten-2-one.* The Panel concludes that 5-(3,3-dimethyl-2-norbornyliden)-3-penten-2-one is safe, but there are insufficient data available to permit final classification of its effectiveness for use as an OTC sunscreen as specified in the dosage section discussed below.

(1) *Safety.* Clinical use and marketing experience have confirmed that 5-(3,3-dimethyl-2-norbornyliden)-3-penten-2-one is safe in the dosage range used as an OTC sunscreen.

Eye irritation was studied using the Draize method. The investigator applied 0.1 ml of a 3 percent solution of 5-(3,3-dimethyl-2-norbornyliden)-3-penten-2-one in isopropyl myristate to the conjuctival sacks of nine albino rabbits. The rabbits tested had an average weight of 2 kg. The conjuctivae of three of the rabbits were washed with 20 ml water, 2 seconds after application. In three other rabbits the conjunctivae were washed with 20 ml, but after 4 seconds; and the last three rabbits' conjunctivae were not washed following application. Observations recorded after 24 hours showed that the three rabbits with no conjunctival washing and one rabbit in the 2 second washing developed a slight reddening of the conjuctivae and a slight swelling of the eye lids. At 48 hours no clearly defined eye irritation could be observed in any of the nine test animals (ref. *1*).

A sensitivity dermatological patch test using 5-(3,3-dimethyl-2-norbornyliden)-3-penten-2-one was applied to 50 healthy personnel and 50 skin disease patients of the University Dermatological Hospital, Goettingen, Germany. Testing of both groups was accomplished using 100 percent 5-(3,3-dimethyl-2-norbornyliden)-3-penten-2-one and a 5 percent concentration in Eucerin anhydricum base. The test material was applied to the upper arm or back using small disks of test adhesive for a period of 24 hours. Readings were taken at 24 and 48 hours, and observations were recorded on an evaluation ranging from no reaction to blistering type of reddening. The first reading (24 hours) showed two test subjects with slight reddening, one of them showing the slight reddening from both the 5 and 100 percent concentration. The other of the two subjects was affected by the 5 percent concentration only. A 48-hour observation showed no reaction.

The second group consisting of the 50 skin-diseased patients showed reactions in 7 of those tested. The 100 percent concentration gave six readings of slight reddening after 24 hours. Five of these patients showed no reaction at the second reading at 48 hours; the other showed a slight increase in reddening. Another patient showed no reaction at 24 hours, but a slight reddening at 48 hours. The 5 percent concentration showed three patient reactions, all three of which had also reacted to the 100 percent concentration. Two test subjects showed slight reddening at 24 hours, but only one showed no reaction at 48 hours. The third subject showed increased reddening at both 24 and 48 hour readings (ref. *1*).

In another test, 1 and 2 percent 5-(3,3-dimethyl-2-norbornyliden)-3-penten-2-one was placed on the upper back of 20 test subjects. Six preparations in oil, oil in water, and water in oil emulsions were used. Irradiation was by means of four Ostran Ultravitalux bulbs placed 16 inches from the skin surface for a maximum time of 11.2 minutes. Readings were taken after 24 hours. No reactions (irritation or reddening) occurred (ref. *1*).

Based on the available data, the Panel concludes that 5-(3,3-dimethyl-2-norbornyliden)-3-penten-2-one is a safe sunscreen ingredient for OTC use.

(2) *Effectiveness.* There are no studies documenting the effectiveness of 5-(3,3-dimethyl-2-norbornyliden)-3-penten-2-one as an OTC sunscreen.

The Panel received one submission for the ingredient. The manufacturer indicated the ingredient had been marketed as a sunscreen since 1973 in concentrations varying from 0.5 to 2.5 percent. No effectiveness data were submitted. However, the manufacturer stated that "we are in the process of performing the efficacy tests recommended by your panel." In a more recent communication, the same manufacturer indicated that other sunscreens have replaced 5-(3,3-dimethyl-2-norbornyliden)-3-penten-2-one in marketed products (ref. *1*).

Based on the available data, the Panel concludes that there are insufficient data to determine the effectiveness of 5-(3,3-dimethyl-2-norbornyliden)-3-penten-2-one as a sunscreen ingredient for OTC use.

(3) *Proposed dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 0.5 to 2.5 percent 5-(3,3-dimethyl-2-norbornyliden)-3-penten-2-one: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 0.5 to 2.5 percent 5-(3,3-dimethyl-2-norbornyliden)-3-penten-2-one: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the category I labeling for sunscreen active ingredients. (See part III. paragraph B.1. above—category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for sunscreen active ingredients. (See part III. paragraph C. below—data required for evaluation.)

REFERENCE

(1) OTC Volume 060120.

c. *Dipropylene glycol salicylate.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effec-

tiveness of dipropylene glycol salicylate for use as an OTC sunscreen as specified in the dosage section discussed below.

Dipropylene glycol salicylate is a clear viscous liquid with a specific gravity of 1.16 and a faint yellow color. It is soluble in alcohols, blycolesters, ketones, and glycols. It is insoluble in water and mineral oil.

(1) *Safety.* Clinical use has not confirmed that dipropylene glycol salicylate is safe in the dosage range used as an OTC sunscreen.

Toxicity testing was performed using normal, healthy CFW mice of the Carworth strain. Weights ranged from 18 to 21 g. The mice received dipropylene glycol salicylate by means of a rigid stomach pump in groups of 10, in doses of 2.5, 3.75, 5 and 10 ml per kg. The mice were observed for a period of 7 days. Six deaths were observed in the 3.75 ml/kg dose, 7 deaths in the 5 ml/kg dose, and all 10 mice died at the 10 ml/kg dose. There were no mice deaths at the 2.5 ml/kg dose (ref. *1*).

In another test, three normal, healthy albino rabbits had a 0.1 ml solution of a 7 percent dipropylene glycol salicylate instilled into the right eye. There was no rinsing of the eye or any other treatment given to the eye. The left eye served as a control. Observations were recorded every 24 hours for 4 days and again on the 7th day. The findings of this test showed that cornea, conjunctival, and iris irritation was not observed in any of the rabbits tested (ref. *1*).

A skin sensitivity test using a 7 percent concentration of dipropylene glycol salicylate was applied to the clipped intact and abraded skin of three healthy normal albino rabbits. The abraded area was chafed with minor abrasions penetrating the stratum corneum, but not influencing the derma. The dipropylene glycol salicylate was applied in a 0.5 ml volume and then covered with surgical tape. Evaluation of the skin for edema, erythema, and escher formation were recorded at 24 and 72 hours after application. Observations showed no irritation at these times on both abraded and intact skin (ref. *1*).

No human safety data or marketing data were submited or were available. Based on the lack of available human safety data, the Panel concludes that there are insufficient data to permit final classification of the safe use of dipropylene glycol salicylate as an OTC sunscreen.

(2) *Effectiveness.* There are no studies documenting the effectiveness of dipropylene glycol salicylate as an OTC sunscreen.

A manufacturer of the chemical ingredient submitted data not related to a marketed product.

A technical bulletin was submitted describing the physical and chemical properties of dipropylene glycol salicylate. The spectral absorption of a 0.1 percent solution showing different values depending upon the thickness of the film was included. The ingredient appears to absorb UV radiation between 290 and 320 nm. The submission also included military specifications for a sunburn-preventive preparation (cream-base) which was dated January 30, 1967. The composition of the preparation is described as containing light amber petrolatum, stearyl alcohol, mineral oil, sesame oil, calcium stearate, kaolin, and a sunscreen agent. There are six sunscreen agents listed as approved for use in the above formulation. One of these sunscreens listed is dipropylene glycol stearate. No other information is given.

Based on the lack of available data, the Panel concludes that there are insufficient data to permit final classification of the effective use of dipropylene glycol salicylate as an OTC sunscreen.

(3) *Proposed dosage.* (i) For products providing a minimum SPF value of 2 to under 4 containing 3 to 7 percent dipropylene glycol salicylate: Adult and children over 2 years of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For products providing a minimum SPF value of 4 containing 3 to 7 percent dipropylene glycol salicylate: Adult and children over 6 months of age topical dosage is liberal application before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

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

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for sunscreen active ingredients. (See part III. paragraph C. below—Data Required for Evaluation.)

REFERENCE

(1) OTC Volume 060134.

CATEGORY III LABELING

The Panel was unable to identify any category III labeling. Suitable labeling claims for the five product categories have been discussed elsewhere in this document. (See part III. paragraph B.1. above—Category I Labeling.)

C. DATA REQUIRED FOR EVALUATION

The Panel considers the protocols recommended in this document for the studies required to bring a category III ingredient into category I to be in agreement with the present state of the art, and does not intend to preclude the use of any advances or improved methodology in the future.

1. *General comments.* Because the first sunburn preventive drugs were introduced in 1928, when a general knowledge of photobiology already existed, testing in the field has been based on sound scientific methodology. Because of the increased medical, regulatory, scientific and social sophistication, the Panel is of the opinion that certain standards of evaluation are now appropriate to increase efficacy and to increase consumer satisfaction. When an ingredient is available for widespread use in OTC products, its safety and efficacy must be well-documented by data regarding its toxicology, absorption, excretion, and pharmacologic action. The drug must meet certain standards of efficacy.

