9,10-Anthracenedione, 1,8-dihydroxy-: Human health tier II assessment

24 April 2015

CAS Number: 117-10-2

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted

and published separately, using information available at the time, and may be undertaken at different tiers.

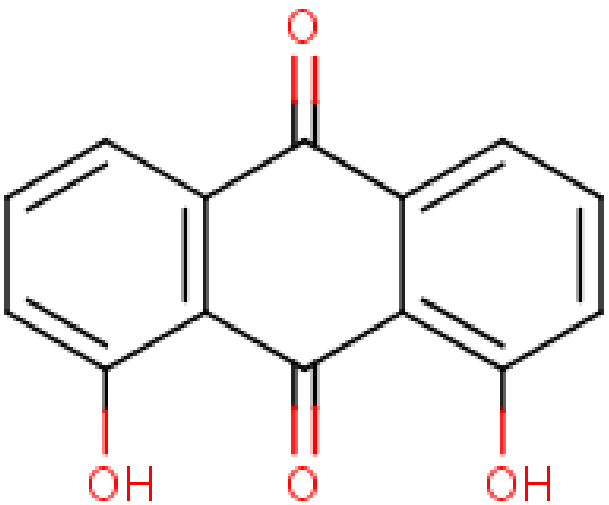
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	1,8-dihydroxy-9,10-anthracenedione 1,8-dihydroxyanthraquinone Chrysazin Danthron Antrapurol
Structural Formula	
Molecular Formula	C14H8O4
Molecular Weight (g/mol)	240.213
Appearance and Odour (where available)	Reddish or orange crystalline powder.
SMILES	c12C(=O)c3c(C(=O)c1c(O)ccc2)c(O)ccc3

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses have been identified through Galleria Chemica;

United States (US) National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments (IARC, 1990; NTP, 1999; NTP, 2014).

The chemical has reported site-limited uses including:

- as an intermediate in manufacturing textile dyes (Mori et al., 1985) such as alizarin and indrathrene dyes;
- in manufacturing pigment lakes (calcium, barium, and lead); and
- as an antioxidant in synthetic lubricants.

Other

The chemical has reported non-industrial uses as a laxative and a fungicide.

The chemical is also naturally occuring and can be found in some plants (e.g. *Xyris semifuscata*) and insects (e.g. elm-leaf beetle) (NTP, 2014).

Restrictions

Australian

This chemical is listed in the *Poisons Standard—the Standard for the uniform scheduling of medicines and poisons* (SUSMP) in Schedule 4 (SUSMP, 2015).

International

No known restrictions have been identified for industrial uses of the chemical.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

The toxicokinetics of the chemical (Danthron) have been investigated in laboratory animals using different exposure routes and also through human observations. The chemical is significantly absorbed in the upper gastrointestinal tract and excreted in the urine and bile as conjugates. The chemical has been demonstrated to transfer across the placenta. Milk transfer of the chemical from lactating mothers to infants has also been reported (IARC, 1990; NTP, 1999; NTP, 2014).

In Wistar rats, Danthron was administered by the following routes: intravenous (i.v.) infusion with doses 1.2 (low dose), 5.3 (intermediate dose) or 14 mg/kg bw (high dose); and gastric intubation of 28.8 mg/kg bw (Sund, 1987; IARC, 1990). The metabolites were identified as monosulfate, β-glucuronide, two diconjugates and several phase I metabolites (IARC, 1990; NTP, 1999). After five hours, fractions of 20 %, 30 %, and 40 % of the low-, intermediate- and high dose were excreted. Smaller fractions of the administered doses were also identified in the urine: 16 % (low dose), 12 % (intermediate dose); and 10 % (high dose). Following gastric intubation, cumulative excretion of the metabolites via urine and bile were 6 % (0–6 hours), 8 % (6–12 hours) and 5 % (12–18 hours). The recovered Danthron conjugates only accounted for 30–50 % of the administered dose (Sund, 1987).

