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Food and Drug Administration
Human drugs: Sunscreens; photochemistry and photobiology; meeting, << 42398>>

★ First Match

PROPOSED RULES

Human drugs: Sunscreens; photochemistry and photobiology; meeting, << 42398>>

Vol. 61 No. 159 Thursday, August 15, 1996 p << 42398>> (Proposed Rule) 1/399
DEPAR'TMENTOF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 352

[Docket No. 78N-0038]

RIN 0910-AA01

Discussion of the Photochemistry and Photobiology of Sunscreens; Public Meeting and Reopening of the Administrative Record

AGENCY: Food and Drug Administration, HHS.

ACTION: Notification of public meeting and reopening of the administrative record.

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SUMMARY: The Food and Drug Administration (FDA) is announcing a public meeting to obtain data and information on the photochemistry and photobiology of sunscreens. Meeting attendees are invited to address issues described in this notice. In addition, FDA is reopening the administrative record for the proposed rulemakinq for over-the-counter (OTC) sunscreen drug products to allow for comment on matters considered in this notice and at the meeting. This meeting is part of the ongoing review of OTC drug products conducted by FDA.

DATES: The meeting will be held on September 19 and 20, 1996, 8:30 a.m. Submit notice of participation by September 6, 1996. Submit comments regarding matters discussed in this notice or raised at the rneeting by December 6, 1996. The administrative record will rernain open until December 6, 1996.

ADDRESSES: Submit notice of participation, and written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. The meeting will be held at the Doubletree Hotel, Plaza I and II, 1750 Rockville Pike, Rockville, MD 20852, 301-468-1100.

FOR FURTHER INFORMATION CONTACT: Donald Dobbs, Center for Drug

Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, -Rockville, MD 20857, 301-827-2222, FAX 301-827-2316.

SUPPLEMENTARY INFORMATION:

I. Background

The agency believes that the use of sunscreen products is helpful as a component of a regimen for sun protection. A joint panel of the American Academy of Dermatology and the Centers for Disease Control and Prevention recently recommended the use of sunscreen products in addition to limiting exposure to ultraviolet (UV) radiation, wearing protective clothing, avoiding artificial tanning devices, and seeking shade when your shadow is shorter than your height (Ref. 1).

The agency is not at this time proposing to amend the tentative final monograph for OTC sunscreen drug products published on May 12, 1993 (58 FR 28194), and this notice does not intend to imply concerns about sunscreen agents as a class. However, recent scientific advances in understanding of the photochemistry and photobiology of sunscreen active ingredients have raised issues for discussion regarding use of sunscreen ingredients singly and in combinations; specifically, about zinc oxide and 'titanium dioxide. The agency is seeking to incorporate these recent scientific advances into the base of regulatory information supporting the final monograph for OTC sunscreen drug products.

II. Request for Data and Information

A. Photostability and photobiology of titanium dioxide and zinc oxide

In the Federal Register of August 25, 1978 (43 FR 38206), the agency published an advance notice of proposed rulemaking to establish a monograph for OTC sunscreen drug products based on the report and recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn,

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and Sunburn Prevention and Treatment Drug Products (the Panel). In its report (43 FR 38206 at 38250), the Panel stated that titanium dioxide is recognized as an effective opaque chemical for use as a physical sunscreen because it reflects and scatters both UV (290 to 400 nanometers (nm)) and visible light (400 to 700 nm) radiation, rather than absorbing the rays, thereby providing a barrier for sun-sensitive individuals. The Panel concluded that titanium dioxide was both safe and effective for sunscreen use. The Panel classified zinc oxide as an inactive ingredient (43 FR 38206 at 38208) and did not review it for safety and effectiveness.

In the tentative final monograph for OTC sunscreen drug products (58 FR 28194), the agency concurred with the Panel's recommendation on titanium dioxide and proposed to classify it as a Category I (generally recognized as safe and effective) sunscreen used alone or in combination with other Category I sunscreens (58 FR 28194 at 28295 to 28296). The agency reviewed the data on zinc oxide that had been submitted to the Panel (one study)

and other available data and concluded that the data were insufficient to determine effectiveness. The agency classified zinc oxide as a Category III (available data are insufficient to classify as safe and effective and further testing is required) sunscreen (58 FR 28194 at 28213). The agency is currently evaluating additional effectiveness data to support Category I status for zinc oxide in the final monograph for OTC sunscreen drug products.

There has been a renewed interest in incorporating titanium dioxide and zinc oxide in sunscreen formulations because these ingredients may confer protection for a broad range of the UV spectrum. In addition, ultra-fine forms of these ingredients have been developed that are more esthetically pleasing (Refs. 2, 3, and 4).

