1(3H)-Isobenzofuranone, 3,3-bis(4-hydroxyphenyl)-: Human health tier II assessment

25 November 2016

CAS Number: 77-09-8

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.

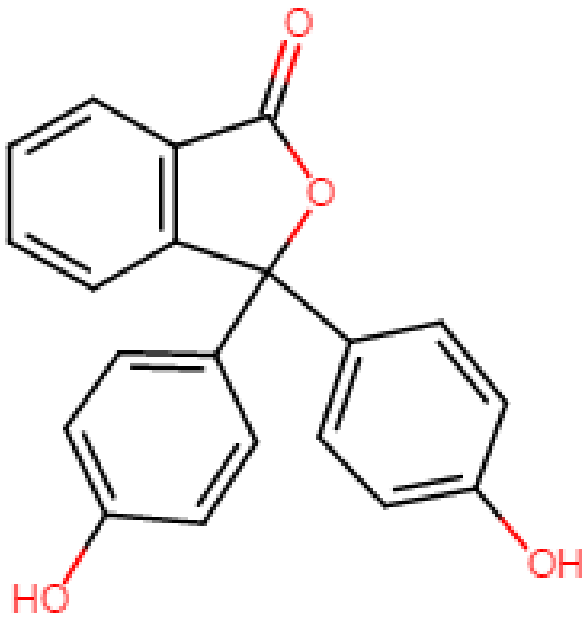
For more detail on this program please visit:www.nicnas.gov.au

Disclaimer

NICNAS has made every effort to assure the quality of information available in this report. However, before relying on it for a specific purpose, users should obtain advice relevant to their particular circumstances. This report has been prepared by NICNAS using a range of sources, including information from databases maintained by third parties, which include data supplied by industry. NICNAS has not verified and cannot guarantee the correctness of all information obtained from those databases. Reproduction or further distribution of this information may be subject to copyright

Acronyms & Abbreviations

Chemical Identity

Synonyms	phenolphthalein 3,3-bis(4-hydroxyphenyl)phthalide 3,3-bis(p-hydroxyphenyl)phthalide
Structural Formula	
Molecular Formula	C20H14O4
Molecular Weight (g/mol)	318.3
Appearance and Odour (where available)	Odourless white or yellow powder
SMILES	c1(C2(c3ccc(O)cc3)c3c(C(=O)O2)cccc3)ccc(O)cc1

Import, Manufacture and Use

Australian

The total volume of phenolphthalein introduced into Australia, reported under previous mandatory or voluntary calls for information, was less than 100 tonnes in 2000 (NICNAS, 2000).

The chemical has reported domestic use, including in car radiator cleaner.

The chemical has reported commercial use, including as a pH indicator in water testing.

The chemical has reported site-limited use, including as a corrosion inhibitor.

The chemical has reported non-industrial use as an agricultural pesticide (APVMA PubCRIS).

International

The following international uses have been identified through: the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US Environmental Protection Agency Aggregated Computer Toxicology Resource (ACToR); the US Environmental Protection Agency Chemical and Product Categories (CPCat) database; and the US National Library of Medicine Hazardous Substances Data Bank (HSDB).

The chemical has reported domestic use, including in washing and cleaning products.

The chemical has reported commercial use, including:

- as a pH indicator in water treatment;
- in surface treatments as a corrosion inhibitor; and
- in adhesives and fasteners for electronics.

The chemical has reported site-limited use, including:

- as an intermediate;
- as a component of pH regulators, flocculants, precipitants and neutralisation agents;
- in the manufacture of pulp, paper and paper products;
- in the manufacture of wood products; and
- in the manufacture of textiles, leather and fur products.

The chemical has reported non-industrial use, including:

- in non-agricultural pesticides and preservatives; and
- human and veterinary pharmaceuticals.

Restrictions

Australian

This chemical is listed in the Poisons Standard—*the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) in Schedule 4 for human therapeutic use (SUSMP, 2016).

Schedule 4 chemicals are described as 'Substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription.' Schedule 4 chemicals are labelled with 'Prescription Only Medicine', or 'Prescription Animal Remedy' (SUSMP, 2016).

The Schedule 4 entry is specific to therapeutic use, and does not impact on the industrial use of the chemical.