In an oral study in rats, only 30–40 % of the administered dose of Danthron was recovered in the faeces and urine, mostly within 24 hours of exposure (IARC, 1990).

Anthraquinones can undergo aromatic ring hydroxylation in the liver, facilitated by cytochrome P450 enzymes (CYP1A2 and CYP2B1), with subsequent formation of sulfate and glucuronide conjugates (Doi et al., 2005; NICNASa). Although data for hepatic metabolism are limited, a study on a substituted 1,8-dihydroxy-9,10-anthracenedione, (CAS No. 518-82-1; not listed on the AICS), indicated that the chemical could be transformed in the liver. In this study, rat hepatic microsomes transformed the chemical into several hydroxylated metabolites via the enzymatic activity of cytochrome P450s (Masuda et al., 1985).

Consistent with the parent anthraquinone (9,10-anthacenedione; CAS No. 84-65-1) (NICNASa), Danthron is catalysed by NADPH-cytochrome P450 reductase through a one-electron reduction to form a semiquinone free radical, and by NADPH-quinone oxidoreductase (DT-diaphorase) via a two-electron reduction to form a hydroquinone derivative (Zhang et al., 2011). Upon auto-oxidation, the free radical can produce cytotoxic reactive oxygen species (Doi et al., 2005).

Similarly to 9,10-anthacenedione, the chemical could interact directly with DNA via intercalation due to the size and planarity of the ring system (van Gorkom et al., 1999; NICNASa).

In vitro, the chemical was indiscriminately metabolised by the bacteria from all intestinal regions of mice (Moreau et al., 1985). In vitro, metabolism of the chemical in everted sacs of rat jejunum and stripped colon was also reported (IARC, 1990; NTP, 1999).

Acute Toxicity

Oral

Limited data are available. A reported median lethal dose (LD50) of 7000 mg/kg was reported for mice, which indicates that the chemical has low acute toxicity (Case et al., 1978).

Apoptosis of the colonic surface epithelial cells was observed in guinea pigs following a single exposure to 25 mg/kg bw/day (see **Repeated dose toxicity** section for study details).

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

In two separate studies, deep skin discolouration was observed in one woman (first study; age not specified) and in several elderly patients, all of whom had ingested large amounts of laxatives containing Danthron (IARC, 1990). In the elderly patients, this effect was more noticeable in the buttocks and thighs, accompanied by minor inflammation.

Corrosion / Irritation

Skin Irritation

No data are available.

Eye Irritation

No data are available.

Sensitisation

Skin Sensitisation

No data are available for the chemical. Quantitative Structure Activity Relationship (QSAR) modelling using OASIS–TIMES (Optimized Approach based on Structural Indices Set–Tissue MEtabolism Simulator) gave negative results for skin sensitisation. However, both 9,10-anthracenedione and a substituted anthraquinone (1,4,5,8-tetraaminoanthraquinone; CAS No. 2475-45-8) are both considered to be skin sensitisers (NICNASa; NICNASb).

Repeated Dose Toxicity

Oral

Limited data are available.

Results from a subacute and a chronic oral study conducted in outbred male English shorthair guinea pigs showed colonic changes in the treated animals (Walker et al., 1988). In this study, guinea pigs were fed with a diet containing either 2.5 (low dose) or 25 mg/kg (high dose) of the chemical once or daily up to 12 weeks. In the high dose group, 24 hours following a single exposure to the chemical, fine brown pigment granules were observed in the surface epithelial cells of the caecum and coarser brown granules in the lamina propia macrophages. With further treatment, the number and size of macrophages increased (Walker et al., 1988). The progressive pigment accumulation in guinea pigs that were exposed to daily doses of Danthron was reported to result from repeated waves of apoptosis in the surface epithelium. Only minor pigmentation of surface epithelial cells was observed in the low dose group and the intensity of the lamina propia macrophage pigmentation was lower in this group than in the high dose animals.

Dermal

Limited data are available.