The Panel concludes that it is reasonable to allow 2 years for the development and review of evidence that will permit final classification of the effectiveness of the category III ingredients. The ingredients pose no safety problems for the consumer. Marketing need not cease during this time if adequate testing is undertaken. If data regarding adequate effectiveness and safety are not obtained within 2 years, the ingredients should no longer be marketed in OTC products.

2. *Methods of study*—a. *Toxicological data.* A variety of toxicological data can be obtained to demonstrate that a sunburn preventive is safe. The Panel recommends that the following data be obtained in appropriate studies on the final formulation to be marketed for topical application:

(1) *Patch tests.* A number of patch test methods are applicable to human safety testing of products. These tests have proven valuable for predicting skin irritancy and sensitization. The Panel recommends one of the following methods of patch testing:

(i) The Draize human skin irritancy and sensitization tests and its various modifications in which the subject's back or arm may be used (refs. *1* through *4*);

(ii) The method of Shelanski and Shelanski (ref. *5*); or

(iii) The maximization procedure of Kligman (ref. *6*).

In the first two tests, the formulation is applied many times to the test site for 3 to 4 weeks. A 2-week rest period follows, and then a single challenge application of the drug or formulation is made. The early applications are to detect primary skin irritants, and the last dose is to detect al-

lergic skin sensitizers. The Kligman test uses sodium lauryl sulfate to irritate the test site, thereby hastening and accentuating the allergic skin sensitizing potential of a substance.

b. *Effectiveness data.* For proof of effectiveness of sunscreen active ingredients and formulations, the Panel recommends sunscreen product testing procedures for determining the Sun Protection Factor (SPF) value and related labeling claims. (See part III, paragraph D, below—Sunscreen Product Testing Procedures for Determination of the Sun Protection Factor (SPF) Value and Related Labeling Claims.)

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D. SUNSCREEN PRODUCT TESTING PROCEDURES FOR DETERMINATION OF THE SUN PROTECTION FACTOR (SPF) VALUE AND RELATED LABELING CLAIMS

1. *Sunscreen active ingredients contained in sunscreen products.* The active sunscreen ingredients of the product consist of one or more of the ingredients classified as Category I within any established, maximum daily dosage limit and the finished product provides an SPF value of not less than 2.

2. *Sun protection factor (SPF) value.* An SPF value is defined as the UV energy required to produce a minimal erythema dose (MED) on protected skin divided by the UV energy required to produce an MED on unprotected skin. In effect, the SPF value is the reciprocal of the effective transmission of the product viewed as a light filter. The UV light (UVL) energy is measured by various photodetectors as described below.

The SPF value may also be defined by the following ratio:

$$\text{SPF value} = \frac{\text{MED (protected Skin (PS))}}{\text{MED (unprotected skin (US))}}$$

where, MED (PS) is the minimal erythema dose for protected skin after application of 2 mg/cm^2 or 2 μl/cm^2 of the final formulation of the sunscreen product, and MED (US) is the minimal erythema dose for unprotected skin, i.e., skin to which no sunscreen product has been applied.

The SPF value is the value that can be directly compared between individuals and between products.

3. *Standard sunscreen.*—a. *Laboratory validation.* The use of standard sunscreens for testing purposes permits the direct comparison of results between laboratories to assure uniform evaluation of sunscreen products. Comparing the mean SPF values between laboratories assures that the proper SPF value categorization of a product is maintained. By comparing the standard deviations of the mean SPF values between laboratories, the relative precision of sunscreen testing can be monitored.

A sunscreen preparation containing homosalate was tested by five laboratories in a cooperative trial using solar simulators (ref. *1*). The information accumulated from these studies makes this preparation a suitable standard for use in monitoring the tests for SPF value of sunscreen products. This preparation gave a mean SPF value of 4.24 (standard deviation=1.14). The Panel, therefore, recommends this sunscreen preparation as a standard sunscreen.

b. *Preparation of the standard homosalate sunscreen.* The standard homosalate sunscreen is prepared from two different preparations (part A and part B) with the following compositions:

PREPARATION OF PART A AND PART B OF THE STANDARD SUNSCREEN

PART A

Ingredients	Percent by weight
Homosalate	8.00
White petrolatum	2.00
Stearic acid	3.00
Stearyl alcohol	2.00
Propylparaben	0.015

PART B

Methylparaben	0.025
Sequestrene Na_2 (EDTA disodium)	0.05
Sodium lauryl sulfate	0.50
Propylene glycol	12.00
Purified water U.S.P.	72.41

Part A and part B are heated separately to 77 to 82° C with constant stirring until the contents of each part are solubilized. Add part A slowly to part B while stirring. Continue stirring until the emulsion formed is cooled down to room temperature (15 to 30 C). Add sufficient purified water to obtain 100 g of standard sunscreen preparation.

c. *Assay of the standard homosalate sunscreen.* Assay the standard homosalate sunscreen preparation by the following method to ensure proper concentration:

(1) *Preparation of the assay solvent.* The solvent consists of 1 percent glacial acetic acid (V/V) in denatured ethanol. The denatured ethanol should not contain a UV-absorbing denaturant.

(2) *Preparation of a 1 percent solution of the standard homosalate sunscreen preparation.* Accurately weigh 1 g of the standard homosalate sunscreen preparation into a 100 ml volumetric flask. Add 50 ml of the assay solvent. Heat on a steam bath and mix well. Cool the solution to room temperature (15 to 30° C). Then dilute the solution to volume with the assay solvent and mix well to make a 1 percent solution.

(3) *Preparation of the test solution (1:50 dilution of the 1 percent solution).* Filter a portion of the 1 percent solution through number 1 filter paper. Discard the first 10 to 15 ml of the filtrate. Collect the next 20 ml of the filtrate (second collection).

Add 1 ml of the second collection of the filtrate to a 50 ml volumetric flask. Dilute this solution to volume with assay solvent and mix well. This is the test solution (1:50 dilution of the 1 percent solution).

(4) *Spectrophotometric determination.* The absorbance of the test solution is measured in a suitable double beam spectrophotometer with the assay solvent and reference beam at a wavelength near 306 nm.

(5) *Calculation of the concentration of homosalate.* The concentration of homosalate is determined by the following formula which takes into consideration the absorbance of the sample of the test solution, the dilution of the 1 percent solution to prepare the test solution (1:50), the weight of the sample of the standard homosalate sunscreen preparation (1 g), and the standard absorbance value (172) of homosalate as determined by averaging the absorbance of a large number of batches of raw homosalate:

Concentration of homosalate=absorbance $\times 50 \times 100/1 \times 172$=percent concentration by weight.

4. *Light source and light monitoring.*—a. *Artificial light source (solar simulator) and monitoring.* A solar simulator for sunscreen testing shall be defined as a light source having:

(1) A continuous emission spectrum in the UV–B (290 to 320 nm);

(2) Less than 1 percent of its total energy contributed by nonsolar wave-

lengths (wavelengths shorter than 290 nm); and

(3) Not more than 5 percent of its erythemically effective energy contributed by nonsolar wavelengths.

The instrument must be monitored periodically to assure that it delivers the appropriate spectrum described above. The monitoring procedure is described below.

The xenon arc solar simulator is the preferred artificial light source. Test data using other artifical light sources to establish the degree of efficacy at UV-B wavelengths of sunscreens must have corroborating natural sunlight testing for acceptance.

Xenon solar simulators presently utilize xenon arcs from 150 to more than 6,000 watts. For example, to produce 1 MED with a 150-watt lamp requires 120±30 seconds at the exit port of the instrument when the irradiated site is 1 cm in diameter. Depending upon instrumental design, other irradiation sizes and times can be utilized. Solar simulators of 150 watts usually produce 10 or 12 solar constants. A solar constant is the total amount of energy at all wavelengths per square meter, available from the sun, at the Earth's surface. For example, if the MED for a normal subject is 20 minutes of sunlight exposure, then the solar simulator would produce an MED of 2 minutes at 10 solar constants in the same subjects. The more powerful solar simulators can produce up to 40 solar constants. Irradiated sites more than 4 mm in diameter present no difficulty in determining skin erythema.

A solar simulator uses filters to absorb (cut off) the shorter UV wavelengths which do not reach the earth's surface from the sun. The primary filter is a suitable filter of colorless glass, sharp cut in the UV range, with a $^{0}/_{H}$ (50 percent transmittance point) cut location approximately at 310 nm±6. Dichroic or heat-absorbing filters are used to reduce unnecessary visible and infrared radiation.

