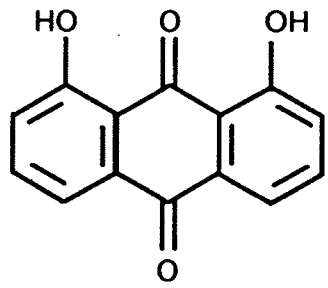
DANTRON (CHRYSAZIN; 1,8-DIHYDROXYANTHRAQUINONE)

1. Chemical and Physical Data

1.1 Synonyms

Chem. Abstr. Services Reg. No.: 117-10-2 (replaces CAS Reg. No. 32073-07-7)
Chem. Abstr. Name: 9,10-Anthracenedione, 1,8-dihydroxy-
Synonyms: Antrapurol; danthron; dianthon; dihydroxyanthraquinone; 1,8-dihydroxy-9,10-anthraquinone; dioxyanthrachinonum; 1,8-dioxyanthraquinone

1.2 Structural and molecular formulae and molecular weight



$C_{14}H_8O_4$ Mol. wt: 240.23

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Red or reddish-yellow needles or leaves (from ethanol) (Weast, 1985); orange crystalline powder (Anon., 1981)

(*b*) *Melting-point*: 193°C (Weast, 1985); 195°C (Anon., 1981)

(*c*) *Spectroscopy data*[1]: Infrared (Coblenz [5147]; Aldrich, prism [900D]; Aldrich, prism-FT [87D]), ultraviolet (Sadtler [4318]), proton nuclear

[1]Bracketed numbers are spectrum numbers in the relevant compilation.

magnetic resonance (Aldrich [91B]) and mass (Aldermaston [195]) spectral data have been reported (Sadtler Research Laboratories, 1980; Pouchert, 1981, 1983, 1985; Weast & Astle, 1985).

(*d*) *Solubility*: Very soluble in aqueous alkali hydroxides; soluble in acetone, chloroform, diethyl ether and ethanol; almost insoluble in water (Enviro Control, 1981; Weast, 1985)

1.4 Technical products and impurities

Trade Names: Altan; Antrapurol; Bancon; Benno; DanSunate D; Danthron; Diaquone; Dionone; Dorban; Dorbane; Duolax; Fructines-Vichy; Istin; Istizin; Julax; Laxanorm; Laxans; Laxanthreen; Laxenta; Laxipur; Laxipurin; Modane; Neokutin S; Pastomin; Prugol; Roydan; Scatron D; Solven; Unilax; Zwitsalax

The following trade names are those of multi-ingredient preparations containing dantron: Agarol Capsules; Coloxyl; Dorbanate; Dorbanex; Dorbantyl; Doss; Doxidan; Normax (Reynolds, 1989).

Dantron is available commercially at a purity of 95-99% (Aldrich Chemical Co., 1988; Lancaster Synthesis Ltd, 1988; Sigma Chemical Co., 1988).

2. Production, Occurrence, Use and Analysis

2.1 Production and occurrence

(*a*) *Production*

Dantron has been prepared by several processes, including the alkaline hydrolysis of 1,8-dinitroanthraquinone, the caustic fusion of 1,8-anthraquinone-disulfonic acid, the diazotization of 1,8-diaminoanthraquinone followed by hydrolysis of the bisdiazo compound, the acid hydrolysis of 1,8-dimethoxyanthraquinone in glacial acetic acid-sulfuric acid, the alkaline hydrolysis of 1,8-anthraquinone-disulfonic acid using calcium oxide, and the reaction of 1,8-dinitroanthraquinone with sodium formate or potassium formate (Michalowicz, 1981).

In 1987, US manufacturers voluntarily withdrew production of all human drug products containing dantron (Anon., 1987).

Dantron is synthesized in the Federal Republic of Germany, India, Japan, Poland, the UK and the USA (Chemical Information Services Ltd, 1989-90).

(*b*) *Natural occurrence*

Dantron has been isolated from dried leaves and stems of *Xyris semifuscata* harvested in Madagascar (Fournier *et al.*, 1975). Dantron is the basic structure of

the aglycones of naturally occurring laxative glycosides, in, e.g., *Cassia* (senna), *Aloe*, *Rheum* and *Rhamnus* (cascara) species (Baars *et al.*, 1976; Reynolds, 1989).

Dantron 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 (Howard *et al.*, 1982).

2.2 Use

Dantron has been widely used since the beginning of this century as a laxative and as an intermediate for dyes (Enviro Control, 1981; Michalowicz, 1981).