Sugie et al., 1994 demonstrated that subcutanenous chronic exposure (42 weeks) to the chemical (0.2 %) in male ICR/CD-1 mice resulted in the thickening of the colon mucosa and submucosa, and caecum. This observation is associated with melanosis coli (colorectal pigmentation). Other changes included mucosal gland hypertrophy associated with infiltration of immune-related cells (also seen in submucosal areas), and mucosal gland fibrosis. Adenomatous hyperplasia, erosion and incidences of crypt abscess were noted in some parts of the colon (Sugie et al., 1994).

Observation in humans

Long-term use of Danthron-containing laxatives has been suggested to cause tissue damage in humans. One woman developed liver damage after one year of taking a laxative containing Danthron and dioctyl calcium sulfosuccinate (IARC, 1990). When the treatment was discontinued, the symptoms also disappeared and reappeared when treatment was resumed. However, neither Danthron nor dioctyl calcium sulfosuccinate alone caused liver damage (IARC, 1990).

Walker et al. (1988) performed colonic biopsies in patients with melanosis coli (colorectal pigmentation) associated with-long term use of laxatives containing the chemical. Compared with controls, significantly increased numbers of apoptotic bodies within the macrophages of the epithelium and superficial lamina propia (similar to that observed in animal studies) was observed.

Genotoxicity

Based on the limited data available, it is not possible to draw a definite conclusion regarding the in vivo genotoxicity of the chemical. Although available data are neither sufficient nor adequately comprehensive for classification, a genotoxic mode of action cannot be ruled out.

Data indicate that oxidative stress could be involved in the genotoxicity of the chemical (Zhang et al., 2011). Interaction with DNA through intercalation could also play a role (Van Gorkom et al., 1999).

In vitro, the chemical gave positive results in *Salmonella typhimurium* point mutation test in strains TA102 with metabolic activation (Zhang et al., 2011). This strain is sensitive for detecting DNA oxidative damage or cross-linking damage. The chemical was also mutagenic in *S. typhimurium* strains TA1537 with and without metabolic activation and TA2637 and TA104 with metabolic activation (IARC; 1990). It was mutagenic in cytokinesis-block micronucleus (CBMN) and comet assays in Balb/c mice 3T3 cells without metabolic activation (Zhang et al., 2011). The chemical also induced DNA damage, chromatin condensation and reactive oxygen species (ROS) production in SNU-1 human gastric cells (Chiang et al., 2011). Danthron induced DNA damage and inhibited expression of DNA repair genes in GM 8401 human brain glioblastoma multiforme cells (Lu et al., 2010).

In earlier in vitro studies, the chemical induced:

- unscheduled DNA synthesis in hepatocytes of ACI rats and C3H/HeN mice (Mori et al., 1984);
- chromosomal aberrations in human peripheral lymphocytes without metabolic activation (IARC, 1990); and

- respiration-deficient mutants in yeast (Brown & Brown, 1976; IARC, 1990).

A substituted 1,8-dihydroxy-9,10-anthracenedione, (Emodin; CAS No. 518-82-1 – not listed on the AICS) induced micronuclei formation in mouse lymphoma L5178Y cells (Mueller et al., 1998).

The chemical did not cause any morphological transformation in mouse C3H/M2 fibroblasts. The chemical did not inhibit gap-junction intercellular communication in vitro in human fibroblasts and in Chinese hamster lung V79 cells; the results were equivocal (NTP, 1999).

Limited data are available on the in vivo genotoxicity of Danthron. In one study, the chemical did not induce micronuclei formation in rodent bone marrow polychromatic erythrocytes or in mouse peripheral blood erythrocytes (no further details provided) (NTP, 1999).

Carcinogenicity

Data from a robust and guideline-compliant study demonstrated that long-term exposure of rats and mice to the chemical induces benign and malignant liver and intestinal-tract tumours. The available data support the recommendation for classification (see **Recommendation** section).