International

The chemical is listed on the following (Galleria Chemica):

- Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products;
- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain; and
- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient ‘Hotlist’).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- R45 Carc. Cat 2 (carcinogenicity)
- R68 Mut. Cat 3 (mutagenicity)
- R62 Repr. Cat 3 (reproductive toxicity)

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

The Temporary Emergency Exposure Limits (TEELs) defined by the US Department of Energy for phenolphthalein are reported as:

- TEEL-1 = 0.58 mg/m^3;
- TEEL-2 = 6.3 mg/m^3; and
- TEEL-3 = 200 mg/m^3.

Health Hazard Information

The chemical phenolphthalein is a synthetic bisphenolic compound that has been used for therapeutic purposes as a laxative (IARC, 2000). The human effects, such as gastrointestinal disturbances and effects related to electrolyte imbalances, are well documented (IARC, 2000). It is used in many industrial processes and laboratories (including teaching or instructional laboratories) as a visual indicator in acid-base titrations.

Toxicokinetics

Absorption

The chemical can be absorbed via the oral, dermal and inhalation routes (NTP RoC, 2014). The absorption of the chemical in humans has been estimated as 15 % of an oral dose. In mice, 56 % of an oral dose was recovered in the urine within 48 hours of administration, while 38 % was recovered from the faeces. Absorption following oral administration primarily occurs in the small intestine (IARC, 2000).

Distribution

Phenolphthalein has been shown to be widely and evenly distributed throughout all tissues in the body in studies carried out with radiolabelled chemical in mice and dogs (NTP, 1996). At 30–60 minutes after dosing in mice, the most radioactivity was observed in the liver, gall bladder and small intestine, with higher levels of radioactivity observed in the large intestine over the next six hours.

Metabolism

Following absorption in the small intestine, the chemical undergoes extensive first-pass metabolism in the liver and intestinal epithelium to form phenolphthalein glucuronide, which is eliminated in the bile. As it passes through the small intestine it is partially deconjugated to regenerate phenolphthalein which can be reabsorbed in a cyclic process that results in the retention of a small amount of the chemical (IARC, 2000). The chemical and its glucuronide conjugate have both been shown to enhance the production of reactive oxygen species (ROS) and cause oxidative damage in vitro (Sipe et al., 1997; NTP RoC, 2014); however, free radical species of phenolphthalein have not yet been isolated in vivo.

Excretion

The chemical is excreted primarily in the urine as its phenolic-hydroxyglucuronide conjugate or sulfate conjugates (IARC, 2000). Some conjugated material is also excreted in the faeces via the bile, and the resulting enterohepatic recirculation probably contributes to prolongation of the laxative effect. This hypothesis is supported by the observation that phenolphthalein is ineffective as a laxative in patients suffering from obstructive jaundice and in experimental animals with ligated common bile ducts. Small doses in humans are excreted entirely as the glucuronide conjugate, while larger doses result in excretion of both free and conjugated chemical. Use of the chemical by women during breast feeding may cause diarrhoea in infants, suggesting that phenolphthalein can also be excreted in breast milk (IARC, 2000).

Acute Toxicity

Oral

Limited data are available. The chemical is expected to have low acute toxicity based on results from animal tests following oral exposure, as well as a lack of lethal effects observed in repeat dose studies in rodents when tested at high daily doses (>2000 mg/kg bodyweight (bw)/day) (see **Repeat Dose Toxicity - Oral** section). The median lethal dose (LD50) in rats is >1000 mg/kg bw. No study details were provided (RTECS).

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

Acute overdose of laxatives containing phenolphthalein is reported to result in gastrointestinal disturbances such as abdominal pain, diarrhoea and vomiting. Other observed renal, hepatic and neurological effects are thought to be due to resulting electrolyte imbalances (NTP, 1996).

Fatal phenolphthalein poisoning of children has been reported (doses unknown). Signs of toxicity, including pulmonary and cerebral oedema, multiple organ toxicity and encephalitis were attributed to hypersensitivity reactions (NTP, 1996).

Corrosion / Irritation

Skin Irritation

Based on the available in vitro data, the chemical is irritating to skin. The effects are not sufficient to warrant hazard classification.

