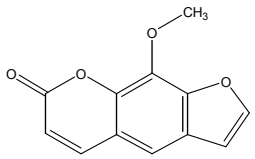
METHOXSALEN WITH ULTRAVIOLET A THERAPY (PUVA)*

First Listed in the *Fourth Annual Report on Carcinogens*



CARCINOGENICITY

Methoxsalen (methoxypsoralen) (CAS No. 298-81-7) with ultraviolet A (long-wave) therapy (PUVA) is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans (IARC 1982, 1987). The development of basal cell and squamous cell skin cancers has been reported in patients treated with methoxsalen and long-wave ultraviolet light. Three cases of malignant melanoma of the skin have been reported in patients with psoriasis treated with PUVA. The strongest evidence for a casual association between PUVA treatment and nonmelanocytic skin cancer is found in the follow-up study of 1,380 psoriatic patients. The standardized incidence ratio (SIR) for squamous cell carcinoma increased from 4.1 (95% confidence interval, 2.3 to 6.8) at low dose levels to 22.3 (13.5 to 34.1) at medium dose levels and 56.8 (42.7 to 74.2) at high dose levels; this effect was independent of possible confounding effects of therapy with ionizing radiation and topical tar. The effect on basal cell cancer incidence was much weaker (high doses: SIR, 4.5; 2.8 to 6.9). One cohort study of 525 psoriatic patients treated with PUVA did not suggest an increase in the incidence of skin cancer (mean follow-up period, 2.1 years), but this "negative" result could have been due to lack of statistical power and to the low doses used in the study. Another study with 5-year follow-up showed no skin tumor in 94 patients treated with PUVA. Methoxsalen alone did not alter the incidence of skin cancer over 2 years in two small controlled trials of its use (IARC 1980, 1982).

An IARC Working Group reported that there is sufficient evidence of carcinogenicity of PUVA in experimental animals (IARC 1980, 1982, 1987). When administered topically, methoxsalen plus exposure to ultraviolet light induced skin tumors, primarily epidermal papillomas and carcinomas, squamous cell carcinomas, fibrosarcomas, and basal cell tumors in mice. Some squamous cell and basal cell carcinomas metastasized. When injected intraperitoneally with methoxsalen and exposed to ultraviolet irradiation, female mice developed increased incidences of epidermal fibrosarcomas and squamous carcinomas of the ears and eye region and epidermal papillomas and carcinomas of the ears (IARC 1980, 1982).

PROPERTIES

Methoxsalen occurs as white to cream-colored, fluffy, needle-like crystals soluble in boiling alcohol, acetone, acetic acid, propylene glycol, and benzene, and sparingly soluble in boiling water, liquid petrolatum, and ether (HSDB 2000). It has a bitter taste and is odorless; it reacts with strong oxidizers, is sensitive to light, and is easily hydrolyzed (NTP 2001).

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* No separate CAS Registry Number is assigned to methoxsalen (methoxypsoralen) with ultraviolet A (PUVA).

Methoxsalen is a psoralen derivative that is structurally and pharmacologically related to trioxsalen (HSDB 2000). Methoxsalen is a naturally occurring substance that is produced by several plants and a fungus (IARC 1980).

USE

Methoxsalen is used primarily in combination with sunlight or long-wave (320 to 400 nm) ultraviolet light in the treatment of vitiligo and severe psoriasis. Methoxsalen is also used to increase skin tolerance to sunlight (IARC 1980), as a sunburn protector, and as a suntan accelerator (HSDB 2000).

PRODUCTION

Current production data on methoxsalen were not available. Chem Sources identified 10 domestic suppliers in 2001 (Chem Sources 2001). The 1998 Chemical Buyers Directory listed three U.S. suppliers of the chemical, and Chemcyclopedia 98 named one supplier (Tilton 1997, Rodnan 1997). In 1980, there was one producer of methoxsalen in the United States, but no data were available on the amount produced (IARC 1980).

EXPOSURE

The primary routes of potential human exposure to methoxsalen are dermal contact and ingestion. Methoxsalen rapidly penetrates the epidermis and dermis upon contact with the skin. For medicinal effectiveness, both oral and topical administration requires subsequent exposure to sunlight or ultraviolet light. Oral dosage is 20 to 50 mg, no more than every other day. When applied topically, a 0.1% to 0.15% solution is used for psoriasis treatment, and a 1.0% solution is used for vitiligo treatment. Methoxsalen treatment is generally followed within 2 to 4 hours by a 5-minute exposure to sunlight or long-wave (320 to 400 nm) ultraviolet light. Exposure to light may be gradually increased to 30 minutes. FDA requires that the pharmaceutical product be labeled with a warning regarding a 9-fold increased risk of squamous cell carcinoma among PUVA-treated patients. Potential occupational exposure to methoxsalen may occur during preparation, formulation, administration, or application of the pharmaceutical. Occupational exposure to ultraviolet light may also occur during therapy.

REGULATIONS

FDA regulates methoxsalen as a prescription drug approved for human use under the Food, Drug, and Cosmetic Act (FD&CA).

NIOSH recommends that exposure to ultraviolet light of wavelength 315 to 400 nm should not exceed 1.0 mW/cm^2 for >1,000 seconds, and 1 J/cm^2 for exposure <1,000 seconds OSHA regulates methoxsalen with ultraviolet A radiation under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 104.

REFERENCES

Chem Sources. Chem Sources International, Inc. http://www.chemsources.com, 2001.

HSDB. Hazardous Substances Data Bank. Online database produced by the National Library of Medicine. 8-Methoxypsoralen. Profile last updated November 6, 2000. Last review date, September 9, 1993.

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