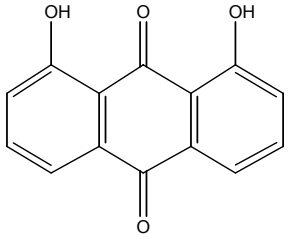
DANTHRON (1,8-DIHYDROXYANTHRAQUINONE)
CAS No. 117-10-2
First Listed in the *Eighth Report on Carcinogens*



CARCINOGENICITY

Danthron is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of malignant tumor formation in multiple species of experimental animals (IARC 1990). When administered in the diet to male rats, danthron induced adenomas and adenocarcinomas of the colon and adenomas of the cecum. When administered in the diet to male mice, danthron caused an increase in the incidence of hepatocellular carcinomas.

No adequate data were available to evaluate the carcinogenicity of danthron in humans.

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

Danthron has been evaluated in studies for its ability to enhance the expression of tumors induced by other chemicals. When danthron was administered in the feed to mice that also received 1,2-dimethylhydrazine, the incidence and multiplicity of adenomas of the colon and liver were significantly increased (Sugie *et al*. 1994). When evaluated in skin painting studies in mice given 7,12-dimethylbenz[*a*]anthracene, or in rats given 1,2-dimethylhydrazine, danthron produced negative results (IARC 1990). When administered in the diet without other chemicals, danthron caused a large increase in the incidence of a preneoplastic lesion, adenomatous polyploid hyperplasia of the cecum and colon in male mice. Danthron has been found to induce genetic damage in a limited number of prokaryotic, lower eukaryotic, and mammalian *in vitro* test systems.

No data were available that would suggest that the mechanisms thought to account for tumor induction by danthron in experimental animals would not also operate in humans.

PROPERTIES

Danthron occurs as an orange crystalline powder, orange crystals or plates, or as red to reddish-yellow needles or leaves. It begins to sublime at its boiling point of approximately 75°C, and has a melting point of 193 to 196°C. Danthron is very soluble in aqueous alkali hydroxides, soluble in acetone, chloroform, diethyl ether, and ethanol, and practically insoluble in water (NTP 2001, HSDB 2001).

USE

Danthron has been widely used since the beginning of this century as a laxative (IARC 1990). In 1987, the FDA ordered its withdrawal from the market for its use as a laxative (FDA 1993), and U.S. manufacturers voluntarily withdrew production of all human drug products containing the compound (IARC 1990). It is currently used as an antioxidant in synthetic lubricants, in the synthesis of experimental antitumor agents, and as a fungicide for control of powdery mildew (HSDB 2001). It is also used, to a lesser extent, as an intermediate in the manufacture of dyes and forms lakes with calcium, barium, and lead (Kirk-Othmer 1980).

PRODUCTION

Danthron is synthesized in Germany, India, Japan, Poland, the United Kingdom, and the United States (IARC 1990). The *Directory of Chemical Producers*, however, listed no current producers for danthron, but it did report that one U.S. company produced an unknown quantity in 1992 (SRI 1992, 1997). The 1998 Chemical Buyers Directory and *Chemcyclopedia 98* did not identify any current domestic suppliers of the chemical (Tilton 1997, Rodnan 1997). In 2001, nine U.S. suppliers of danthron were identified (Chem Sources 2001). The TSCA inventory for U.S. plants and producers listed eight industrial facilities that produced or imported danthron in 1977. Three of the eight were known manufacturers, three were known importers, and it was not known whether the other two were importers or manufacturers. The order of magnitude of the production volume was given for only one known manufacturer (100,000 to 1,000,000 lb/year). One producer or importer handled 1,000 to 10,000 lb/year. Two of the three known producers did not ship danthron out of the plant (i.e., its production and use were site-limited) (TSCAPP 1983 update). No data on imports or exports of danthron were available. In 1987, approximately 40 small manufacturers of danthron-containing pharmaceuticals were directed by FDA to withdraw their products from the market (Diogenes 1996).