Sunscreens have been generally classified as chemical (organic) or physical (inorganic), depending on whether they absorb specific wavelength bands of UV radiation or reflect and scatter UV radiation. Although titanium dioxide and zinc oxide have been described as chemically inert ingredients that attenuate through reflection and scattering, new data and information indicate that they also absorb UV radiation, as well as scatter visible light (Ref. 5). Various authors (Refs. 5 through 10) have shown that these ingredients exhibit a semiconductor optical absorption gap. They absorb most radiation at wavelengths shorter than the gap (approximately 380 nm) and scatter radiation at wavelengths longer than the gap. When titanium dioxide and zinc oxide are irradiated with light containing energy greater than the gap (approximately 3 electron volts), an electron from the valence band can be excited to the conduction band, thus creating an electron-hole pair. Because of these semiconductor properties, titanium dioxide and zinc oxide have been used as photocatalysts to degrade organic substances and pesticides in the environment (Refs. 11 through 15). In addition, titanium dioxide is being currently developed as a photooxidative self-cleaning and/or biocidal coating for industrial surfaces (Ref. 16).

In vitro, it has been demonstrated that titanium dioxide in the presence of UV radiation can be cytotoxic to certain cancer cells (HeLa cells and T-24 human bladder cancer cells) even though titanium dioxide or UV radiation alone were nontoxic under study conditions (Refs. 17 and 18). Because these cells are transformed cell lines and are not normal human cells, the relevance of these in vitro findings to sunscreen use by humans (i.e., in sunlight) is not known for zinc oxide and titanium dioxide.

Mineral components, particle size, surface area, crystalline structure, particle coatings, pH of the medium, differences in the refractive index of medium, and other properties of the formulation may affect the photocatalyst properties of titanium dioxide (Refs. 2 through 5 and 19 through 22). These characteristics are not mentioned in the United States Pharmacopeia (USP) compendial monographs, which contain no discussion of trace ions that may affect the absorption band gap between the valence and conduction bands or electronic energy levels, e.g., the range of wavelengths that are absorbed.

The agency would like to receive information and data that address the following issues: (1) Characterize the potential systemic absorption and long-term safety of the topical application of titanium dioxide and/or zinc oxide in sunscreen drug products; (2) ascertain whether titanium dioxide and/or zinc oxide in sunscreen drug products can, under conditions of combination with certain ingredients, time, temperature, and/or exposure

to water, photocatalyze. If so, determine whether this occurs at a rate such that the effectiveness of the sunscreen drug products would be significantly reduced; and (3) determine whether current compendial monograph specifications are sufficient to ensure manufacture of safe and effective titanium dioxide and/or zinc oxide in sunscreen drug products.

B. Photochemistry and photobiology of sunscreen ingredients alone and in combination

In the advance notice of proposed rulemaking for OTC sunscreen drug products (43 FR 38206), the Panel recommended that 21 ingredients be considered generally recognized as safe and effective as OTC sunscreens. Based on the available data, the Panel determined that these sunscreens could be used alone or in any combination (without reference to final formulation) as long as the finished product has a minimum sun protectant factor (SPF) of 2. For the majority of these ingredients, the available data consisted of short-term animal and human toxicity studies on individual ingredients in the absence of UV radiation.

In the tentative final monograph for OTC sunscreen drug products (58 FR 28194), the agency concurred with most of the Panel's recommendations and classified 20 of the 21 ingredients as Category I sunscreens when used alone or in combination with other Category I sunscreens (58 FR 28194 at 28295 to 28296). Padimate A was classified as Category II (concentrations 5 percent or higher) and Category III (concentrations less than 5 percent) on the basis of data and information on its phototoxicity that was not available to the Panel at the time of its review (58 FR 28194 at 28211).

Consumers' increased awareness of the need to protect themselves against the harmful effects of both UVA (320 to 400 nm) and UVB (290 to 320 nm) radiation has created a demand for sunscreen products with higher SPF's and better broad-spectrum (290 to 400 nm) protection of longer duration. Manufacturers have responded by creating products with higher SPF's that claim to provide protection against both UVA and UVB radiation. Manufacturing products with such characteristics often requires that the products contain combinations of several Category I sunscreen ingredients (usually three or more) that absorb over different parts of the UV spectrum.

The agency is interested in the photostability of sunscreen ingredients and the effects that a lack of stability could have on these sunscreen products. Some sunscreen ingredients may undergo photodegradation (Refs. 23 through 29), producing byproducts which may affect product safety or effectiveness (Refs. 30 through 35). Photodegradation of some active sunscreen ingredients may occur in the presence of certain inactive ingredients (Refs. 36 arid 37).

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Therefore, the agency is interested in photostability methodologies for sunscreen ingredients. The agency would like to know how to test the photostability of sunscreen ingredients and to characterize potential byproducts in sunscreen product combinations and in different formulations.