Regardles of the light source employed, some uncertainties in interpreting results of in vivo testing, using sunlight or artificial sources, include:

(i) Between individual investigators reading the minimal erythema dose response (MED) (the minimal perceptible erythema) on skin, the readings vary ±20 percent. However, each individual investigator is remarkably consistent after some experience. To partially overcome the variation between observers, the investigator indoors should use a constant light source like an incandescent or a warm white fluorescent lamp at a fixed distance and read the results on the subject in a room with white or light grey walls. No instrument has proven so reliable and consistent as the human eye, but the investigator may use a color gauge, a reflectometer, or a series of color-correcting red filters of increasing red intensity. The filters are placed over the irradiated site where the correct filter will eliminate the erythema and produce a uniform color. The reliability of reproducing results obtained from such a system of filters would have to be verified. In addition, it would be difficult to translate such data into SPF values unless there could be shown to be a 1:1 correlation between a color filter and a known standard sunscreen.

(ii) The same dose of UV light produces different intensities of erythema in different people. This is why the MED must be determined for each subject whatever the light source.

(iii) Inherent differences in the erythemic exposure-color relationship occur between individuals because the same dose of UV light causes different degrees of erythema depending on the time or reading after exposure.

The advantages of a xenon lamp solar simulator for in vivo testing include the following: The continuous spectrum mimics the sun in the UV range with comparable output over the 290 to 400 nm range; a constant spectrum at a constant angle with high output is obtained; and the lamp produces a stable spectrum over long use.

The disadvantages of using the xenon lamp for in vivo testing include the following: The full solar spectrum output is low in the visible and infrared wavelengths; using the xenon lamp is time consuming if only one test site can be irradiated at a time; and it is difficult to measure the output, but instrumentation is available for this purpose.

The xenon arc solar simulator can be monitored. Calibrated thermopiles (instruments that measure the xenon UV total output by converting it to heat energy) can be used to successfully measure the output of solar simulators. The total energy output (solar and nonsolar) of the xenon lamp solar simulator can be measured by a thermopile which should be accurate to 1 percent. If the thermopile has a window, it should be constructed of quartz. Such devices are accurate to at least 1 percent when properly used. Other devices have been used to measure solar simulators, including photocells, photodiodes, photomultipliers, with and without filters. The basic requirements for a suitable monitoring device are that they be stable for several hours, be sensitive to UV-B radiation, and provide values reproducible daily.

The output of a solar simulator is measured in units of Joules. A Joule (J) is an absolute unit of work or energy equal to 1 million ergs. One Joule (J)=1×10^{7} ergs=1 watt.second =10^{6} microwatt.second=2.4×10^{-4} kilocalories. The UVL intensity of a solar simulator will be reported in J/m^{2}.

b. *Natural light source (sunlight) and monitoring.* Testing sunscreen products in sunlight offers several advantages. The test situation more closely approximates the actual ways the sunscreen product will be used by the consumer. The test subject is exposed simultaneously to the full solar spectrum, the heat, and the humidity. Testing of several sunscreen products simultaneously can be done. An estimation of tanning efficacy can be made. Uncontrollable variables in outdoor testing include vagaries of the weather, changing cloud cover, changing radiation intensity with time, changing sun angle to the body surface with time, and variable heat-induced sweating. Monitoring the amount of exposure to natural sunlight is more difficult than for solar simulators. The vagaries of each environment together with the changes in solar altitude with time make timing solar exposure inexact for determing total erythemic exposure. If solar exposures based on time are utilized, the results of 1 day's testing probably cannot be duplicated on another day.

Recently, the Robertson-Berger meter (R-B meter) (ref. 2) has proved successful in monitoring and reproducing solar erythemic exposures (ref. 3). An instrument of this type is recommended for monitoring all outdoor studies. Other recording radiometers are in use which permit continuous measurement of the sun's intensity in J/m^{2} (ref. 4).

The R-B meter records a measure of the cumulative amount of UV radiation that passes through its filters and photosensors after each 30-minute interval. Such 30-minute recordings may range from 0 to slightly over 1,000 depending on the geographical location and the meteorological conditions prevailing at the test location. A count of approximately 400 is estimated to produce one MED on the "typical" Caucasian skin.

5. *General guidelines for all testing procedures.*—a. *Selection of test subjects (male and female).* Only fair-skin volunteers with skin types I, II, and III, using the following guidelines, should be selected:

SELECTION OF FAIR-SKIN SUBJECTS

Skin Type and Sunburn and Tanning History [1]

I—Always burns easily; never tans (sensitive).

II—Always burns easily; tans minimally (sensitive).

III—Burns moderately; tans gradually (light brown) (normal).

[1] Based on first 30 to 45 minutes sun exposure after a winter season of no sun exposure.

IV—Burns minimally; always tans well (moderate brown) (normal).
V—Rarely burns; tans profusely (dark brown) (insensitive).
VI—Never burns; deeply pigmented (insensitive).

A medical history will be obtained from each volunteer with emphasis on the effects of sunlight on his/her skin. To be ascertained are the general health of the individual, the individual's skin type (I, II, or III), whether the individual is taking medication, topical or systemic, that is known to produce abnormal sunlight responses, e.g., declomycin or chlorpromazine, and whether the individual is subject to any abnormal responses to sunlight, such as a phototoxic or photoallergic response.

b. *Test site inspection.* The physical examination should determine the presence of sunburn, suntan, scars, active dermal lesions, and uneven skin tones on the areas of the back to be tested. The presence of nevi, blemishes, or moles will be acceptable if in the physician's judgment they will not interfere with the study results. Excess hair on the back is acceptable if the hair is clipped or shaved.

Some investigators have found a reflectometer useful to ensure uniformity of skin tone to the average skin reflectance in the test areas. Reflectance readings should not vary by more than 5 percent (refs. *4* and *5*).

c. *Informed consent.* Legally effective written informed consent must be obtained from each individual.

d. *Test site delineation.*—(1) *Test site area.* A test site area serves as an area for determining the subject's MED after application of either the sunscreen standard or the test sunscreen product, or for determining the subject's MED when the skin is unprotected (control site). The area to be tested is the back between the beltline and the shoulder blade (scapulae) and lateral to the midline. The test site areas may be horizontal or vertical, and rectangular or square. Depending upon the test scheme, each test site area for applying a product or standard control should be a minimum of 50 cm^2, e.g., 5×10 cm. The test sites are outlined with ink. If the person is to be tested in an upright position, the lines should be drawn on the skin with the subject upright. If the subject is to be tested while prone, the markings should be made with the subject prone. Change of position between marking and testing can change the test area as much as 40 percent.

(2) *Test subsite area.* Each test site area is divided into at least three test subsite areas that are at least 1 cm^2. Usually four or five subsites are employed. Each test subsite area within a test site area is subjected for a time interval, in a series of time intervals, in which the test site area is exposed for the determination of the MED as described below.

e. *Application of test materials.* To insure standardized reporting and to define a product's SPF value, the application of the product will be expressed on a weight basis per unit area which establishes a standard film. The Panel recommends that the test sunscreen product and the sunscreen standard application be 2 mg/cm^2 or 2 ul/cm^2. For some products, lesser amounts may be justified based on intended usage.

The specific gravity of the product is determined according to standard techniques. In testing situations, it is easier to accurately measure volumes for applications. Most sunscreen products have a specific gravity near unity. The 50 cm^2 test site area previously recommended above would require 100 mg of a product or 100 ul (assuming a specifc gravity of 1 to obtain a standard 2 mg/cm^2 test application.

For oils and most lotions, the viscosity is such that the material can be applied with a volumetric syringe. For creams, heavy gels, and butters, the product is warmed slightly so that it can be applied volumetrically. On heating, care must be taken so as not to alter the product's physical characteristics, especially separation of the formulations. Pastes and ointments should be weighed, then applied by spreading on the test site. Numerous investigators have obtained more reproducible results by spreading a product using a finger cot than by spreading with a glass or plastic rod.

f. *Waiting period.* Before exposing the test site areas after applying a product, a waiting period is employed. This waiting period will be at least 15 minutes, or depending upon the product's labeling to the consumer, the waiting period before testing will be the amount of time specified on the labeling.

g. *Number of subjects.* The Panel recommends that groups of at least 20 subjects be used for each test panel. One reason for the panel's decision is that the MED testing is done in 25 percent increments of exposure. The 25 percent exposure increments are reasonably close to the standard deviations observed in test results (ref. *5*). The standard error for a 20-subject test panel would be 25 percent divided by the square root of 20, i.e.,

$$\text{Standard error} = (25 \text{ percent})/\sqrt{20}$$

The Panel agreed that a sunscreen product categorizes itself if the mean of the SPF test values fall within the limits of a PCD as described elsewhere in this doecument (see part II, paragraph A.7. above—Categories of sunscreen products.) The standard error should not exceed ± 5 percent of the mean. An appropriate number of additional subjects should be used to determine the PCD, if a PCD does not fall within the limits of the standard error.

6. *Specific guidelines for all testing procedures.* The Panel has provided the following table of specific testing procedures which are discussed more fully below.

Summary of Sunscreen Testing Procedures for Determining Product labeling

Type of test	Light[1] source	Total test time (min)
SPF Value	A	(2)
SPF Value	N	(2)
Sweat Resistance	A	30
Water Resistance	A	40
Waterproof	A	80

[1] A=artificial light source, N=natural light source.
[2] Variable.