In a skin corrosion study carried out similarly to the Organisation of Economic Co-operation and Development (OECD) Test Guideline (TG) 431 (in vitro skin corrosion: reconstructed human epidermis (RHE) test method), the chemical (16 mg—concentration not provided) was applied topically to a three-dimensional RHE skin model for 42 minutes. A test chemical is considered to be an irritant if the cell viability after exposure and post-treatment incubation is ≤50 %. The chemical was concluded to have the potential for skin irritation, as the cell viability was calculated to be 36 % following 42 minutes exposure compared to positive and negative controls over the same duration (REACH).

In another skin corrosion study carried out according to OECD TG 431, the chemical (20 mg) was applied to a RHE model for time periods of three minutes and one hour. The mean relative tissue viability after one hour treatment with the chemical did not significantly decrease compared to controls (82.5 %). Under these experimental conditions, the chemical was not reported to be corrosive (REACH).

Eye Irritation

Based on the available in vitro data, the chemical is slightly irritating to eyes. The effects are not sufficient to warrant hazard classification.

In an eye irritation study conducted according to OECD TG 437 (bovine corneal opacity and permeability test method for identifying ocular corrosives and severe irritants), bovine eyes were isolated from donor cattle (nine months of age and older), and treated with phenolphthalein (dose not specified) in 0.9 % (w/v) sodium chloride in deionised water for four hours. The chemical caused a slight increase in corneal opacity but permeability effects were not observed. The mean in vitro eye irritation score was 11.21 (the threshold for corrosivity or severe irritancy is ≥55.1). Based on this study, the chemical is slightly irritating to eyes (REACH).

Sensitisation

Skin Sensitisation

The chemical was found not to induce dermal sensitisation in animal studies.

In a study conducted according to OECD TG 429 (skin sensitisation: local lymph node assay), the chemical was reported to be not sensitising in an in vivo mouse local lymph node assay. Mice were administered the chemical at 5, 10 or 25 % (w/v) in dimethyl formamide. Stimulation indices of 1.06, 1.55 and 1.24 were reported respectively. An EC3 value (concentration required to provoke a three-fold increase in lymph node cell proliferation compared with controls) could not be determined, and it was concluded that the chemical is non-sensitising (REACH).

Observation in humans

Allergic skin responses following oral administration of phenolphthalein have been reported in humans using phenolphthalein-containing laxatives (IARC, 2000). They have been described as cutaneous inflammatory reactions or fixed drug eruptions, such as erythematous macules that may progress to vesicles or bullae, or both. These lesions typically reoccur with increasing severity in the same location, with hyperpigmentation that increases in intensity with subsequent exposures to the chemical (NTP, 1996).

Repeated Dose Toxicity

Oral

Based on the available animal studies, the chemical is not considered to cause serious damage to health from repeated oral exposure, apart from those considered in the hazard classification of the chemical for carcinogenicity and reproductive and developmental toxicity (see relevant sections). Serious effects have been associated with long-term, high-level oral exposure in humans (see **Observation in humans** section).

Data from chronic studies in rats indicate that the chemical may cause or increase the severity of chronic nephropathy. However, it is unclear whether this is treatment-related, as the condition is common in ageing rats (particularly males). In addition, these and any other observed renal effects occurred at high doses (>500 mg/kg bw/day), and did not increase in a dose-related manner (NTP, 1996). In the absence of further information, hazard classification of the chemical for renal effects is not warranted.

In two 13-week studies, rats and mice were exposed to the chemical at doses equivalent to 500, 1000, 2000, 4100 or 9000 mg/kg bw/day (male) and 600, 1200, 2400, 5000 or 10500 mg/kg bw/day (females). No chemical-related clinical signs of toxicity were observed in either species (NTP, 1996).

Administration of phenolphthalein to F344/N rats (50 animals/sex/dose) at 0, 500, 1000 or 2000 mg/kg bw/day (males) or 0, 500, 1000 or 2500 mg/kg bw/day (females) in feed for two years resulted in an increased incidence of focal hyperplasia of the adrenal medulla in males. Increased incidences or severity of nephropathy and atypical hyperplasia of the thymus were observed in both males and females. Degeneration of the testicular germinal epithelium in males, and ovarian hyperplasia in females was also observed. Decreased incidences of hepatocellular neoplasms and nonneoplastic lesions in male and female rats were also reported (NTP, 1996).