The agency is interested in data and information on the following issues: (1) The potential of active sunscreen ingredients, alone and in combination, to interact in the presence of UV radiation

and/or certain inactive ingredients; (2) characterization of potential byproducts of such interactions and description of impact, if any, on safety or effectiveness of final sunscreen formulations; and (3) descriptive measurement methods and characterization of local or possible systemic effects in vivo.

The agency has concluded that it would be in the public interest to hold a public meeting, in accordance with 21 CFR 10.65, to discuss the issues associated with the photochemistry and photobiology of sunscreens. The proposed rulemaking for OTC sunscreen drug products involves 21 CFR parts 352, 700, and 740; however, the discussion at the public meeting will be limited to proposed part 352, i.e., sunscreens for use as OTC drugs.

Any individual or group interested in making a presentation at the meeting should contact Donald Dobbs (address above). Presentations should only address the issues listed in this notice. Persons interested in participating in the meeting must also send a notice of participation on or before September 6, 1996, to the Dockets Management Branch (address above). All notices of participation submitted should be identified with the docket number found in brackets in the heading of this notice and should contain the following information: Name, address, telephone number, business affiliation, if any, of the person desiring to make a presentation, summary of the presentation, and the approximate amount of time requested for the presentation.

Groups having similar interests are requested to consolidate their comments and present them through a single representative. Depending on the time available and the number of participants, FDA may require joint presentations by persons with common interests. After reviewing the notices of participation, FDA will notify each participant of the schedule and time allotted to each person.

The administrative record for the OTC sunscreen drug products rulemaking is being reopened to specifically allow for comments on matters raised in this notice and at the meeting. The agency requests data and information regarding the photochemistry and photobiology of sunscreens from any interested person. Any individual or group may, on or before December 6, 1996, submit to the Dockets Management Branch (address above), comments and data specifically limited and relevant to the issues in this notice or addressed at the meeting. Two copies of any comments are to be submitted, except that individuals may submit one copy. All comments are to be identified with the docket number found in brackets in the heading of this document. The administrative record will remain open until December 6, 1996.

References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Goldsmith, L., et al., "Proceedings from the National Conference to Develop a National Skin Cancer Agenda," Journal of the American Academy of Dermatology, 34:822-3, 1996.

2. Catlow, B., "Formulating With Ultrafine TiO2," Seifen Oele Fette Wachse, 119:497-500, 1993.

3. Alexander, P., "Ultrafine Titanium Dioxide Makes the Grade," Manufacturing Chemist, 62:21,23, 1991.-

4. Brown, M. W., and E. Galley, "Testing UVA and UVB Protection from Microfine Titanium Dioxide," Cosmetics and Toiletries, 105:69-73, 1990.

