Update of Sunscreen Ingredients Nomination to NTP

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May 23, 2006

Summary

In 2001, at the request of the NCI Project Officer, Technical Resources International, Inc., (TRI) examined the presence of sunscreen ingredients in products and reaffirmed that there was widespread exposure to octyl methoxycinnamate. It recently came to the attention of TRI and NCI that this information and the interests of the Chemical Selection Planning Group (CSPG)in pursuing the nomination of this chemical were not conveyed to the National Toxicology Program (NTP).

To ensure that the CSPG's concerns in 2001 remain valid in 2006, TRI again analyzed the usage of octyl methoxycinnamate as a sunscreen ingredient. The widespread use of octyl methoxycinnamate worldwide was again reaffirmed; indeed, it is the most widely used of all sunscreen active ingredients.. Octyl methoxycinnamate is found both in topically applied sunscreens and in lipsticks.

Studies of percutaneous absorption indicate that 1 to 2% of the applied material may be absorbed through the skin. Most of the octyl methoxycinnamate appears to be trapped in the stratus corneum in adults. However, concerns have been expressed about the use of this sunscreen ingredient in children where the stratus corneum is less likely to be protective. Industry is taking measures to address this exposure to octyl methoxycinnamate through the dermal route by microencapsulation.

Toxicologically, octyl methoxycinnamate has repeatedly demonstrated weak estrogenic effects. This chemical also caused slight but measurable effects in a 2-generation study in rats; the effects in offspring may have reflected maternal toxicity.

Updated Chemical & Physical Property Data

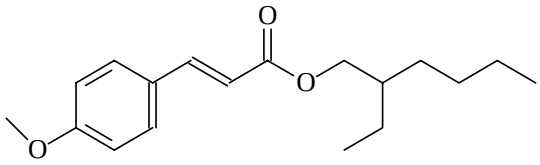
Common name: octyl methoxycinnamate

FDA approved name change to octinoxate (FDA, 2003)

INCI Name: ethylhexyl methoxycinnamate (BASF, 2006)

EINECS 226-775-7

Trade Name: Uvinul® MC 80: stabilized with 0.07 ± 0.02% BHT and Uvinul® MC 80 N: unstabilized (BASF, 2006)



Structure of octyl methoxycinnamate

Updated Exposure Data

The most widely used sunscreen ingredient in the United States, octyl methoxycinnamate is thought to be the UVB filter in 90% of sun lotions (Brown, 2000). The National Library of Medicine Household Products Database lists 90 personal care products, including hair color products and shampoos, lipstick, nail polish, and skin creams, and one pesticide (Repel Sun & Bug Stuff Insect Repellent) that contain octyl methoxycinnamate (NLM, 2006).

This chemical is also widely used in Europe. In a study of 18 chemical UV filters in 75 sunscreen products used in Denmark, octyl methoxycinnamate (1.4-4.7%) and butyl methoxydibenzoyl-methane (0.4-4.8%) were the most frequently used UV filters, present, respectively, in 49% and 44% of the investigated products (Rastogi, 2002).

According to information submitted to comply with the Toxic Substances Control Act (TSCA) Inventory Update Rule (IUR), the following nonconfidential quantities of octyl methoxy-cinnamate were produced or imported into the United States (EPA, 2006):

1986	10,000 to 500,000 lb
1990	>500,000 to 1 million lb
1994	>1 million to 10 million lb
1998	>1 million to 10 million lb
2002	No reports

While the figures for 2002 appear to represent a reduction in usage, it actually represents a change in TSCA since octyl methoxycinnamate is now exempted from TSCA reporting rules (ChemID, 2006).

Human Studies

Transdermal resorption of octyl methoxycinnamate has been reported in intact human skin (Hayden *et al.*, 1997; Janjua *et al.*, 2004).