EXPOSURE

The primary route of potential human exposure to danthron is oral administration. Shortly before its withdrawal from the market, danthron was available from nine companies in 14 over-the-counter (OTC) products with the following trade names: Danivac, Doctate-P, Dorbane, Dorbantyl, Dorbantyl Forte, Doxan, Doxidan, Magcyl, Modane, Tonelax, West-Ward Dioctyl with Danthron, and Valax. Tablet formulations contained 37.5, 50, or 75 mg danthron; capsule formulations, 25, 40, or 50 mg; and a liquid formulation, 37.5 mg/5 mL (5 mL = 1 teaspoonful) (CTCP 1985). Potential exposure of health professionals may occur during the preparation and administration of the compound. Potential occupational exposure may also occur for workers involved in the formulation and packaging of the pharmaceutical. The National Occupational Exposure Survey (1981-1983) indicated that 357 workers, including 187 women, were potentially exposed to danthron (NIOSH 1990). This estimate was derived from observations of the use of the actual compound (47% of total observations) and trade name products (54%). The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 3,120 workers were potentially exposed to danthron in the workplace (NIOSH 1976). Danthron occurs naturally in several species of plants and insects. It has been isolated from dried leaves and stems of *Xyris semifuscata* harvested in Madagascar and is the basic structure of the aglycones of naturally occurring laxative glycosides. The compound has been identified in larvae of the elm-leaf beetle, *Pyrrhalta luteola*. The presence of a mixture of anthraquinones and anthrones was suggested to be a means of protection from predators, and these compounds appear to be biosynthesized by the insect (IARC 1990).

REGULATIONS

In 1987, the FDA published a letter and a press release to recall all danthron-containing drug products by approximately 40 small manufacturers. Larger manufacturers had voluntarily halted production before the advisement.

OSHA regulates the compound under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 55.

REFERENCES

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

CTCP. Clinical Toxicology of Commercial Products. Online database available from the Chemical Information System. Last update in 1985.

Diogenes 1996. DIALOG file 158. Contains FDA regulatory information from news stories and unpublished documents including listings of approved products, documentation of approval process for specific products, recall and regulatory action documentation, 1996.

FDA. U.S. Food and Drug Administration. 58 FR 46589. Proposed Rule 21 CFR Part 334. Laxative Drug Products for Over-the-Counter Human Use; Proposed Amendment to the Tentative Final Monograph. Fed. Regist. Vol. 58, No. 169, pp. 46589 ff, September 02, 1993.

HSDB. Hazardous Substances Data Bank. Online database produced by the National Library of Medicine. Danthron. Profile last updated August 9, 2001. Last review date, not provided.

IARC. International Agency for Research on Cancer. IARC Monographs on the Carcinogenic Risk of Chemicals to Humans. Pharmaceutical Drugs. Vol. 50. 415 pp. Lyon, France, IARC, 1990.

Kirk-Othmer Encyclopedia of Chemical Technology, Third Edition. Vol. 11. New York, NY: John Wiley and Sons, 1980.

NIOSH. National Institute for Occupational Safety and Health. National Occupational Hazard Survey (1972-74). Cincinnati, OH: Department of Health, Education, and Welfare, 1976.

NIOSH. National Institute for Occupational Safety and Health. National Occupational Exposure Survey (1981-83). Unpublished provisional data as of 7/1/90. Cincinnati, OH: Department of Health and Human Services, 1990.

NTP. National Toxicology Program. NTP Chemical Repository. Danthron. Last updated August 13, 2001. (http://ntp-server.niehs.nih.gov and search 117-10-2).

Rodnan, N., Ed. Chemcylopedia '98. The Manual of Commercially Available Chemicals. Washington, DC: American Chemical Society. Vol. 16, 1997, pp. 33-214.

SRI. Directory of Chemical Producers, United States, 1992. Stanford Research Institute, Menlo Park, CA: SRI International, 1992.

SRI. Directory of Chemical Producers, United States, 1997. Stanford Research Institute, Menlo

Park, CA: SRI International, 1997.

Sugie, S., Y. Mori, A. Okumura, N. Yoshimi, K. Okamoto, S. Sato, T. Tanaka, and H. Mori. Promoting and Synergistic Effects of Chrysazin on 1,2-Dimethylhydrazine-Induced Carcinogenesis in Male ICR/CD-1 Mice. Carcinogenesis Vol. 15, No. 6, 1994, pp. 1175-1179.

Tilton, H., Ed. OPD Chemical Buyers Directory 1998. The Green Book. 85th Edition. New York, NY: Schnell Publishing, 1997.

TSCAPP. Toxic Substances Control Act Plant and Producers. Database available on the Chemical Information System, Version 5.0/2.0, September 1983.