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

Historically, the use of phenolphthalein as an over-the-counter laxative was generally regarded as nontoxic and safe for consumption; however, due to concerns regarding potential carcinogenic, mutagenic and reproductive effects, the chemical has largely been phased out for therapeutic use (Coogan et al., 2000).

Oral doses of the chemical (30–270 mg/day for adults and children over 12 years) have been known to cause abdominal discomfort, diarrhoea, nausea, low blood pressure, faintness and red urine and faeces (NTP, 1996). Additional side effects have been associated with long-term abuse of phenolphthalein-containing laxatives, including electrolyte imbalances (hypokalaemia, hypocalcaemia and/or metabolic acidosis or alkalosis), dehydration, malabsorption, protein-losing gastroenteropathy, steatorrhea, anorexia, weight loss, polydipsia, polyuria, cardiac arrhythmias, muscle weakness, prostration and histopathologic abnormalities (NTP, 1996). These are likely secondary to the laxative effects of the chemical.

Repeated administration of phenolphthalein-containing laxatives to children has led to serious illnesses and multiple hospitalisations (NTP, 1996).

Genotoxicity

The chemical is classified as hazardous—Category 3 mutagenic substance—with the risk phrase 'Possible risk of irreversible effects' (Xn; R68) in the HSIS (Safe Work Australia). The positive results reported in several in vitro and in vivo tests for clastogenicity in mammalian cells support this

classification.

In bacterial reverse mutation assays conducted according to OECD TG 471 (bacterial reverse mutation test), the chemical was tested for point mutations in *Salmonella typhimurium* strains TA 98, TA 100, TA 1538, TA 1535 and TA 1537 at test concentrations of 0, 32, 100, 320 and 1000 µg/plate. No increase in the number of revertant colonies was observed at any concentration tested, with or without metabolic activation (NTP, 1996; REACH).

No induction of sister chromatid exchanges was observed in cultured Chinese hamster ovary (CHO) cells treated with the chemical at concentrations of 0.5, 1.7, 5, 17 and 50 µg/mL per plate, with or without metabolic activation (NTP, 1996).

Significant increases in chromosomal aberrations (mostly chromosomal breaks) were observed after treatment of cultured CHO cells with the chemical at concentrations of 0, 11, 23 and 50 µg/mL per plate, in the presence of metabolic activation. No increase in chromosomal aberrations was observed in the absence of metabolic activation (NTP, 1996).

In a 13-week in vivo peripheral blood micronucleus test, blood samples were taken from male and female mice that had been administered the chemical in feed at doses of 500, 1000, 2000, 4100 or 9000 mg/kg bw/day (male) and 600, 1200, 2400, 5000 or 10500 mg/kg bw/day (females). An increase in the frequency of micronucleated polychromatic erythrocytes (PCEs) was observed at the two highest doses tested, while increases in normochromatic erythrocytes (NCEs) were observed at all doses tested (NTP, 1996). A change in the ratio of PCEs to NCEs indicated that the chemical reached the bone marrow.

Carcinogenicity

The chemical is classified as hazardous—Category 2 carcinogenic substance—with the risk phrase ‘May cause cancer’ (T; R45) in the HSIS (Safe Work Australia). The available data from animal studies support this classification. The mechanism of action is currently unknown; however, possible initiators of tumourigenesis include the mutagenic potential of the chemical, its ability to form reactive oxygen species (ROS), and its demonstrated oestrogenic activity (NTP, 1996; NTP RoC, 2014). The observed effects occur at high doses.

In a two year study, dietary administration of the chemical to F344/N rats (50 animals/sex/dose) at doses equivalent to 0, 500, 1000 or 2000 mg/kg bw/day (males) or 0, 500, 1000 or 2500 mg/kg bw/day (females), resulted in increased incidences of benign pheochromocytomas of the adrenal medulla in males and females, increased renal tubule adenomas in males, as well as an increased incidence of other adenomas and carcinomas in males (NTP, 1996).

The chemical was administered daily in feed to B6C3F1 mice (50 animals/sex/dose) at doses equivalent to 0, 300, 600 or 1200 mg/kg bw/day (males), or 0, 400, 800 or 1500 mg/kg bw/day (females) for two years. The incidence of histiocytic sacrcoma (principally in the liver but also at other sites) was significantly greater in males and females at the two highest doses compared with controls. The incidence of malignant lymphoma (all types) was significantly greater in female mice at all doses compared with controls, but not in males. The incidence of lymphoma of thymic origin was significantly increased in all groups of exposed females, and in males dosed at 600 mg/kg bw/day. Increased incidences of benign ovarian sex-cord stromal tumours in female mice were also observed (NTP, 1996).

