NTP Chemical Nomination

Benzoic acid, 4-(dimethylamino)-, 2-ethylhexyl ester
CASNO 21245-02-3

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Chemical Identification

CAS Preferred name

- Benzoic acid, 4-(dimethylamino)-, 2-ethylhexyl ester (9CI)

Common Names, Synonyms

- 2-Ethylhexyl-p-dimethylaminobenzoic acid
- Octyl dimethyl PABA
- ODAP
- Padimate O

CAS Registry Number

- 21245-02-3

Chemical Class and Related Compounds

- Tertiary amine
- Benzoic ester

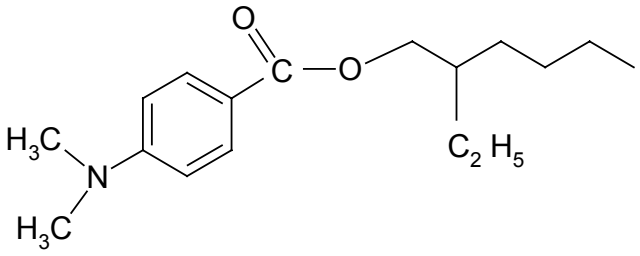
Physical and Chemical Properties

Physical Descriptor

- Lquid

Structural and Molecular Formula and Molecular Weight

The structure is:



Molecular Weight =277.41
Exact Mass =277
Molecular Formula =C17H27NO2
Molecular Composition =C 73.61% H 9.81% N 5.05% O 11.53%

Melting Point and Boiling Points

- Boiling Point 325˚ C

Solubility

- Essentially insoluble in water.
- Soluble in most organic solvents

Stability and Reactivity

- Stable at neutral pH values
- Generally unreactive

Commercial Products and Composition

Some of the commercial US products listed as containing ODAP (1) are:

- Chap Stick
- Chap Stick Sunblock Lip Balm
- Mentholatum Lip Balm
- Vaseline Intensive Care Blockout Moisturizing
- Tropical Blend Dark Tanning
- Total Eclipse Oily and Acne Prone Skin Sunscreen
- Eclipse Original Sunscreen
- Eclipse Lip & Face Protectant
- PreSun Moisturizing Sunscreen with Keri
- Presun Spray Mist for Kids
- Banana Boat Sunblock
- Hawaiian Tropic Dark Tanning
- Blistex Medicated Lip Conditioner
- Blistex Sunblock
- Formula 405 Solar

Production, Use Occurrences and Analysis

Production

Current production levels are not available. This material appeared on the 1994 EPA IUR list of High Production Volume Chemicals but not on the 1990 list. This indicates increasing production and likely current production or importation in excess of a million pounds per annum in the United States.

Uses

The only known use is in cosmetics as a sunscreen. It is permitted at levels up to 8% of the finished product in the US (2) and the EU (3).

Occurrences in the Environment

No specifics found. Based on production and use the annual release is expected to be greater than one million pounds from sunscreen application. Use as sunscreen suggests potential for release into surface waters used for recreation.

Analysis

An hplc method for quantitative determination of ODAP has been recently published (4).

Toxicology

Human Data

Human data are limited to case studies of potential contact sensitization reactions (5).

Experimental Animal Information

Acute data were not located in the open literature and few other data were found. A 4-week oral study in rats was conducted at doses of 0, 100, 300, and 1,000 mg/kg/day of ODAP administered by corn oil gavage using 10 to 15 rats/group/sex. A 4-week recovery period was included to assess the persistence or reversibility of any toxic effects. At the end of the 4-week treatment period, toxic effects were seen in four target organs: Testes, epididymis, spleen, and liver. The effects on reproductive organs were notable with atrophy of the germinal epithelium in the testes a significant finding in 10/10 males at the high dose. The NOEL in this study was 100 mg/kg/day for both males and females. Toxic effects appeared reversible in the animals necropsied after the 4-week recovery period with the exception of marked epididymal hypospermia at the 1,000 mg/kg/day dose (5/5 animals). (6)

In Vitro and Other Short Term Tests.

Xu and Parsons (7) recently published a paper showing that ODAP inhibited cell growth and DNA synthesis and retarded cycle progression at low concentrations.

It has been reported that ODAP is photomutagenic and attacks DNA on illumination with simulated sunlight, producing strand breaks and lesions that are labile to N,N'-dimethylethylenediamine. Reportedly, the damage can be completely suppressed by free radical quenchers commonly used as solvents in photomutagenicity assays (8).

DNA strand breaks in human keratinocytes in the presence of ODAP and illumination have been reported (9). These authors estimate that applying an SPF-15 sunscreen which contains ODAP to human skin followed by exposure to only 5 minimum erythemal doses (MED) of sunlight could increase strand breaks in cells under the epidermis by at least 75-fold compared to exposure to 1 MED in the absence of sunscreen.

A number of studies have been conducted investigating the formation of nitroso compounds in sunscreens containing ODAP (10) and the potential genotoxicity of these nitroso materials (11).

Potential phototoxicity by ODAP appears to be an ongoing area of research.