The Panel has not proposed tests to determine if a sunscreen product is water resistant, sweat resistant or waterproof, using a natural light source (sunlight), for several reasons.

There are three major difficulties with testing sunscreen products outdoors for water resistance, sweat resistance, and waterproof claims. These are the lack of protection of the subject's untreated skin against sunburn during the long exposures, the determination of the quantity of sunlight striking the skin when immersed and penetrating the wet stratum corneum, and the maintenance of the protective template on the test site during water immersion. The exposed skin outside the test sites can be protected by applying sunscreens between water immersions. Wet clothing usually transmits significant amounts of UVL.

The Panel believes the testing of sunscreen products for water resistance, sweat resistance, and waterproof claims is easier and more reproducible in an indoor pool. The Panel believes that water immersion is a more severe test of a sunscreen product than is sweating. It, therefore, recommends that the claim "Resists removal by sweating" is appropriate if the product proves water resistant or waterproof in the tests described below.

Because of the difficulties inherent in sunlight water resistance, waterproof and sweat resistance testing for substantivity discussed above, the Panel does not recommend that this method of testing be required. It does recommend that ways to test for substantivity of sunscreen products against water immersion and during copious sweating in natural sunlight be developed.

a. *Determination of SPF value using artificial light source.* This test determines the SPF value of a sunscreen

product after UV-A and UV-B irradiation of the skin.

A series of UV light exposures (units of time) are administered to the subsites on each volunteer with the solar simulator. One series of exposures is administered to the untreated, unprotected skin to determine the volunteer's inherent MED. The time intervals selected are a geometric series represented by $(1.25)^n$, where in each exposure time interval is 25 percent greater than the previous time. The reason for using the geometric sequence of UV exposure is to maintain the same relative uncertainity (expressed as a constant percentage), independent of the volunteer' sensitivity to UV light, regardless of whether the subject has a high or low MED. One example is the time intervals of 1, 1.25, 1.56, 1.96, and 2.44 minutes. This series would be suitable for a normal person exposed to the 150-watt xenon lamp solar simulator. Usually, the MED of a person's unprotected skin is determined the day prior to testing a product.

The protected test sites (standard and/or test sunscreen product) usually are exposed to UV light the next day. The exact series of exposures to be given is determined by the MED of the unprotected skin. For example, for the 8 percent homosalate standard sunscreen with an SPF of 4, the time intervals to be selected are 4, 5, 6.24, 7.84, and 9.76 minutes for a person with an MED of 1.56 minutes on the unprotected skin.

Specifically, what is needed is a series of exposures of the sites in which the lower exposure times produce no effect on the skin. Also, at 16 to 24 hours later, the longer exposure times should produce light and moderately red exposure sites. The MED is the time of exposure that produces the minimally perceptible erythema at 16 to 24 hours postexposure. The SPF of the test sunscreen is then calculated from the exposure time interval required to produce the MED of the protected skin, and from the exposure time interval required to produce the MED of the unprotected skin (control site), i.e.,

SPF value=Exposure time interval (MED (PS))/Exposure time interval (MED (US).)

b. *Determination of SPF value using natural light source (sunlight).* This test determines the SPF value of a suncreen product in sunlight.

Applications will dry in at least 15 minutes or longer as specified on the labeling. Common practice utilizes an opaque template or grid of opaque materials to cover the test sites to control the time exposures of the subsites to the sun after the product has dried. The remainder of the back is covered with heavy toweling or other opaque materials when a suncreen is applied to the exposed parts of the subject's skin during the test. The subject will lie in the prone position in direct sunlight for a predetermined period of time. The day of sun exposure may not be the same for all subjects. However, sun exposure of individual subjects will be completed during one continuous exposure period. Sun exposure of all subjects must be completed within 2 weeks for any one test and must be conducted at the same geographical location for any one test. During each exposure, the sun intensity will be measured continuously by a recording radiometer or a recording R-B meter. Empirically, approximately 6×10^6 Joules/m^2, as measured by a recording radiometer, will evoke 1 MED in skin types I and II subjects when read 16 to 24 hours later. Using the recording R-B meter, 400 counts are equivalent to 1 MED in skin type III subjects (ref. *3*), and MED's as low as 200 counts may be expected of skin type I. Duration of sun exposure will be documented in Joules/m^2 or in R-B counts. Temperature and humidity will be measured in R-B meter counts. Temperature and humidity will be measured at the beginning, the end, and at the maximal sun intensity for the exposure period. Descriptive comments about wind and cloud conditions will be made at times, but the primary measure of variations in cloud cover during exposure will be the continuous radiometer or R-B meter record.

At preestablished exposure times as determined by the meter reading, the subsite areas of the test site area will be exposed so that graded exposures will be obtained. Identical sequence of exposures will be administered to all test sites.

The Panel has reviewed several suggested test protocols of varying design that effectively determine the SPF of a sunscreen product. One example test protocol follows. It assumes a subject of skin type I with an MED of 15 minutes, 4.5×10^6 Joules/m^2, or 300 R-B meter counts (ref. *3*). The study is a controlled test of a sunscreen product, a standard sunscreen product, and an untreated control.

With the protective template in place, the approximate dose of sun exposure of individual subsites within the treated and unprotected test sites were as follows:

Robertson-Berger Meter Counts (exposure Count Intervals) (Ref. 3). 160, 213, 283, 376, 501, 666, and 886.

The R-B meter count intervals selected are a geometric series represented by $(1.33)^n$, wherein each exposure count interval is 33 percent greater than the previous exposure count interval. For the unprotected subsite, usually a miximum of 800 R-B meter counts assures 3 MED's in skin types I and II, and 2 MED's in normal skin type III subjects. Greater exposures increase the risk of severe sunburn, but provide little additional useful data.

For test and standard sunscreen products with different SPF values, the dose of exposure will vary accordingly. Often a pilot study is performed in three to six subjects to obtain the approximate SPF of a new product.

The SPF value of the test sunscreen using the R-B meter is calculated as follows:

SPF value=exposure count interval (MED (PS))/exposure count interval (MED (US)).

c. *Determination of sweat resistance using artifical light source.* This test determines the sweat resistance and substantivity of a sunscreen product after 30 minutes of copious sweating to substantiate the claim of sweat resistance. The claim as appropriate will be allowed if the sunscreen product retains the same PCD, as described elsewhere in this document, after the sweat test as before the sweat test. (See part II. paragraph A.7. above—Categories of sunscreen products.)

The Panel concludes that a 30-minute period of copious sweating induced under controlled environmental conditions is an appropriate test for determinng sweat resistance and substantivity claims of a sunscreen product. If a subject fails to sweat profusely, he will be dropped from the study and another subject selected. The MED of the unprotected test site area on each subject is determined using the solar simulator. Usually the next day, the SPF of the test sunscreen product is determined for each subject using the solar simulator. The same day or the next day the test sunscreen product is applied. The subjects sit quietly in a controlled environment at a temperature of 35 to 38° C (95 to 100° F) and a relative humidity of 70 to 80 percent. To prevent evaporative cooling of the skin with resulting decreased sweating, there should be little air movement. A few subjects may require an air temperature of 105° F, with a relative humidity of 60 percent. For safety purposes, older persons should not be used. All subjects exposed to heat stress should have their pulse and temperature taken every 15 minutes. If a subject's pulse exceeds 160 counts per minute, and oral temperature of 38.9° C (102° F) or a rectal temperature of 39.2° C (102.5° F), the subject's participation must stop.

The 30-minute test period begins when the subject starts to sweat profusely, drops or rivulets of sweat running down the test site. Most subjects will sweat profusely within 10 minutes, but a few may take up to 20 minutes to develop copious sweating. After the

30-minute period of heavy sweating, the subject leaves the controlled environment, permits the test site area to air dry, and then the postsweating SPF of the sunscreen product is determined. The test sunscreen product must permit delivery of sweat through the film. No standard sweat resistant product is available as yet.

If the test sunscreen product retains the same PCD after the sweat test as before the sweat test, the claim of "sweat resistant" will be allowed.

d. *Determinating if a sunscreen is water resistant or waterproof using artifical light source.* This test determines the water resistance of a sunscreen product after 40 minutes of moderate activity (swim and play activity) in water (swimming pool) to substantiate the claim of water resistance, and after 80 minutes of moderate activity to substantiate the claim of waterproof. The claims as appropriate will be allowed if the sunscreen product retains the same PCD, as described elsewhere in this document, after the test as before the test. (See part II., paragraph A.7. above—Categories of sunscreen products.) Because it is impossible to produce even, controlled sweating among individuals, the Panel recommends that the claim "resists removal by perspiration" is appropriate if the product proves water resistant or waterproof in the water test. The Panel believes that water immersion is a more severe test of a sunscreen product than is sweating.

No water resistant or waterproof standard sunscreen product is available; so a standard sunscreen product is not used in the test.