Heterozygous p53-deficient (±) female mice (20 animals/dose) were administered the chemical at doses equivalent to 0, 43, 84, 174, 689 or 2375 mg/kg bw/day in feed for 26 weeks. The incidence of malignant lymphoma of the thymus was significantly increased in mice administered the two highest doses (17/20 and 14/20 at 689 and 2375 mg/kg bw/day, respectively) compared with controls (0/20). Atypical thymic hyperplasia, observed in 3/20, 3/20 and 5/20 animals at doses of 174, 689 and 2375 mg/kg bw/day, respectively, was considered to represent proliferative change preceding lymphoma (Dunnick et al., 1997).

In a 27-week dietary study, there was no evidence of carcinogenic activity in male or female haploinsufficient $p16^{Ink4a}/p19^{Arf}$ mice (genetically-modified to be predisposed to carcinogen-mediated tumourigenesis) exposed to 0, 200, 375, 750, 3000 or 12000 ppm phenolphthalein in feed (equivalent to 0, 35, 65, 135, 540 and 2170 mg/kg bw/day in males, and 0, 50, 90, 170, 680 and 2770 mg/kg bw/day in females). However, there was some uncertainty regarding whether the study possessed sufficient sensitivity to detect carcinogenic activity during the short duration of the experiments, and whether higher doses would have been more appropriate (NTP, 2007).

Observation in humans:

A study on 1408 subjects with colorectal cancer in Melbourne demonstrated that there was no statistically significant increase in risk for colorectal cancer in phenolphthalein-containing laxative users compared with controls. In another study following 11888 residents of a retirement community in California for 4.5 years, the association between laxative use and risk of colorectal cancer was not significant. Information on other cancer sites was not reported (IARC, 2000; NTP, 1996).

Analysis of data collected on patients with cancer from multiple hospitals in the US suggested that the routine use of phenolphthalein-containing laxatives did not increase the risk of cancer types implicated in animal studies (such as ovarian cancer, kidney cancer, leukaemias and lymphomas). However, it was concluded that the data did not account for the effects of heavy use or abuse of phenolphthalein-containing laxatives (Coogan et al., 2000).

The International Agency for Research on Cancer (IARC) has classified the chemical as a Group 2B carcinogen: "Possibly carcinogenic to humans" (IARC, 2000), while the US National Toxicology Program (NTP) has classified the chemical as "Reasonably anticipated to be a human carcinogen" (NTP RoC, 2014).

Reproductive and Developmental Toxicity

The chemical is classified as hazardous—Category 3 substance toxic to reproduction—with the risk phrase ‘Possible risk of impaired fertility’ (Xn; R62) in the HSIS (Safe Work Australia). The available data from animal studies support this classification.

The mechanism for reproductive toxicity is currently unknown; however, it has been demonstrated that phenolphthalein acts as a weak oestrogen agonist or antagonist through interaction with the oestrogen receptor in vitro (Ravdin et al., 1987; NTP, 1996; IARC, 2000).

In 13-week studies carried out in F344/N rats and B6C3F1 mice (10 animals/dose/sex), doses of 0, 500, 1000, 2000, 4100 or 9000 mg/kg bw/day (males) and 0, 600, 1200, 2400, 5000 or 10500 mg/kg bw/day (females), were administered in feed (NTP, 1996). No reproductive effects were observed in male rats or female rats and female mice. Effects seen on the male mouse reproductive system included lower epididymal weights and sperm density, and an increased incidence of abnormal sperm was observed in male mice at doses of 2000, 4100 and 9000 mg/kg bw/day. There were also abnormal distributions of germ cells in some of the seminiferous tubules examined.

Significant reproductive and developmental effects were also observed in a continuous breeding study carried out in Swiss (CD-1) mice (NTP, 1996). Animals (20/dose/sex) were given 1000, 7000 or 30000 ppm (equivalent to approximately 150, 1056 and 4530 mg/kg bw/day) in feed per day for a 98-day cohabitation period. Lower fertility was observed in the two highest dose groups, with 24 % and 50 % fewer number of litters in the 7000 and 30000 ppm groups compared with controls, respectively. The number of live pups in each litter was also less (58 % and 59 %) in these groups. There was also postnatal toxicity in the F1 generation, as indicated by a lower survival rate (30–70 % compared to controls), with all deaths occurring during the first four days of life (NTP, 1996).