2.3 Analysis

Dantron can be determined in pharmaceutical preparations by high-performance liquid chromatography with ultraviolet detection (Wurster & Upadrashta, 1986) and by fluorimetry (Miller & Danielson, 1987). It has been determined in urine and faeces by gas chromatography with flame ionization detection (Baars *et al.*, 1976) and in urine by gas chromatography with mass spectrometry (Kok & Faber, 1981) and high-performance liquid chromatography with fluorimetry (Miller & Danielson, 1987).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

(*a*) *Oral administration*

Mouse: A group of 20 male C3H/HeN mice, eight weeks of age, was fed dantron (commercial grade; no impurity detected on thin-layer chromatography) at 200 mg/kg diet for 540 days, at which time the experiment was terminated. A group of 20 untreated male mice served as controls. Hepatocellular adenomas were found in 9/17 treated and 5/19 control mice. Hepatocellular carcinomas were found in 4/17 treated mice (all also had adenomas), an incidence that was significantly different ($p < 0.05$; Fisher exact test) from that in controls (0/19). Adenomatous [polypoid] hyperplasia, occasionally associated with dysplastic changes, was observed in the caecum of 17/17 treated mice and in the remainder of the colon of 5/17 treated mice, but not in controls (Mori *et al.*, 1986).

Rat: A group of 18 male ACI rats, eight weeks of age, was fed dantron [purity unspecified] at 10 000 mg/kg diet for 16 months. A group of 15 untreated males

served as controls. Twelve treated and 14 untreated rats survived more than one year. Nine tumours of the large intestine were found in 7/12 treated rats (three adenomas and four adenocarcinomas ($p < 0.02$) of the colon and two adenomas of the caecum). In addition, focal epithelial hyperplasia was observed frequently in the mucosa of the colon and caecum of treated rats with and without intestinal tumours. No intestinal tumour or hyperplastic lesion was found in the 14 controls (Mori *et al.*, 1985).

(*b*) *Administration with known carcinogens*

Mouse: In a two-stage carcinogenesis experiment, a group of 20 female ICR/Ha Swiss mice, seven weeks of age, received a single skin application of 7,12-dimethylbenz[*a*]anthracene at 20 μg in 0.1 ml acetone, followed two weeks later by applications three times a week of commercial-grade dantron at 170 μg in 0.1 ml acetone. A control group of 20 female mice received only skin applications of dantron at 170 μg in 0.1 ml acetone three times a week. Median survival time of animals in both groups was greater than 490 days, when the experiment was terminated. No skin tumour was found in either group (Segal *et al.*, 1971).

Rat: In a two-stage carcinogenicity study, groups of 30 male Sprague-Dawley rats, 50 days of age, received a single subcutaneous injection of 1,2-dimethylhydrazine (DMH) at 150 mg/kg bw. After one week they were fed dantron (purity, > 97%) at 0, 600 or 2400 mg/kg diet; the average daily intakes were approximately 30 and 60 mg/kg bw. After 26 weeks, all animals were killed. Two additional groups of 30 male rats received either no treatment or were given the diet with the higher concentration of dantron alone. There was no significant difference in mean body weight gain between treated and control animals. In the rats treated with DMH plus dantron, the combined incidences of intestinal adenomas and adenocarcinomas were 4/30 in the low-dose and 2/30 in the high-dose group. The incidences of intestinal adenocarcinomas were 0/30 in untreated controls, 0/30 in the group treated with dantron alone and 2/30 in the group treated with DMH alone. The difference in tumour incidence between animals treated with DMH alone and DMH plus dantron was not significant (Sjöberg *et al.*, 1988)

3.2 Other relevant data

(*a*) *Experimental systems*

(i) *Absorption, distribution, excretion and metabolism*

Male Wistar rats were given the sodium salt of dantron intravenously at 4.8, 22 or 58 μmol/kg [1.2, 5.3 or 14 mg/kg] bw or at 120 μmol/kg [28.8 mg/kg] bw by gastric tube. Metabolites identified in the bile and urine following administration by either

route included the monosulfate, β-glucuronide and other unidentified metabolites. Following intravenous administration, about 80% of the dantron conjugates in bile were excreted after 1 h; the dose fractions found after 5 h represented about 20%, 30% and 40% of the low-, intermediate- and high-dose levels, respectively. The corresponding fractions in urine were 16%, 12% and 10%, giving rise to bile:urine excretion ratios of 1.3, 2.7 and 4.0, respectively. Only 30-50% of the dose could be accounted for by conjugates (Sund, 1987). Earlier studies also showed that after oral administration of dantron only 30-40% of the total dose administered could be recovered in faeces and urine, mostly during the first 24 h (Breimer & Baars, 1976).

In vitro, rat jejunum and colon transformed dantron into its monoglucuronide and monosulfate, the monoglucuronide being the major metabolite (Sund & Elvegård, 1988).

(ii) *Toxic effects*

The oral LD_{50} for dantron in male ARS/ICR mice was > 7 g/kg bw. Groups of four male and four female beagle dogs received either a vehicle capsule or a capsule containing dantron at 5 or 15 mg/kg bw daily for one year. No adverse effect was observed. The doses employed were reported to be several-fold higher than the usual clinical dose (Case *et al.*, 1977-78).

Apoptosis together with accumulation of lipofuscin pigment in gut wall was noted in guinea-pigs given dantron orally at 25 mg/kg bw (Walker *et al.*, 1988).

Male rats given dantron at 600 or 2400 mg/kg diet for 26 weeks (Sjöberg *et al.*, 1988) had enlarged lymph nodes in the mesocolon, which were brownish due to pigmentation of the accumulated mononuclear phagocytes. In kidney, pigment deposition was seen in the cortical region.