Environmental Toxicity and Considerations

No data were found for ODAP concerning fish, invertebrate or algal toxicity. Its use pattern as a sunscreen suggests that these effects should be taken into consideration, as some water contamination is inevitable. The following parameters are estimates taken from the EPIWIN (v3.05) modeling program:

Estimated Aquatic Toxicity Parameters (EPIWIN)	
Water Solubility	0.2 mg/l
Octanol-water partition coefficient	Log $K_{o/w}$ = 5.77
Hydrolysis $T_{1/2}$ at pH 7 and 8	590 years and 59 years
Fish 96-hour LD_{50}	0.4 mg/l
Fish ChV	0.01 mg/l
Daphnid 48-hour EC_{50}	0.08 mg/l
Green algae ChV	0.31 mg/l

These parameters suggest that adverse effects on aquatic species should be considered in any comprehensive risk assessment for this material.

Disposition and Ongoing Studies

No ongoing study known except there is evidence in the literature of activity in phototoxicity. The FDA evaluated the results of the 28-day oral study and determined that there was not enough evidence of potential human adverse effects to exclude this material from the Sunscreen Monograph (2).

Rationale for Recommendation and Suggested Studies

Significant human exposure and be anticipated from the widespread use of this material in commercial sunscreen products. Assuming an eight percent preparation and three applications of 20 grams sunscreen product per day, the subsequent exposure potential is 4800 mg or about 70 mg/kg for the average human. Neither dermal nor oral absorption and bioavailability are known.

The 4-week rat study indicates potential testicular toxicity, which was severe for rats exposed orally to 1000 mg/kg/day. It is assumed that the same target organs may be sensitive in humans but the relative sensitivity and safety factor for exposure are not known.

The NTP conducted 90-day toxicity studies on 2-Hydroxy-4-methoxybenzophenone (HMB), another sunscreen component (12). In these studies, male rats treated orally with HMB at 50,000 ppm for 13-weeks showed markedly lower epididymal sperm density and an increase in the length of the estrous cycle at the end of the 13-week study period. Thus, a dose level of about 2500 mg/kg/day for 13 weeks produced effects on sperm. In the case of ODAP, similar effects were produced with an oral dose of 300 mg/kg/day for only 4 weeks, indicating a higher degree of potency.

The mechanism of action is also unknown and if it is hormonal in nature, there exists the possibility of high sensitivity of the human conceptus and immature developing children. As children are encouraged to apply sun-blocking agents, and their surface area to mass ratio is greater than that of an adult, dose levels in children may exceed those in adults. In addition, the dermal bioavailability in children may be greater than in adults due to more permeable skin. The current product usage also includes products designated for children and for use on lips.

Suggested studies

- Dermal pharmacokinetics
- Subchronic dermal study in male rats and mice
- Reproductive toxicity evaluation
- Developmental toxicity (Pre-natal)
- Post-natal developmental toxicity.
- Fish, daphnids and algae

References

1 http://www.mayohealth.org/usp/html/202782.htm#GXX22

2 FDA. Sunscreen products for over-the-counter human use; final monograph. Federal Register 64:27666-63 (May 21 1999)

3 EU Council Directive 83/574/EEC – OJEC L322, 1983.

4 Vanquerp V et al. High-performance liquid chromatographic method for the comparison of the photostability of five sunscreen agents. J Chromatog A; 832: 273-277(1999).

5 Ricci C, Vaccari S, Cavalli M, Vincenzi C. Contact sensitization to sunscreens. Photochem Photobiol 66: 276-81 (1997).

6 EPA/OTS; Doc #88-920000887. Initial Submission: 2-Ethylhexyl-p-Dimethylaminobenzoate: 4-Week Repeated Dose, 4-Week Recovery, Oral Toxicity In Rats (Final Report) With Cover Letter Dated 021092

7 Xu, C, and P Parsons. Cell cycle delay, mitochondrial stress and uptake of hydrophobic cations induced by sunscreens in cultured human cells. Photochemistry and Photobiology 69: 611-616 (1999).

8 McHugh P., and J Knowland. Characterization of DNA damage inflicted by free radicals from a mutagenic sunscreen ingredient and its location using an in vitro genetic reversion assay. Photochem Photobiol. 66: 276-81 (1997).

9 Gulston M., and J. Knowland. Illumination of human keratinocytes in the presence of the sunscreen ingredient Padimate-O and through an SPF-15 sunscreen reduces direct photodamage to DNA but increases strand breaks. Mutat Res 444:49-60 (1999).

10 Loeppky RN, et al. Nitrosation of tertiary aromatic amines related to sunscreen ingredients. IARC Sci Publ, ISS 105, 1991, P244-52.

11 Dunkel VC, et al. Evaluation of the mutagenicity of an N-nitroso contaminant of the sunscreen Padimate O: N-nitroso-N-methyl-p-aminobenzoic acid, 2-ethylhexyl ester (NPABAO). Environ Mol Mutagen 20: 188-98 (1992).

12 NTP Tox 21. Toxicity Studies of 2-Hydroxy-4-methoxybenzophenone (CAS No.131-57-7) Adminstered Topically and in Dosed Feed to F344/N Rats and B6C3F1 Mice (1992).