The absorption of octyl methoxycinnamate and two other sunscreen ingredients, benzophenone-3, and 3-(4-methylbenzylidene) camphor, was examined in a 2-week single-blinded study of 32 healthy volunteers. These volunteers were 15 young men and 17 postmenopausal women. Following daily whole-body topical application of 2 mg/cm^2 of basic cream formulation without (week 1) or with (week 2) the three sunscreens, each at 10% (wt/wt), maximum plasma concentrations were 200 ng/mL (females) and 300 ng/mL (males) for benzophenone-3, 20 ng/mL (females and males) for 3-(4-methylbenzylidene)camphor, and 10 ng/mL (females) and 20 ng/mL (males) for octyl methoxycinnamate. All three sunscreens were detected in urine. Although the authors noted some statistically significant differences between the control week and the treatment week in testosterone, estradiol, and inhibin B levels, they did not view these minor changes as biologically significant (Janjua *et al*., 2004).

A group of nine healthy human volunteers, age 29 ± 1.8 years applied commercially available SPF-15+ sunscreen product containing oxybenzone (6 % w/v), octyl methoxycinnamate (7.5% w/v), octyl salicylate (5% w/v), and octocrylene (7% w/v) to the entire surface of their forearms.

Estimates were that 13.0 g of sunscreen product was applied to a surface area of 1051 cm^2. The unoccluded formulation remained for 12 hours and was then removed with soap and water. The volunteers collected urine just before application and for 48 hours after application. Based on oxybenzone and oxybenzone metabolites recovered in urine, the authors estimated that between 1 and 2% of the applied sunscreen was absorbed over a 10-hour period. Whether the other sunscreen ingredients were also present in the urine was not addressed (Hayden *et al.*, 1997).

A total of 360 women, ages 19-65, were recruited at 10 U.S. locations to participate in a two week study designed to determine exposure to the active ingredients in various lipsticks, body lotions, and face creams. Each woman recorded daily usage information, and samples were weighed at the beginning and end of the exposure period to determine the amount of material applied. For lipstick, the mean of the total amount applied was 0.272 grams with an average amount applied per use day of 0.214 grams. For body lotion, the mean of the total amount applied was 103.21 grams with an average amount applied per use day of 8.69. For face creams, the corresponding figures were 22.36 and 2.05 grams, respectively. Variability was a very large, and use tended to diminish over the course of the study (Loretz *et al.*, 2005).

Whole Animal Studies

Female Sprague-Dawley rats (n = 8 to 11 animals/group) were ovariectomized at 14 weeks of age and then treated for 12 weeks with octyl methoxycinnamate or 4-MBC[1] at 2.5 or 12.5 g/kg in the diet. Positive controls received 17-β-estradiol (E2), 5α-androstane-3β,17β-diol (Adiol), and 4-nonylphenol (NP). Groups were also varied by either a soy-free or a soy-rich diet. The authors determined the effects of these chemicals on malic enzyme, a well-characterized endpoint of thyroid hormone action. Liver malic enzyme activity was significantly increased by E2 and Adiol and slightly increased by MBC and octyl methoxycinnamate. Soy-containing diet significantly decreased malic enzyme activity as compared to soy-free diet. Hepatic 5′-deiodinase activity was significantly reduced by all treatments. Serum T4, T3 and TSH levels were affected as follows: T4 was increased in E2 treated rats but decreased in octyl methoxycinnamate and 4-MBC treated rats.

[1] At the present time (2004), 4-MBC is only approved in Europe (Janjua *et al.*, 2004).

In general, T3 levels were affected less than T4 levels. TSH was increased by E2, octylmethyl cinnamate (low dose), and 4-MBC. The authors commented that there appeared to be no consistent pattern in the effects of the endrocrine active compound used, each compound eliciting its own spectrum of alterations, suggesting that there might be multiple targets of interference with the complex network of thyroid hormone action and metabolism (Schmutzler *et al.*, 2004).