(iii) *Effects on reproduction and prenatal toxicity*

No data were available to the Working Group.

(iv) *Genetic and related effects*

Dantron was mutagenic to *Salmonella typhimurium* TA1537 in the presence and absence of an exogenous metabolic system (Brown & Brown, 1976; Liberman *et al.*, 1982). It was also mutagenic to TA2637 (Tikkanen *et al.*, 1983), TA102 (Levin *et al.*, 1984) and TA104 (Chesis *et al.*, 1984) in the presence of an exogenous metabolic system. In TA104, the results were not significantly changed by the addition of superoxide dismutase and catalase (Chesis *et al.*, 1984). In *S. typhimurium* TA100, TA1535, TA1538 and TA98, dantron was not mutagenic in the presence or absence of an exogenous metabolic system (Brown & Brown, 1976; Liberman *et al.*, 1982; Tikkanen *et al.*, 1983).

Dantron induced respiration-deficient mutants in yeast (Zetterberg & Swanbeck, 1971).

It induced unscheduled DNA synthesis in hepatocytes from mice (Mori *et al.*, 1984) and rats (Mori *et al.*, 1984; Kawai *et al.*, 1986) but not in another study with rat hepatocytes (Probst *et al.*, 1981). Dantron induced chromosomal aberrations in human peripheral lymphocytes *in vitro* in the absence of an exogenous metabolic system (Carballo *et al.*, 1981). In some studies, dantron inhibited gap-junctional intercellular communication in Chinese hamster V79 cells (Umeda *et al.*, 1980 [The Working Group noted that the way in which the data were presented precluded statistical analysis.]; Trosko *et al.*, 1982 [one dose]), but in other studies no such effect was found in Chinese hamster V79 cells (Kinsella, 1982; Zeilmaker & Yamasaki, 1986) or in human fibroblasts (Si *et al.*, 1988).

(*b*) *Humans*

(i) *Pharmacokinetics*

Following its administration within 24 h of the induction of labour in 12 women, dantron was found in maternal urine, neonatal urine and amniotic fluid. Most of the drug appeared as a glucuronide in both mothers and babies (Blair *et al.*, 1977).

(ii) *Adverse effects*

Liver damage was reported in a woman who had used a laxative containing dantron and dioctyl calcium sulfosuccinate for one year. The symptoms disappeared after discontinuation of the medication but reappeared upon resumption; none of the compounds given alone had any effect on the results of hepatic function tests (Tolman *et al.*, 1976).

A woman developed deep discoloration of the skin following ingestion of large amounts of a laxative containing dantron (Darke & Cooper, 1978). Such staining was also found in other studies, predominantly in elderly subjects, and was localized to the buttocks and thighs, with minor inflammatory symptoms (Bunney & Noble, 1974; Cox & Vickers, 1984). Contact of skin with faeces or urine containing the drug seems to be a prerequisite for discoloration. Inflammation, when present, may result from reduction of the parent compound in the colon to the diol derivative, which irritates both the gut and skin (Puschmann, 1983; Ippen, 1974), while the parent compound does not (Green *et al.*, 1988).

Melanosis coli, a state involving apoptosis and lipofuscin pigment accumulation in macrophages in colonic lamina propria, has been described in persons using anthraquinone laxatives (Bockus *et al.*, 1933; Speare, 1951; Wittoesch *et al.*, 1958; Steer & Colin-Jones, 1975; Badiali *et al.*, 1985; Walker *et al.*, 1988).

3.3 Case reports and epidemiological studies of carcinogenicity to humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Dantron occurs naturally in several species of plants and in insects. It has been produced and widely used since the beginning of the century as a laxative and, to a lesser extent, as an intermediate for dyes. No data on occupational exposure levels were available.

4.2 Experimental carcinogenicity data

Dantron was tested for carcinogenicity by oral administration in single studies in male mice of one strain and in male rats of one strain. In mice, a small increase in the incidence of hepatocellular carcinomas and a large increase in adenomatous polypoid hyperplasia of the colon were observed; there was also an increased combined incidence of adenomas and adenocarcinomas of the colon and caecum. In rats, dantron increased the incidence of adenocarcinomas of the colon.

4.3 Human carcinogenicity data

No data were available to the Working Group.

4.4 Other relevant data

In one study, dantron caused chromosomal aberrations in human lymphocytes *in vitro*. It gave contradictory results with respect to the induction of unscheduled DNA synthesis in rodent cells and was mutagenic to yeast in one study and to *Salmonella typhimurium*. Dantron did not inhibit gap-junctional intercellular communication in human cells, but conflicting results were obtained in Chinese hamster cells. (See Appendix 1.)

4.5 Evaluation[1]

There is *sufficient evidence* for the carcinogenicity of dantron in experimental animals.

No data were available from studies in humans on the carcinogenicity of dantron.

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[1]For definition of the italicized terms, see Preamble, pp. 26–29.

Overall evaluation

Dantron *is possibly carcinogenic to humans (Group 2B).*

5. References

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