5. Sayre, T., et al., "Physical Sunscreens," Journal of the Society of Cosmetic Chemists, 41:103-109, 1990.
6. Fox, M. A., "Mechanistic Photocatalysis in Organic Synthesis,'' "Photocatalysis: Fundamentals and Applications," John Wiley & Sons, New York, NY, pp. 421-455, 1989.
7. Russell, J., et al., "The Assessment of the OH Scavenging Action of Therapeutic Agents," Journal of Pharmaceutical & Biomedical Analysis, 12:863-866, 1994.
8. Harbour, J. H., J. Tromp, and M. L. Hair, "Photogeneration of Hydrogen Peroxide in Aqueous Ti02 Dispersions," Canadian Journal of Chemistry, 63:204-208, 1985.
9. Rao, M. V., et al., "Photosynthesis Production of H2 and H202 on Semiconducting Oxide Grains in Aqueous Solutions," Journal of Physical Chemistry, 84:1987-91, 1980.
10. Schwitzgebel, J., et al., "Role of Oxygen Molecule and the Photogenerated Electron in TiO2-Photocatalyzed Air Oxidation Reactions," Journal of Physical Chemistry, 99:5633-38, 1995.
11. Hidaka, H., et al., "Photodegradation of Surfactants. XV: Formation of SO4↑2-Ions in the Photooxidation of Sulfur-Containing Surfactants," Chemosphere, 29:2619-2624, 1994.
12. Minero, C., et al., "Photocatalyzed Transformation of Nitrobenzene on Ti02 and ZnO,'' Chemosphere, 28:1229-1244, 1994.
13. Dieckmann, M. S., K. A. Gray, and P. V. Kamat, "Photocatalyzed Degradation of Adsorbed Nitrophenolic Compounds on Semiconductor Surfaces," Water Science Technology, 25:277-279, 1992.
14. Mak, M. K. S., and S. T. Hung, "Degradation of Neat and Commercial Samples of Organophosphate Pesticides in Illuminated Ti02 Suspensions," Toxicology and Environmental Chemistry, 36:155-168, 1992.
15. Borello, R., et al., "Photocatalytic Degradation of DDT Mediated in Aqueous Semiconductor Slurries by Simulated Sunlight," Environmental Toxicology and Chemistry, 8:997-1002, 1989.
16. Heller, A., "Chemistry and Applications of Photocatalytic Oxidation of Thin Organic Films," Accounts of Chemistry Research, 28:503-508, 1995.
17. Cai, R., et al., "Induction of Cytotoxicity by Photoexcited Ti02 Particles,'' Cancer Research, 52:2346-2348, 1992.
18. Kubota, Y., et al., "Photokilling of T-24 Human Bladder Cancer Cells With Titanium Dioxide," British Journal of Cancer, 70:1107-1111, 1994.
19. Anonymous, "Formulators Fine-Tune Ti02-Based Screens," Manufacturing Chemist, 64:26,27,29, 1993.
20. Tichy, S., "Transparent Ti02 for UV Protection," Seifen Oele Fette Wachse, 118:612-620, 1992.
21. Ortyl, T. T., and G. E. Peck, "Surface Charge of Titanium Oxide and Its Effect on Dye Adsorption and Aqueous Suspension Stability,'' Drug Development and Industrial Pharmacy, 17:2245-2268, 1991.
22. Macleod, T. M., and W. Fran-Bell, "Study of Physical Light Screening Agents," British Journal of Dermatology, 92:149-156, 1975.
23. Roscher, N. M., et al., "Photodecomposition of Several Compounds Commonly Used as Sunscreen Agents" Journal of Photochemistry, Photobiology, and Chemistry, 80:417-21, 1994.
24. Comment SUP20, Docket No. 78N-0038, Dockets Management Branch.
25. Deflandre, A., and G. Lang, "Photostability Assessment of Sunscreens; Benzylidene Camphor and Dibenzoylmethane Derivatives," International Journal of Cosmetic Science, 10:53-62, 1988.

26. Flindt-Hansen, H., C. J. Nielsen, and P. Thune, "Measurements of the Photodegradation of PABA and Some PABA Derivatives," Photodermatology, 5:257-261, 1988.
27. Stenberg, C., T. Mellstrand, and O. Larko, "Stability of PABA after UV Radiation In Vivo and In Vitro," Photodermatology, 4:201-204, 1987.
28. Gasparro, F. P., "UV-Induced Photo Products of Para-Aminobenziod Acid," Photodermatology, 2:151-157, 1985.
29. Broadbent, J. K., et al., "Capillary Supercritical Fluid Chromatography Combined With Atmospheric Pressure Chemical Ionisation Mass Spectrometry for the Investigation of Photoproduct Formation in the Sunscreen Absorber 2-Ethylhexyl-p-

Methoxycinnamate," Journal of Chromatography A, 732:101-110, 1996.
30. Schallreuter, K. U., et al., "Oxybenzone Oxidation Following Solar Irradiation of Skin: Photoprotection Verses Antioxidant Inactivation," Journal of Investigative Dermatology, 106:583-586, 1996.
31. Gasparro, F. P., "The Molecular Basis of UV-Induced Mutagenicity of Sunscreens," FEBS letters, 336:184-185, 1993.
32. Knowland, J. S., "Reply of Dr. Knowland to Gasparro's Comment," FEBS letters, 336:186, 1993.
33. Knowland, J., et al., "Sunlight-Induced Mutagenicity of a Common Sunscreen Ingredient" FEBS letters, 324:309-313, 1993.
34. Shimoi, K., et al., "Enhancing Effects of Cinoxate and Methyl Sinapate on the Frequencies on Sister-Chromatid Exchanges and Chromosome Aberrations in Cultured Mammalian Cells," Mutation Research, 212:213-221, 1989.
35. Gallagher, C. H., et al., "Ultraviolet Carcinogenesis in the Hairless Mouse Skin; Influence of the Sunscreen 2-Ethylhexyl-P-Methoxycinnamate," Australian Journal of Experimental Biology & Medical Science, 62:577-588, 1984.
36. Shaath, N. A., H. M. Fares, and K. K. Klien, "Photodegradation of Sunscreen Chemicals: Solvent Considerations," Cosmetics & Toiletries, 105:41-44, 1990.
37. Agrapidis-Paloympis, L. E., R. A. Nash, and N. A. Shaath, "The Effect of Solvents on the Ultraviolet Absorbance of Sunscreens," Journal of the Society of Cosmetic Chemists, 38:209-221, 1987.

Dated: August 9, 1996.

William K. Hubbard,
Associate Commissioner for Policy Coordination.

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