The Panel concludes that a 20-minute period of moderate activity in the water in a swimming pool after the application of the test sunscreen product, followed by a 20-minute rest period, then a second 20-minute period of moderate activity is an appropriate test for determining water resistance and substantivity claims of a sunscreen product. The test site areas are then exposed to the solar simulator. The pool and air temperature and the relative humidity should be recorded. A sample schedule of a water test for a water-resistant sunscreen product is as follows:

9:30—Apply sunscreen product (followed by the waiting period after application of the sunscreen product indicated on the product labeling).
10:00—20 minutes moderate activity.
10:20—Rest period
10:40—20 minutes moderate activity
11:00—Conclude water test (air dry test sites without toweling).
11:10—Begin solar simulator exposure to test site area in the manner described above.

A sample schedule of a water test for a waterproof sunscreen product is as follows:

9:30—Apply sunscreen product (followed by the waiting period after application of the sunscreen product indicated on the product labeling).
10:00—20 minutes moderate activity.
10:20—Rest period.
10:40—20 minutes moderate activity.
11:00—Rest period.
11:20—20 minutes moderate activity.
11:40—Rest period.
12:00—20 minutes moderate activity.
12:20—Conclude water test (air dry test sites without toweling).
12:30—Begin solar simulator exposure to test sites in the manner described above.

Sunscreen active ingredients dissolve much more slowly in seawater than in freshwater because seawater contains about 3 percent salts. Therefore, a freshwater pool (21 to 32° C) should be used. The Panel recommends that this substantivity test should be conducted in an indoor pool to diminish the risk of exposure to natural sunlight during the conduct of the test, especially in skin types I and II.

The solar simulator-exposed test site areas are read at 16 to 24 hours after exposure determine the SPF for the subjects as described above. The Panel believes that a sunscreen product that can withstand 80 minutes of water immersion can reasonably claim to be waterproof. The Panel chose the 20-minute water periods because some unpublished marketing data revealed that the average person goes into the water 3.6 times for an average duration of 21 minutes per immersion at the beach or pool (Ref. 4).

7. *Response criteria.* After UVL exposure to natural or artificial sources is completed, all immediate responses are recorded. These include several types of typical responses such as the following:

a. An immediate darkening or tanning, typically grayish or purplish in color, fading in 30 to 60 minutes, and attributed to photo-oxidation of existing melanin granules;

b. Immediate reddening, fading rapidly, and viewed as a normal response of capillaries and venules to heat, visible and infrared radiation; and

c. An immediate generalized heat response, resembling prickly heat rash, fading in 30 to 60 minutes, and apparently caused by heat and moisture generally irritating to the skin's surface.

After the immediate responses are noted, each subject shields the exposed area from further UV radiation for the remainder of the test day. The MED is determined 16 to 24 hours after exposure.

Specifically, these tests depend upon determining the light energy corresponding to a minimally perceptible erythema of a subject's skin at 16 to 24 hours postexposure for each series of exposures. To determine the MED, somewhat more intense erythemas usually must also be produced. The goal is to have some exposures that produce absolutely no effect, while of those exposures that produce an effect, the maximal exposure should be no more than twice the total energy of the minimal exposure. The maximum exposure anticipated in these tests corresponds to what most individuals would describe as a light to moderate sunburn.

8. *Rejection of test data.* These tests occasionally fail, and must be discarded. There are only the following two technical reasons for rejection of test data:

a. Sometimes the exposure series fails to elicit an MED response on either the treated or unprotected skin sites. In either event, that test is a technical failure and must be discarded. If the subject reacts to one or more exposure on the unprotected control site, but not on the treated site, then a minimal estimate of the SPF can be obtained.

b. The responses on the treated sites are randomly absent, which indicates the product was not spread evenly. Therefore, no assessment of protection is possible.

9. *Treatment of data.* The SPF value will be calculated for each test of a sunscreen product as follows:

a. *Calculation of the SPF value from data obtained in tests using a solar simulator.* The measurement units in tests using a solar simulator to obtain MED's for calculation of the SPF value are time units, usually seconds. The following is an example of the calculation of the SPF value from MED's obtained using a solar simulator:

SPF value=Exposure time interval (MED(PS))/Exposure time interval (MED(US))

SPF value=180 seconds (MED(PS))/60 seconds (MED(US))

Therefore, the SPF value=3.

The PCD for a sunscreen product with an SPF value of 3 would be categorized as a minimal sun protection products because the SPF value of 3 is more than a value of 2 and less than an SPF value of 4.

b. *Calculation of the SPF value from data obtained in tests using a recording radiometer or a Robertson-Berger meter*—(1) *Recording radiometer.* The measurement units in tests using a recording radiometer are energy units, Joules/m^2. The following is an example of the calculation of the SPF value from MED's obtained using a recording radiometer:

SPF value=Joules/m^2 (MED(PS))/Joules/m^2(MED(US))

SPF value=28×10^6 Joules/m^2 (MED(PS))/6×10^6 Joules/m^2(MED(US))

Therefore; the SPF value=4.6.

The PCD for a sunscreen product with an SPF value of 4.6 would be categorized as a moderate sun protection product because the SPF value of 4.6 is more than a value of 4 and less than an SPF value of 6.

(2) *Robertson-Berger meter (R-B meter).* The measurement units in tests using a Robertson-Berger meter are counts. The following is an example of the calculation of the SPF value from MED's obtained using a Robertson-Berger meter:

SPF value=Exposure count interval (MED(PS))/Exposure count interval (MED(US))

SPF value=2,600 counts (MED(PS))/400 counts (MED(US))

Therefore, the SPF value=6.5.

The PCD for a sunscreen product with an SPF value of 6.5 would be categorized as an extra sun protection product because the SPF value of 6.5 is more than a value of 6 and less than an SPF value of 8.

REFERENCES

(1) OTC Volume 060169.
(2) Proceedings of the Third Conference on Climatic Impact Assessment Program, February 26-March 1, 1974, DOT, TSC-OST 74-15.
(3) Measurement of Ultraviolet Radiation in the United States and Comparisons with Skin Cancer Data, U.S. Department of Health, Education, and Welfare, National Institutes of Health (DHEW No. 76-1029), November 1975.
(4) OTC Volume 060158.
(5) OTC Volume 060166.

The Food and Drug Administration has determined that this document does not contain an agency action covered by 21 CFR 25.1(b) and consideration by the agency of the need for preparing an environmental impact statement is not required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371) and the Administrative Procedure Acts (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704) and under authority delegated to him (21 CFR 5.1)), the Commissioner proposes that subchapter D of chapter I of title 21 of the Code of Federal Regulations be amended by adding new part 352, to read as follows:

PART 352—SUNSCREEN PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
352.1 Scope.
352.3 Definitions.

Subpart B—Active Ingredients

352.10 Sunscreen active ingredients.
352.20 Combinations of sunscreen active ingredients.

Subpart C—Testing Procedures

352.40 Standard sunscreen.
352.41 Light source and light monitoring.
352.42 General testing procedures.
352.43 Determination of SPF value using artificial light source.
352.44 Determination of SPF value using natural light source (sunlight).
352.45 Determination of sweat resistance using artifical light source.
352.46 Determination if a sunscreen is water resistant or waterproof using artificial light source.

Subpart D—Labeling

352.50 Labeling of sunscreen products.

AUTHORITY: Secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371) (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 352.1 Scope.

An over-the-counter sunscreen 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 following conditions and each of the general conditions established in § 330.1 of this chapter.

§ 352.3 Definitions.

(a) *Product category designation (PCD).* A labeling designation for sunscreen products to aid in selecting the type of product best suited to the individual's complexion (pigmentation) and desired response to ultraviolet (UV) light.

(1) *Mineral sun protection product.* Sunscreen products that provide an SPF value of 2 to under 4, and offer the least protection, but permit suntanning.

(2) *Moderate sun protection product.* Sunscreen products that provide an SPF value of 4 to under 6, and offer moderate protection from sunburning, but permit some suntanning.

(3) *Extra sun protection product.* Sunscreen products that provide an SPF value of 6 to under 8, offer extra protection from sunburning, and permit limited suntanning.

(4) *Maximal sun protection product.* Sunscreen products that provide an SPF value of 8 to under 15, offer maximal protection from sunburning, and permit little or no suntanning.

(5) *Ultra sun protection product.* Sunscreen products that provide an SPF value of 15 or greater, offer the most protection from sunburning, and permit no suntanning.

(b) *Sunscreen active ingredient.* An active ingredient that absorbs at least 85 percent of the light in the UV range at wavelengths from 290 to 320 nanometers, but transmits UV light at wavelengths longer than 320 nanometers. Such agents permit tanning in the average individual and also permit some reddening (erythema) without pain.

(c) *Sunscreen opaque sunblock.* An opaque sunscreen active ingredient that reflects or scatters all light in the UV and visible range at wavelengths from 290 to 777 nanometers and thereby prevents or minimizes suntan and sunburn.

(d) *Sun protection factor (SPF) value.* An SPF value is defined as the UV energy required to produce a minimal erythema dose (MED) on protected skin divided by the UV energy required to produce a MED on unprotected skin. In effect, the SPF value is the reciprocal of the effective transmission of the product viewed as a light filter. The SPF value may also be defined by the following ratio:

SPF value=MED (protected skin (PS)/MED (unprotected skin (US)).