Male and female Wistar rats, 25 per group, received octyl methoxycinnamate in the diet continuously through two successive generations at doses of 0, 150, 400, or 1,000 mg/kg bw/day in accordance with OECD test guideline 416. (Nominal dietary concentrations ranged from 674 to 16,090 ppm). No adverse effects on estrous cycles, mating behavior, conception, parturition, lactation and weaning, sperm and follicle parameters, macropathology and histopathology of the sexual organs was observed. Doses were based on a prior 1-generation range finding study in which animals receiving 10,000 ppm of the test compound in the diet had an uptake of 1,190 mg/kg bw/day; these animals showed a 10% reduction in body weight relative to controls, decreased female plasma urea, creatinine, total protein and albumin, increased cholesterol, and reduced ovary weight (20%); pup weaning body weights were reduced 37%. In the multi-generation study, at 1,000 mg/kg bw/day, reduced body weight gain, probably associated with reduced food consumption was observed. These animals also had increased liver weight, hepatic cytoplasmic eosinophilia, and erosion/ulceration of the glandular stomach mucosa. There was a statistically significant reduction of number of implantation sites at 1,000 mg/kg bw/day in both parental generations and also at 450 mg/kg bw/day in F_1 dams compared with concurrent controls. The high dose F_1 and F_2 pups had reduced lactation weight gain and organ weight and delayed sexual maturation landmarks. Thus, the NOAEL for fertility and reproductive performance and for systemic parental and developmental toxicity was determined to be 450 mg/kg bw/day. Octyl methoxycinnamate had no adverse effect on estrus cycle, sperm number, morpohology and motility, differential follicle counts, mating, fertility, gestation and parturition (Schneider *et al.*, 2005).

Genotoxicology Studies

Octyl methoxycinnamate was not mutagenic in a standard Ames Salmonella battery with and without metabolic activation using the preincubation method (Zeiger *et al.*, 1985, as cited in CCRIS,

2006). This information was available for previous analyses conducted by NCI.

Estrogenicity Studies

Recent studies have demonstrated that octyl methoxycinnamate has estrogenic properties, both *in vitro* and *in vivo* (Klammer *et al.*, 2005).

The prerequisite of a direct estrogenic action and the initial step of estrogen mediated gene regulation is binding of a compound to either estrogen receptor (ER)α or ERβ. Virtually all cells of the body express one or both types of these estrogen receptors. Therefore, a compound, such as octyl methoxycinnamate should affect a variety of estrogen-regulated body functions. To test the hypothesis that determination of estrogenic activity in the uterus only carries the risk of missing other undesirable actions, Klammer and coworkers conducted a pharmacodynamic experiment with daily gavage treatments for five days of octyl methoxycinnamate in adult ovariectomized rats. At 1000 mg/kg bw, uterine weight increased significantly and the Erβ gene was up regulated. In the pituitary a significant increase of the TERP1 gene expression was observed. Octyl methoxycinnamate application resulted in a decrease in IGF1 gene expression, cholesterol, and LDL serum levels; triglyceride serum levels were decreased although leptin and HDL serum levels were unaffected. The most sensitive parameter, truncated estrogen receptor protein 1 gene expression in the pituitary, occurred at levels below those permitted in formulations for skin protection in humans (Klammer *et al.*, 2005).

According to Schlumpf and colleagues, recent data on bioaccumulation in wildlife and humans point to a need for in-depth analysis of systemic toxicology of UV sunscreen ingredients. The authors examined six frequently used UVA and UVB ingredients for estrogenicity in *in vitro* and *in vivo* systems. In MCF-7 breast cancer cells, five of the six sunscreen ingredients, including octyl methoxycinnamate, increased cell proliferation. In the uterotropic assay using immature Long-Evans rats that received the chemicals for four days in powdered feed, uterine weight was dose-dependently increased by octyl methoxycinnamate (Schlumpf *et al.*, 2001).