The carcinogenic potential of Danthron has been investigated in long-term feeding studies (16–18 months) in ACI rats (dose: 10000 mg/kg dose) and C3H/HeN mice (dose: 200 mg/kg) (Mori et al., 1985; IARC, 1990). Based on the results, Danthron caused adenomas and adenocarcinomas of the colon, and adenomas of the caecum in rats (IARC, 1990). In mice, hepatocellular adenomas and hepatocellular carcinomas were reported. Epithelial hyperplasia of the colon and caecum was also observed in both animals whether or not tumours were present (IARC, 1990).

The chemical was reported to promote tumour induction in mice co-exposed to 1,2-dimethylhydrazine (DMH). The incidence and multiplicity of colon and liver adenomas was increased (NTP, 2014). In a similar study in rats, no significant difference in tumour incidence between animals treated with DMH alone and DMH plus Danthron was observed. In a two-stage skin painting study (~70 weeks) in female ICR/Ha Swiss mice and rats, Danthron + dimethylbenz(a) anthracene (co-administration) did not induce skin tumours (IARC, 1990; NTP, 1999; NTP, 2014).

The long-term use (or misuse) of Danthron-containing laxatives has been implicated in human colorectal cancer (Siegers et al., 1993). However, there are no available studies showing unequivocally that it causes cancer in humans. Additionally, the available case reports and epidemiological studies produced conflicting results.

In a retrospective study, Siegers et al. reported an increased incidence of pseudomelanosis coli (a measure of chronic laxative abuse) in patients with colonic adenomas. By contrast, other clinical studies showed no higher incidence of cancer in patients with history of laxative abuse (Siegers et al., 1993; van Gokrom et al., 1999).

The death of an 18-year-old woman from leiomyosarcoma of the small intestine has been linked with the use of a Danthron-containing laxative (Dorbanex) for five years and subsequent intermittent lifetime use (Patel et al., 1989). However, the authors noted that this single observation is not sufficient to establish a causal relationship.

The International Agency for Research on Cancer (IARC) has classified the chemical as ‘Possibly carcinogenic to humans’ (Group 2B), based on inadequate evidence for carcinogenicity in humans, but sufficient evidence for carcinogenicity in animal studies. The United States National Toxicology Program's (US NTP) report on carcinogens lists the chemical as 'Reasonably anticipated to be a human carcinogen' (NTP RoC, 2014).

Although the mechanism of action for the carcinogenicity of Danthron is still unclear, the genotoxic mode of action cannot be excluded. Zhang et al. (2011) reported an increase in ROS formation and 8-OHdG levels (oxidative stress marker) in Balb/c mice 3T3 cells following Danthron exposure. These observations were consistent with DNA oxidative damage reported in the parent compound anthraquinone (CAS No. 84-65-1) (NICNASa).

Cell proliferation has been shown to be important for intestinal carcinogenesis caused by another anthraquinone compound. In addition, DNA damage caused by apoptosis has also been shown to correlate with tumour formation in the gut (van Gorkom et al., 1999).

Reproductive and Developmental Toxicity

No data are available.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity). Whilst the mechanism of action for the carcinogenicity of Danthron is still not fully understood, a genotoxic mode of action cannot be ruled out.

Public Risk Characterisation

Based on the available data (refer **Import, manufacture and use** section) the use of the chemical in domestic and cosmetic products is not expected and hence the risk to the public is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, exposure of workers to the chemical might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations can also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term and local health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The *Guidance on the interpretation of workplace exposure standards for airborne contaminants* advises that 'exposure to carcinogens should be eliminated or minimised so far as is reasonably practicable' (Safe Work Australia, 2012).

The data available support an amendment to the hazard classification in the HSIS (Safe Work Australia) (refer to **Recommendation** section.

NICNAS Recommendation

Assessment of the chemical is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)	May cause cancer - Cat. 1B (H350)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for industry

Control measures

Control measures to minimise the risk from dermal and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- health monitoring for any worker who is at risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace*

hazardous chemicals—Code of practice, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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