Where MED (PS) is the minimal erythema dose for protected skin after application of 2 milligrams per square centimeter or 2 microliters per square centimeter of the final formulation of the sunscreen product, and MED (US) is the minimal erythema dose for unprotected skin, i.e., skin to which no sunscreen product has been applied.

Subpart B—Active Ingredients

§ 352.10 Sunscreen active ingredients.

The active ingredients of the product consist of the following when used within the topical dosage limits established and the finished product provides a minimum SPF value of not less than 2 as measured by the testing procedure in subpart C of this part:

Aminobenzoic acid 5 to 15 percent.
Cinoxate 1 to 3 percent.
Diethanolamine *p*-methoxycinnamate 8 to 10 percent.
Digalloyl trioleate 2 to 5 percent.
Dioxybenzone 3 percent.
Ethyl 4-[bis(hydroxypropyl)] aminobenzoate 1 to 5 percent.
2-Ethylhexyl 2-cyano-3, 3-diphenylacrylate 7 to 10 percent.
Ethylhexyl *p*-methoxycinnamate 2.0 to 7.5 percent.
2-Ethylhexyl salicylate 3 to 5 percent.
Glyceryl aminobenzoate 2 to 3 percent.
Homosalate 4 to 15 percent.
Lawsone 0.25 percent with dihydroxyacetone 3 percent.
Menthyl anthranilate 3.5 to 5 percent.
Oxybenzone 2 to 6 percent.
Padimate A 1 to 5 percent.
Padimate O 1.4 to 8.0 percent.
2-Phenylbenzimidazole-5-sulfonic acid 1 to 4 percent.
Red petrolatum 30 to 100 percent.
Sulisobenzone 5 to 10 percent.
Titanium dioxide 2 to 25 percent.
Triethanolamine salicylate 5 to 12 percent.

§ 352.20 Combinations of sunscreen active ingredients.

Two or more sunscreen active ingredients identified in § 352.10 may be combined within the topical dosage limits established: *Provided,* The finished product provides a minimum SPF value of not less than 2 as measured by the testing procedures in subpart C of this part.

Subpart C—Testing Procedures

§ 352.40 Standard sunscreen.

(a) *Laboratory validation.* A standard sunscreen shall be used concomitantly in the testing procedures for determining the SPF value of a sunscreen product to assure the uniform evaluation of sunscreen products. The standard sunscreen shall be an 8 percent homosalate preparation with a mean SPF value of 4.24 (standard deviation=1.14).

(b) *Preparation of the standard homosalate sunscreen.* The standard homosalate sunscreen is prepared from two different preparations (preparation A and preparation B) with the following compositions:

COMPOSITION OF PREPARATION A AND PREPARATION B OF THE STANDARD SUNSCREEN

PREPARATION A

Ingredients	Percent by weight
Homosalate	8.00
White petrolatum	2.00
Stearic acid	3.00
Stearyl alcohol	2.00
Propylparaben	0.015

PREPARATION B

Methylparaben	0.025
Sequestrene Na_2 (EDTA disodium)	0.05
Sodium lauryl sulfate	0.50
Propylene glycol	12.00
Purified water U.S.P.	72.41

Preparation A and preparation B are heated separately to 77 to 82° C with constant stirring until the contents of each part are solubilized. Add preparation A slowly to preparation B while stirring. Continue stirring until the emulsion formed is cooled down to room temperature (15 to 30° C). Add sufficient purified water to obtain 100 grams of standard sunscreen preparation.

(c) *Assay of the standard homosalate sunscreen.* Assay the standard homosalate sunscreen preparation by the following method to ensure proper concentration:

(1) *Preparation of the assay solvent.* The solvent consists of 1 percent glacial acetic acid (V/V) in denatured ethanol. The denatured ethanol should not contain a UV absorbing denaturant.

(2) *Preparation of a 1 percent solution of the standard homosalate sunscreen preparation.* Accurately weight 1 gram of the standard homosalate sunscreen preparation into a 100 milliliter volumetric flask. Add 50 milliliter of the assay solvent. Heat on a steam bath and mix well. Cool the solution to room temperature (15 to 30° FC). Then dilute the solution to volume with the assay solvent and mix well to make a 1 percent solution.

(3) *Preparation of the test solution (1:50 dilution of the 1 percent solution).* Filter a portion of the 1 percent solution through number 1 filter paper. Discard the first 10 to 15 milliliters of the filtrate. Collect the next 20 milliliters of the filtrate (second collection). Add 1 milliliter of the second collection of the filtrate to a 50 milliliter volumetric flask. Dilute this solution to volume with assay solvent and mix well. This is the test solution (1:50 dilution of the 1 percent solution).

(4) *Spectrophotometric determination.* The absorbance of the test solution is measured in a suitable double beam spectrophotometer with the assay solvent and reference beam at a wavelength near 306 nanometers.

(5) *Calculation of the concentration of homosalate.* The concentration of homosalate is determined by the following formula which takes into consideration the absorbance of the sample of the test solution, the dilution of the 1 percent solution to prepare the test solution (1:50), the weight of the sample of the standard homosalate sunscreen preparation (1 gram), and the standard absorbance value (172) of homosalate as determined by averaging the absorbance of a large number of batches of raw homosalate:

Concentration of homosalate=absorbance $\times$ 50 $\times$ 100/1 $\times$ 172=percent concentration by weight.

§ 352.41 Light source and light monitoring.

(a) *Artificial light source (solar simulator).* A solar simulator for sunscreen testing shall be defined as a light source having continuous emission spectrum in the UV-B (290 to 320 nanometers) with less than 1 percent of its total energy contributed by nonsolar wavelengths (wavelengths shorter than 290 nanometers) and not more than 5 percent of its erythemically effective energy contributed by nonsolar wavelengths. The instrument must be monitored periodically to assure that it delivers the appropriate spectrum.

(b) *Natural light source (sunlight).* Sunlight more closely approximates the actual ways the sunscreen product will be used by the consumer. The test subject is exposed simultaneously to the full solar spectrum. However, uncontrollable variables in outdoor testing include vagaries of the weather, changing cloud cover, changing radiation intensity with time, changing sun angle to the body surface with time, and variable heat-induced sweating. A suitable meter should be used for monitoring all outdoor studies.

§ 352.42 General testing procedures.

(a) *Selection of test subjects (male and female).* Only fair-skin volunteers with skin types I, II, and III using the following guidelines shall be selected:

SELECTION OF FAIR SKIN SUBJECTS

Skin Type and Sunburn and Tanning History[1]

I—Always burns easily; never tans (sensitive).
II—Always burns easily; tans minimally (sensitive).
III—Burns moderately; tans gradually (light brown) (normal).
IV—Burns minimally; always tans well (moderate brown) (normal).
V—Rarely burns; tans profusely (dark brown) (insensitive).
VI—Never burns; deeply pigmented (insensitive).

A medical history shall be obtained from each volunteer with emphasis on the effects of sunlight on their skin. To be ascertained are the general health of the individual, the individual's skin type (I, II, or III), whether the individual is taking medication, topical or systemic, that is known to produce abnormal sunlight responses, and whether the individual is subject to any abnormal responses to sunlight, such as a phototoxic or photoallergic response.

(b) *Test site inspection.* The physical examination shall determine the presence of sunburn, suntan, scars, active dermal lesions, and uneven skin tones on the areas of the back to be tested. The presence of nevi, blemishes, or moles will be acceptable if in the physician's judgment they will not interfere with the study results. Excess hair on the back is acceptable if the hair is clipped or shaved.

(c) *Informed consent.* Legally effective written informed consent must be obtained from each individual.

(d) *Test site delineation.*— (1) *Test site area.* A test site area serves as an area for determining the subject's MED after application of either the sunscreen standard or the test sunscreen product, or for determining the subject's MED when the skin is unprotected (control site). The area to be tested shall be the back between the beltline and the shoulder blade (scapulae) and lateral to the midline. Each test site area for applying a product or the standard sunscreen shall be a minimum of 50 square centimeter, e.g.,

[1] Based on first 30 to 45 minutes sun exposure after a winter season of no sun exposure.

5×10 centimeter. The test site areas are outlined with ink. If the person is to be tested in an upright position, the lines shall be drawn on the skin with the subject upright. If the subject is to be tested while prone, the markings shall be made with the subject prone.

(2) *Test subsite area.* Each test site area shall be divided into at least 3 test subsite areas that are at least 1 square centimeter. Usually 4 or 5 subsites are employed. Each test subsite are within a test site area is subjected for a time interval, in a series of time intervals, in which the test site area is exposed for the determination of the MED.

(e) *Application of test materials.* To insure standardized reporting and to define a product's SPF value, the application of the product shall be expressed on a weight basis per unit area which establishes a standard film. Both the test sunscreen product and the standard sunscreen application shall be 2 milligrams per square centimeter or 2 microliters per square centimeter. For oils and most lotions, the viscosity is such that the material can be applied with a volumetric syringe. For creams, heavy gels, and butters, the product shall be warmed slightly so that it can be applied volumetrically. On heating, care shall be taken so as not to alter the product's physical characteristics, especially separation of the formulations. Pastes and ointments shall be weighed, then applied by spreading on the test site area. A product shall be spread by using a finger cot.