The estrogenic activity of octyl methoxycinnamate and 14 other cosmetic components was measured

in three reporter cell lines, HELN, HELN ERα, and HELN ERβ. Eight of the 15 substances, including octyl methoxycinnamate showed specific estrogenic activity; octyl methoxycinnamate also inhibited luciferase expression in the HELN cell line (Gomez *et al.*, 2005).

Inui and coworkers (2003) examined the estrogenicity of octyl methoxycinnamate and 4-methyl benzylidene camphor using the male medaka (*Oryzias latipes*) with regard to production of vitellogenin and choriogenin, known estrogen-responsive gene products. First, using a vitellogenin enzyme-linked immunosorbent assay (ELISA) system, the authors determined the increase in vitellogenin plasma concentration in medaka due to the sunscreen ingredient exposure and compared this concentration to the non-treated control. Next, the authors found increases in mRNA expression levels of vitellogenin subtypes VTG-1 and VTG-2 and choriogenin subtypes CHG-L and CHG-H in liver due to exposure. In addition, the authors found increased mRNA expression levels of ERα in the liver due to exposure to the two sunscreen ingredients.

Absorption through Isolated Skin

In vitro diffusion experiments were conducted to compare the characteristics of human abdominal skin(HS) with pig flank skin (PS) with regard to the percutaneous absorption of octyl methoxycinnamate (oil soluble) and benzophenone-4 (water soluble). After 16 hours, octyl methoxycinnamate and benzophenone-4 remained primarily on the skin surface; 81.2 % (PS) to 87.7% (HS) and 92.6% (PS) to 94.0% (HS) of the applied dose, respectively, could be recovered by washing. Octyl methoxycinnamate had a high affinity for the stratum corneum. In general, quantitative data was in good agreement between human skin and pig skin (Benech-Kieffer *et al.*, 2000).

The pentration and retention of five common sunscreen agents, avobenzone, octinoxate (octyl methoxycinnamate), octocrylene, oxybenzone, and padimate O, in human skin was evaluated. The materials were appliedion in mineral oil to isolated human epidermal membranes for 24 hours. Although 95-98% of the sunscreen agents was recovered on the surface of the epidermis as non-penetrated material, detectable amounts of all sunscreens were present in the stratum corneum and viable epidermis (Hayden *et al.*, 2005).

When 7.5% octyl methoxycinnamate was placed on the excised skin of hairless mice for 24 hours, there was a significant decrease in the lag time and increase in the transdermal penetration of the herbicide, 2,4-dichlorophenoxyacetic acid (Pont *et al.*, 2004).

An *in vitro* model using pig skin was developed to study dermal sunscreen permeation. Two popular sunscreen ingredients, benzophenone-3 and octyl methoxycinnamate un a hydroacloholic or diisopropyl adipate formulation were tested. Both ingredients penetrated the skin, benzophenone-3 to a greater extent than octyl methoxycinnamate (Gupta *et al.*, 1999). In another *in vitro* study of octyl methoxycinnamate absorption through pig skin, considerably greater amounts of this chemical were absorbed when the free chemical was administered in emulsions than when the material was microencapsulated (Jimenez *et al.*, 2004).

Other Studies

Octyl methoxycinnamate has been reported to display no androgenic or antiandrogenic activity at androgen receptor in the human breast carcinoma cell line, MDA-kb2 at any tested concentration (1 nM-10 M) (Ma *et al.*, 2003, cited in Schneider, 2005).

Structure-Activity Predictions

According to DEREK, peroxisome proliferation induced by octyl methoxycinnamate is likely to be weak. Repeated oral dosing or feeding of mice or rats with peroxisome proliferators produces liver hyperplasia and hypertrophy. Histology shows the hypertrophy to be characterized by proliferation of the peroxisomes and the smooth endoplasmic reticulum. Such effects are not seen in higher mammals, including man.