(f) *Waiting period.* Before exposing the test site areas after applying a product, a waiting period of at least 15 minutes is required.

(g) *Number of subjects.* Groups of at least 20 subjects shall be used for each test panel. A sunscreen product categorizes itself if the mean of the SPF test values falls within the limits of a PCD. The standard error shall not exceed ± 5 percent of the mean. An appropriate number of additional subjects shall be used to determine the PCD, if a PCD does not fall within the limits of the standard error.

(h) *Response criteria.* After UVL exposure to natural or artificial sources is completed, all immediate responses shall be recorded. These include several types of typical responses such as the following: An immediate darkening or tanning, typically greyish or purplish in color, fading in 30 to 60 minutes, and attributed to photo-oxidation of existing melanin granules; immediate reddening, fading rapidly, and viewed as a normal response of capillaries and venules to heat, visible and infrared radiation; and an immediate generalized heat response, resembling prickly heat rash, fading in 30 to 60 minutes, and apparently caused by heat and moisture generally irritating to the skin's surface. After the immediate responses are noted, each subject shall shield the exposed area from further UV radiation for the remainder of the test day. The MED is determined 16 to 24 hours after exposure. Testing depends upon determining the light energy corresponding to a minimally perceptible erythema of a subject's skin at 16 to 24 hours postexposure for each series of exposures. To determine the MED, somewhat more intense erythemas must also be produced. The goal is to have some exposures that produce absolutely no effect, while of those exposures that produce an effect, the maximal exposure should be no more than twice the total energy of the minimal exposure.

(i) *Rejection of test data.* Test data shall be rejected if the exposure series fails to elicit an MED response on either the treated or unprotected skin sites or if the responses on the treated sites are randomly absent, which indicates the product was not spread evenly.

§ 352.43 Determination of SPF value using artificial light source.

A series of UV light exposures (units of time) are administered to the subsite areas on each volunteer with a solar simulator. One series of exposures shall be administered to the untreated, unprotected skin to determine the volunteer's inherent MED. The time intervals selected shall be a geometric series represented by $(1.25)^n$, wherein each exposure time interval is 25 percent greater than the previous time to maintain the same relative uncertainty (expressed as a constant percentage), independent of the volunteer's sensitivity to UV light, regardless of whether the subject has high or low MED. One example is the time intervals of 1, 1.25, 1.56, 1.96, and 2.44 minutes. This series would be suitable for a normal person exposed to the 150-watt xenon lamp solar simulator. Usually, the MED of a person's unprotected skin is determined the day prior to testing a product. The protected test sites (standard sunscreen and/or test sunscreen product) usually are exposed to UV light the next day. The exact series of exposures to be given shall be determined by the MED of the unprotected skin. For example, for the 8 percent homosalate standard sunscreen with an SPF value of 4.24, the time intervals to be selected are 4, 5, 6.24, 7.84, and 9.76 minutes for a person with an MED of 1.56 minutes on the unprotected skin. A series of exposures of the sites in which the lower exposure times produce no effect on the skin is required. Also, at 16 to 24 hours later, the longer exposure times should produce light and moderately red exposure sites. The MED is the time of exposure that produces the minimally perceptible erythema at 16 to 24 hours postexposure. The SPF value of the test sunscreen is then calculated from the exposure time interval required to produce the MED of the protected skin, and from the exposure time interval required to produce the MED of the unprotected skin (control site) as follows:

SPF value=Exposure time interval (MED (PS))/exposure time interval (MED (US))

§ 352.44 Determination of SPF value using natural light source (sunlight).

An opaque template or grid of opaque materials shall be used to cover the test sites in order to control the time exposures of the subsite areas to the sun after the product has dried. The remainder of the back shall be covered with heavy toweling or other opaque materials when a sunscreen is applied to the exposed parts of the subject's skin during the test. The subject shall lie in the prone position in direct sunlight for a predetermined period of time. The day of sun exposure may not be the same for all subjects. However, sun exposure of individual subjects shall be completed during one continuous exposure period. Sun exposure of all subjects shall be completed within 2 weeks for any one test and shall be conducted at the same geographical location for any one test. During each exposure, the sun intensity shall be measured continuously by a recording radiometer or a recording Robertson-Berger meter. Duration of sun exposure shall be documented in Joules per square meter or in Robertson-Berger meter counts. Temperature and humidity shall be measured at the beginning, the end, and at the maximal sun intensity for the exposure period. Descriptive comments about wind and cloud conditions shall be made at times, but the primary measure of variations in cloud cover during exposure will be the continuous radiometer or Robertson-Berger meter record. At preestablished exposure times as determined by the meter reading, the subsite areas of the test site area shall be exposed so that graded exposures will be obtained. Identical sequence of exposures shall be administered to all test sites. The SPF value of the test sunscreen product using the Robertson-Berger meter is calculated as follows:

SPF value=Exposure count interval (MED(PS))/Exposure count interval (MED(US))

§ 352.45 Determination of sweat resistance using artificial light source.

A 30-minute period of copious sweating induced under controlled environmental conditions shall determine sweat resistance and substantivity claims of a sunscreen product. A subject that fails to sweat profusely shall

be dropped from the study and another subject selected. The MED of the unprotected test site area on each subject shall be determined using the solar simulator. Usually the next day, the SPF of the test sunscreen product is determined for each subject using the solar simulator. The standard sunscreen is not used in this test. The same day or the next day the test sunscreen product is applied. The subjects sit quietly in a controlled environment at a temperature of 35 to 38° C (95 to 100° F) and a relative humidity of 70 to 80 percent. To prevent evaporative cooling of the skin with resulting decreased sweating, there should be little air movement. A few subjects may require an air temperature of 41° C (105° F) with a relative humidity of 60 percent. For safety purposes, older people should not be used. All subjects exposed to heat stress should have their pulse and temperature taken every 15 minutes. If a subject's pulse exceeds 160 counts per minute, an oral temperature of 38.9° C (102° F), or a rectal temperature of 39.2° C (102.5° F), his/her participation shall stop. The 30-minute test period begins when the subject starts to sweat profusely, drops or rivulets of sweat running down the test site. Most subjects will sweat profusely within 10 minutes, but a few may take up to 20 minutes to develop copious sweating. After the 30-minute period of heavy sweating, the subject leaves the controlled environment, permits the test site area to air dry, and then the postsweating SPF of the test sunscreen product is determined. The test sunscreen product must permit delivery of sweat through the film. If the test sunscreen product retains the same PCD after the sweat test as before the sweat test, the claim of "sweat resistant" will be allowed.

§§ 352.46 Determining if a sunscreen is water resistant or waterproof using artificial light source.

The standard sunscreen is not used in the tests. An indoor fresh water pool (23 to 32° C) shall be used in these testing procedures.

(a) *Procedure for testing the water resistance of a sunscreen product.* A 20-minute period of moderate activity in the water in a swimming pool after the application of the test sunscreen product followed by a 20-minute rest period, then a second 20-minute period of moderate activity shall be used to determine the water resistance and substantivity claims of a sunscreen product. The test site areas are then exposed to the solar simulator. The pool and air temperature and the relative humidity shall be recorded.

The following procedure shall be used for the water resistance test:

(1) Apply sunscreen product (followed by the waiting period after application of the sunscreen product indicated on the product labeling).

(2) 20 minutes moderate activity in water.

(3) 20 minute rest period.

(4) 20-minutes moderate activity in water.

(5) Conclude water test (air dry test sites without toweling).

(6) Begin solar simulator exposure to test site areas in the manner described above.

A sunscreen product that can withstand 40 minutes of water immersion may claim to be water resistant.

(b) *Procedure for testing the waterproof claim of a sunscreen product.* The following procedure shall be used for the waterproof test:

(1) Apply sunscreen product (followed by the waiting period after application of the sunscreen product indicated on the product labeling).

(2) 20 minutes moderate activity in water.

(3) 20-minute rest period.

(4) 20 minutes moderate activity in water.

(5) 20-minutes rest period.

(6) 20 minutes moderate activity in water.

(7) 20-minutes rest period.

(8) 20 minutes moderate activity in water.

(9) Conclude water test (air dry test sites without toweling).

(10) Begin solar simulator exposure to test site areas in the manner described above.

The solar simulator-exposed test site areas shall be read at 16 to 24 hours later to determine the SPF for the subjects as described above. A sunscreen product that can withstand 80 minutes of water immersion may claim to be waterproof.

Subpart D—Labeling

§ 352.50 Labeling of sunscreen products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug(s) identified under § 352.10 and identifies the product as a "sunscreen."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indication(s)" and is limited to one or more of the following phrases:

(1) *For all (minimal, moderate, extra, maximal, and ultra) sunscreen products.* (i) "Sunscreen to help prevent sunburn."

(ii) "Filters (or screen) out the sun's burning rays to prevent sunburn."

(iii) "Screens out the sun's harsh and often harmful rays to prevent sunburn."

(iv) "Overexposure to the sun may lead to premature aging of the skin and skin cancer. The liberal and regular use over the years of this product may help reduce the chance of these harmful effects."

(v) "Overexposure to the sun may lead to premature aging of the skin and skin cancer. The liberal and regular use over the years of this product may help reduce the chance of premature aging of the skin and skin cancer."

(2) *Additional indications.* In addition to the indications provided above in § 352.50(b)(1), the following may be used:

(i) *For minimal sunscreen products:* (*a*) "Affords minimal protection against sunburn."

(*b*) "Prolongs exposure time before sunburn occurs."

(*c*) "Permits tanning (or suntanning) and reduces chance of (or minimizes) sunburning."

(*d*) "Helps prevent sunburn on limited exposure of untanned skin."

(*e*) "Helps to protect the skin against sunburn while permitting tanning."

(*f*) "Allows you to stay in the sun two times longer than without sunscreen protection."

(g) "Provides two times your natural protection from sunburn."

(ii) *For moderate sunscreen products.* (*a*) "Affords moderate protection against sunburn."

(*b*) "Prolongs exposure time before sunburn occurs."

(*c*) "Permits tanning (or suntanning) and reduces chance of (or minimizes) sunburning."

(*d*) "Helps prevent sunburn on moderate exposure of untanned skin."

(*e*) "Allows you to stay in the sun four times longer than without sunscreen protection."

(*f*) "Provides four times your natural protection from sunburn."

(iii) *For extra sunscreen products.* (*a*) "Affords extra protection against sunburn."

(*b*) "Prolongs exposure time before sunburn occurs."

(*c*) "Permits limited tanning (or suntanning) and reduces chance of (or minimizes) sunburn."

(*d*) "Helps prevent sunburn."

(*e*) "For sun-sensitive skin."

(*f*) "Extra protection against sunburn for blondes, redheads and fair-skinned persons."

(*g*) "Allows you to stay in the sun six times longer than without sunscreen protection."

(*h*) "Provides six times your natural protection from sunburn."

(iv) *For maximal sunscreen products.* (*a*) "Affords maximal protection against sunburn."

(*b*) "Prevents sunburn and limits tanning."

(*c*) "For sun-sensitive skin."

(*d*) "Maximal protection against sunburn for blondes, redheads and fair-skinned persons."

(e) "Allows you to stay in the sun eight times longer than without sunscreen protection."

(f) "Provides eight times your natural protection from sunburn."

(v) *For ultra sunscreen products.* (a) "Affords the most protection against sunburn."

(b) "Prevents tanning and sunburn."

(c) "For highly sun-sensitive skin."

(d) "Greatest protection against sunburn for blondes, redheads, and fair-skinned persons."

(e) "Provides the highest degree of sunburn protection and permits no tanning."

(f) "Provides the highest degree of sunscreen protection and permits no tanning."

(3) *For all (maximal and ultra) sunscreen products that contain sunscreen opaque sunblock ingredients.* "Reflects the burning rays of the sun."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings:"

(1) *For all (minimal, moderate, extra, maximal, and ultra) sunscreen products.* The labeling of all sunscreen products contains the following warnings:

(i) "For external use only, not to be swallowed."

(ii) "Avoid contact with the eyes."

(iii) "Discontinue use if signs of irritation or rash appear."

(2) *Specific warnings.*—(i) *For sunscreen products providing an SPF value of 2 to under 4:* "Use on children under 2 years of age only with the advice of a physician."

(ii) *For sunscreen products providing an SPF value of 4 or greater:* "Use on children under 6 months of age only with the advice of a physician."

(iii) *For sunscreen products containing lawsone 0.25 percent with dihydroxyacetone 3 percent.* (a) "This is a two lotion product. Do not mix the contents of the two solutions. Use both solutions, for use of one alone will not provide protection."

(b) "Use only on skin free of rash and abrasions."

(c) "May stain clothing when freshly applied."

(d) *Directions for use.* The labeling of the product shall contain the following statement under the heading "Directions:"

(1) (i) For sunscreen products providing a minimum SPF value of 2 to under 4 for adults and children over 2 years of age: Apply liberally before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) For sunscreen products providing a minimum SPF value of 4 for adults and children over 6 months of age: Apply liberally before sun exposure and reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(2) *For all (minimal, moderate, extra, maximal, and ultra) sunscreen products—(i) That satisfy the water resistant testing procedures.* "Apply liberally before sun exposure and reapply after 40 minutes in the water or after excessive sweating."

(ii) *That satisfy the waterproof testing procedures.* "Apply liberally before sun exposure and reapply after 80 minutes in the water or after excessive sweating."

(iii) *That satisfy the sweat resistance testing procedures.* "Apply liberally before sun exposure and reapply after 30 minutes of excessive sweating."

(3) *For sunscreen products containing lawsone 0.25 percent with dihydroxyacetone 3 percent.* Products are composed of two separate formulations. Solution 1 contains 3 percent dihydroxyacetone and Solution 2 contains 0.25 percent lawsone.

(i) Products providing a minimum SPF value of 2 to under 4 for adults and children over 2 years of age: Apply liberally before sun exposure as follows: *First application.* The evening prior to sun exposure: Apply Solution 1. Wait 15 minutes then apply Solution 2 to the same areas of skin. Wait until dried. Then repeat application of solutions alternately as before until a total of three applications of both lotions have been applied. Leave on skin without washing. *Repeated application.* After first day, apply one application of each lotion. Reapply after swimming or after excessive sweating. There is no recommended dosage for children under 2 years of age except under the advice and supervision of a physician.

(ii) Products providing a minimum SPF value of 4 for adults and children over 6 months of age: Apply liberally before sun exposure as follows: *First application.* The evening prior to sun exposure: Apply Solution 1. Wait 15 minutes then apply Solution 2 to the same areas of skin. Wait until dried. Then repeat application of solutions alternately as before until a total of three applications of both lotions have been applied. Leave on skin without washing. *Repeated application.* After first day, apply one application of each lotion. Reapply after swimming or after excessive sweating. There is no recommended dosage for children under 6 months of age except under the advice and supervision of a physician.

(e) *Statement on product performance—(1) Labeling claims for Product Category Designation (PCD).* The following appropriate labeling statement shall be prominently placed on the principal display panel of the products:

(i) Products containing active ingredient(s) that provide an SPF value of 2 to under 4: "Minimal Sun Protection Product (SPF 2)—Stay in the sun twice as long as before without sunburning."

(ii) Products containing active ingredient(s) that provide an SPF value of 4 to under 6: "Moderate Sun Protection Product (SPF 4)—Stay in the sun 4 times as long as before without sunburning."

(iii) Products containing active ingredient(s) that provide an SPF value of 6 to under 8: "Extra Sun Protection Product (SPF 6)—Stay in the sun 6 times as long as before without sunburning."

(iv) Products containing active ingredient(s) that provide an SPF value of 8 to under 15: "Maximal Sun Protection Product (SPF 8)—Stay in the sun 8 times as long as before without sunburning."

(v) Products containing active ingredient(s) that provide an SPF value of 15 or greater: "Ultra Sun Protection Product (SPF 15)—Stay in the sun 15 times as long as before without sunburning."

(2) *Labeling claims related to the product performance.* One or more of the following labeling claims for sunscreen products that satisfy the sunscreen product testing procedures identified in § 352.40 may be used.

(i) *For all (minimal, moderate, extra, maximal, and ultra) sunscreen products—(a) That satisfy the water resistance testing procedures.*

(*1*) "Water resistant."

(*2*) "Retains its sun protection for at least 40 minutes in the water."

(*3*) "Resists removal by sweating."

(*b*) *That satisfy the waterproof testing procedures.*

(*1*) "Waterproof."

(*2*) "Retains its sun protection for at least 80 minutes in the water."

(*3*) "Resists removal by sweating."

(*c*) *That satisfy the sweat resistance testing procedures.*

(*1*) "Retains its sun protection for at least 30 minutes of heavy sweating."

(*2*) "Sweat resistant."

(3) *Labeling guide for recommended sunscreen product use.* The Panel recommends that the following compilation of skin types and PCD's be appropriately included in labeling as a guide:

RECOMMENDED SUNSCREEN PRODUCT GUIDE

Sunburn and tanning history	Recommended sun protection product
Always burns easily; never tans	Maximal, Ultra.
Always burns easily; tans minimally	Extra.
Burns moderately; tans gradually	Moderate.
Burns minimally; always tans well	Minimal.
Rarely burns; tans profusely	Minimal.

Interested persons are invited to submit their comments in writing (preferably in quadruplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before November 24, 1978. Such comments should be addressed to the Office of the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-65, 5600 Fishers Lane, Rockville, Md. 20857, and may be accompanied by a supporting memorandum or brief. Comments replying to comments may also be submitted on or before December 26, 1978. Comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: August 8, 1978.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

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