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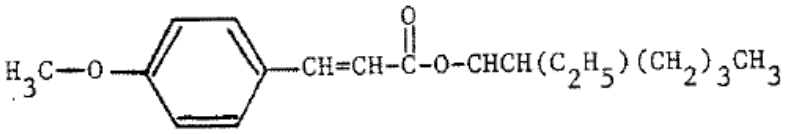
SUMMARY OF DATA FOR CHEMICAL SELECTION

CHEMICAL IDENTIFICATION

CAS Registry No.:	5466-77-3
Chem. Abstr. Name:	3-(4-Methoxyphenyl)-2-propenoic acid, 3-ethylhexyl ester (9 CI)
Synonyms and Trade Names:	2-Ethylhexyl 4-methoxycinnamate; 2-ethylhexyl p-methoxycinnamate; ethylhexyl p-methoxycinnamate; Neo Heliopan AV; Parsol MCX; Parsol MOX; Sunscreen AV

Structure, Molecular Formula and Molecular Weight



$C_{18}H_{26}O_3$ Mol. Wt.: 290.40

Chemical and Physical Properties: No information was found in the standard reference sources on the chemical and physical properties of 2-ethylhexyl p-methoxycinnamate (1-15). Some of the data provided below were submitted to the FDA and published as part of FDA's safety and efficacy evaluation of the sunscreen active ingredients. The CTFA agreed to provide their data but the information has not been received (16).

Description:	Practically odorless, pale yellow, slightly oily liquid	(17)
Boiling Point:	198 - 200° C (3 mm)	(17)
Solubility:	Miscible in alcohols, propylene glycol monomyristate, and various oils; insoluble in water	(17)

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Specific Gravity:	1.01 - 1.02	(17)
Stability:	Stable to light and remains essentially unchanged on exposure to moderate heat	(17)

Technical Products and Impurities: No information was found on the technical products and impurities of 2-ethylhexyl p-methoxycinnamate (1-15,18).

BASIS FOR NOMINATION TO THE CSWG

In the Spring of 1989, Dr. Thomas Cameron, Chairperson of the Chemical Selection Working Group (CSWG), attended an ITC meeting at which there was a discussion about the potential lack of rigorous toxicological characterization of sunscreens was discussed. At the March 8, 1989 Contract Support Planning Group (CSPG) meeting, the subject of sunscreen active agents as appropriate candidates for further evaluation by the CSWG. A class study of sunscreens was presented to the CSPG in June, 1989.

2-Ethylhexyl p-methoxycinnamate is nominated to the CSWG based on structure/activity considerations (known carcinogenicity of the ethylhexyl and cinnamic acid groups), a study implicating the compound as a potential tumor initiator, and high usage.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Contact was made with the FDA division that oversees the sunscreen (ingredient) drug products monograph and the FDA personnel have been very supportive of the potential generation of additional safety data through the DCE and NTP testing programs.

SELECTION STATUS

ACTION BY CSWG: 12/11/89

Studies Requested: Carcinogenicity testing with highest priority

Comments: It was suggested that a nomination for carcinogenicity testing would give an opportunity to explore whether the carcinogenic activity of phthalic and adipic acids is due to the ethylhexyl group or to some other aspect. It is scheduled to be reviewed by the European Community at the end of 1991 to determine whether it will stay on the list of approved compounds. The only sunscreen compound tested in the DCE Short Term Test Program to show some positive results in *Salmonella.*

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EXPOSURE INFORMATION

Commercial Availability

Production and Producers: No information was found on the production and producers of 2-ethylhexyl p-methoxycinnamate (1-15,18-31).

Use Pattern: 2-Ethylhexyl p-methoxycinnamate is a sunscreen active ingredient that absorbs in the UVB (290-320 nm) range, the region responsible for most serious sunburn (17).

Increased public concern about the danger of sun exposure, especially skin cancer, has boosted the consumption of sunscreen ingredients in toiletries and cosmetics. Consumption was 1.1 million pounds in 1977, 1.5 million pounds in 1980, and 2 million pounds in 1985 (32). Sales of sunscreen products also has risen steadily--$2 million in 1975, $39 million in 1980, $150 million in 1985, $270 million in 1987, and $291.8 million in 1988 (33-35) --and is projected to increase 10% between 1989 and 1992 (36).

It was estimated that in 1977 26% of the U.S. population used sun care products (37). A more recent survey of 489 patients during summer months indicated that 41% used sunscreen products (38). Similarly, in a survey of 1,319 women by Glamour magazine, 40% used sun care products (39). According to the American Academy of Dermatology, 33% of adults work on a tan, under 50% apply sunscreens, and 25% take no precautions (40).

The major sales is in products with a Sun Protection Factor (SPF) of 5 or greater. Sales increased by 17% in 1987 and almost 20% in 1988 for products with a SPF of 5 or greater while sales for products with a SPF of less than 5 increased by 3.5% in 1987 and 3% in 1988 (41,42). Products with a SPF of 15 or greater have been the fastest growing segment, accounting for 25% of sales in 1987 vs. 5% in 1986 (43).

Future sunscreen products will focus on broad spectrum protection, higher SPF's and year-round use. In addition, sunscreens will be increasingly used in cosmetics. Although the sunscreen market is growing, it is also becoming saturated. Future growth will be a function of product market differentiation (34).

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Human Exposure: There has been a sharp increase in the number of sunscreen products in the market. There also has been an increase in the number and content of sunscreen ingredients present in these products. As the number of available sunscreens increases, so does potential for human exposure to the ingredients.

Environmental Occurrence: 2-Ethylhexyl p-methoxycinnamate does not occur naturally. No test data were found on environmental transport or persistence of this compound. The extent to which it may dissociate, its concentration and fate are not known (1-15,18).

Regulatory Status: FDA approval for use requires that the sunscreen active ingredient has been or is currently being used commercially. All sunscreen products must currently be labeled with a SPF. The SPF is a ratio of the minimum time required to produce erythema or redness with a sunscreen product to the time required to produce the same redness without the sunscreen. It is determined experimentally in subjects exposed to an artificial light source which simulates solar irradiation, usually a xenon-arc lamp. A SPF of 6 implies the product provides six times the protection the user would have without the sunscreen. The highest SPF rating currently used by the FDA is 15 with an overall range from 2 to 15. To produce the enhanced sunscreen protection required in today's market, combinations of as many as four or five sunscreen ingredients are used. This allows the attainment of SPF's as high as 40.

The FDA has classified products containing a sunscreen as drugs. Current regulatory requirements for labeling of sunscreen products must declare the active ingredients and the quantity, kind and proportion of any alcohol and bear adequate directions for use. An FDA advisory panel reviewed the safety, efficacy and labeling of over-the-counter sunscreen product active ingredients. The panel classified 2-ethylhexyl p-methoxycinnamate as safe and effective when used within the established topical dosage limit of 2 to 7.5% provided the finished product provides a minimum SPF value of not less than 2 (17). The FDA advisory panel will re-evaluate sunscreen active ingredients in 1990.

In October 1983, the European Economic Community (EEC) established a list of UV filters which cosmetic products may provisionally contain. 2-Ethylhexyl p-methoxycinnamate was authorized at a maximum concentration of 10% (44). Then in February 1989, the EEC ruled that 2-ethylhexyl p-methoxycinnamate may only be used until December 31, 1991 (45).

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EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiology studies or case reports associating 2-ethylhexyl p-methoxycinnamate exposure with cancer risk in humans were found in the published literature (3,4,6,11,18,46).

The FDA advisory panel on over-the-counter sunscreen active ingredients concluded that 2-ethylhexyl p-methoxycinnamate is not a skin irritant or photosensitizer (17). Prolonged use of sunscreen products with SPFs over 20 may increase skin sensitization because of irritation by multiple sunscreen materials and their photodegradation products (47).

Animal Data: No mammalian carcinogenicity, chronic or subchronic toxicity, teratogenicity, or reproductive studies were found in the literature for 2-ethylhexyl p-methoxycinnamate (3,4,6,7,11,18,46,48,49).

2-Ethylhexyl p-methoxycinnamate (2-EHMC) was implicated as a potential tumor initiator in an ultraviolet carcinogenesis study in the hairless mouse. In a 9-week treatment regimen, groups of HRA/Skh mice were painted daily on the dorsum with 2-EHMC and were then exposed to low doses of UVB light, treated with 2-EHMC alone, or treated with UVB light alone. 2-EHMC treated mice were protected but subsequent treatment with the tumor promoter, croton oil, produced tumors on a significant number of animals. Statistical analysis of the incidence of promoted tumors indicated that prior UVB irradiation may not have been responsible and indicated that 2-EHMC may initiate tumors in this strain of mice (50).

The following animal data were considered in the FDA advisory panel review of over-the-counter sunscreen active ingredients. The oral LD_{50} in mice is >8 g/kg. It is practically non-irritating in the Draize rabbit eye irritancy test (0.1 ml of the pure chemical). No allergic sensitization was noted in guinea pigs administered approximately 500 mg/kg by either the topical or intradermal route (17).

In Vitro Tests: Bonin *et al.* (51) found 2-EHMC positive in *Salmonella typhimurium* strain TA1538 without S9. The authors concluded that a trace contaminant may have been responsible because samples were obtained from various sources and the test results were batch related. Purities of the test samples were not identified. A later study on 98% pure

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2-EHMC, however, showed the compound was not mutagenic at doses up to 10 mg/plate in strains TA98, TA100, TA1535, and TA1537 with or without metabolic activation (52). The NTP also found 2-EHMC tested negative in *Salmonella typhimurium* (49). Bonin *et al.* (51) and Angus (53) have also reported a positive induction of sex-linked recessive lethals in *Drosophila*. However, it is believed that the mutagenicity is due to some trace contaminant. A number of cinnamaldehydes have been tested for *Salmonella* reversion potential, but no clear pattern emerges (54,55).

Metabolism: No information was found in the literature on the absorption, distribution, or excretion of 2-ethylhexyl p-methoxycinnamate (3,4,6,11,18,46).

Structure/Activity Relationships: Carcinogenic potential may be expected in cinnamyl compounds. The NCI bioassay of cinnamyl anthranilate was positive in male and female mice and male rats, while the test of o-anthranilic acid was negative (56,57). *Salmonella* tests with both compounds were also negative (58,59) but cinnamyl anthranilate tested positive in an *E. coli* reversion assay (60).

In addition, the 2-ethylhexyl moiety may be potentially carcinogenic. The 2-ethylhexyl diester of phthalic and adipic acids were carcinogenic in NCI/NTP bioassays. Another diester of phthalic acid, butyl benzyl phthalate, was positive in female rats (males were inconclusive due to high mortality). Diallyl phthalate was equivocal in mice and female rats but the doses were below an actual MTD. There are ten 2-ethylhexyl compounds in the NTP Chemical Tracking System and twelve phthalates, all of which are negative in the *Salmonella* test except 2-ethylhexyl glycidyl ether (49). There are not adequate data available at this time to clearly implicate the 2-ethylhexyl group per se, but although ethylhexyl adipate is carcinogenic, adipic acid is noncarcinogenic. There is no clear indication that phthalic acid, or esterified phthalates in general, are not carcinogenic in their own right. It is important to note, however, that the butyl and benzyl moieties would not be contributing to the tumorigenicity in the case of butyl benzyl phthalate carcinogenicity. This does, to some extent, implicate phthalate diesters as a general class. The tests underway on dimethyl and diethyl phthalate may shed some light on this in the future. Considering the number of 2-ethylhexyl sunscreen derivatives, however, the question of the ethylhexyl moiety and its role in carcinogenicity is a serious one and should be examined.

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