Other Health Effects

Endocrine Disruption

Based on the available animal data and in vitro human cell studies, the chemical is suspected of contributing to endocrine activity. These effects have been considered in the classification of the chemical for carcinogenicity and reproductive and developmental toxicity (see relevant sections). No additional hazard classification is warranted.

Phenolphthalein has a similar chemical structure to triphenylethylenes, a class of compounds that possess oestrogenic activity. Phenolphthalein (but not its glucuronide conjugate) can bind to the oestrogen receptor, and was a competitive antagonist to oestradiol. Growth stimulation of human MCF-7 breast cancer cells in vitro by both phenolphthalein and oestradiol was blocked by the selective oestrogen receptor modulator, 4-hydroxytamoxifen (Ravdin et al., 1987; NTP, 1996). The chemical has also been shown to bind to human sex hormone-binding globulin, a plasma protein that binds and transports hormones such as oestrogen and androgen into target tissues and cells (Hong et al., 2015).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects such as carcinogenicity, mutagenicity and reproductive and developmental toxicity. These effects occur at high doses.

Public Risk Characterisation

The chemical is currently listed on Schedule 4 of the SUSMP for human therapeutic use as a prescription-only medicine.

Given the uses identified for the chemical, it is unlikely that the public will be significantly exposed. Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, oral, dermal, ocular and inhalation exposure may 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 could 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. Oral exposure is also possible but can be prevented by good hygiene practices.

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

Guidance on the *Interpretation of workplace exposure standards for airborne contaminants* advises that exposure to carcinogens should be eliminated or minimised as far as reasonably practicable (SWA, 2013).

Personal protective equipment should not be solely 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.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

The controls expected to be in place due to the carcinogenicity classification are expected to be sufficient to protect workers from any potential developmental and non-cancer systemic effects.

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]
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)*	Suspected of causing genetic defects - Cat. 2 (H341)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)*	May cause cancer - Cat. 1B (H350)
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)*	Suspected of damaging fertility - Cat. 2 (H361f)

[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 consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal, ocular 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 that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- 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;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- 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.

References

Approved criteria for classifying hazardous substances [NOHSC:1008(2004)]. Third edition [NOHSC:1008 (2004)]. Accessed at http://www.safeworkaustralia.gov.au/sites/swa/about/publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf

Australian Pesticides and Veterinary Medicines Authority (APVMA) Public Chemical Registration Information System (PubCRIS) database. Accessed September 2016 at https://portal.apvma.gov.au/pubcris.

Coogan PF, Rosenberg L, Palmer JR, Strom BL, Zauber AG, Stolley PD and Shapiro S (2000). Phenolphthalein laxatives and risk of cancer. Journal of the National Cancer Institute, 92(23): 1943–1944.

Dunnick JK, Hardisty JF, Herbert RA, Seely JC, Furedi-Machacek EM, Foley JF, Lacks GD, Stasiewicz S and French JE (1997). Phenolphthalein induces thymic lymphomas accompanied by loss of the p53 wild type allele in heterozygous p53-deficient (±) mice. Toxicologic Pathology, 25(6): 533–540.

European Commission Cosmetic Ingredients and Substances (CosIng) database. Accessed September 2016 at http://ec.europa.eu/growth/tools-databases/cosing/

Galleria Chemica. Accessed July 2016 at http://jr.chemwatch.net/galleria/

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

Hong H, Branham WS, Ng HW, Moland CL, Dial SL, Fang H, Perkins R, Sheehan D and Tong W (2015). Human sex hormone-binding globulin binding affinities of 125 structurally diverse chemicals and comparison with their binding to androgen receptor, estrogen receptor and alpha-fetoprotein. Toxicological Sciences, 143(2): 333–348.

International Agency for Research on Cancer (IARC) (2000). Some antiviral and antineoplastic drugs, and other pharmaceutical agents: Phenolphthalein. IARC Monographs Volume 76. Accessed September 2016 at http://monographs.iarc.fr/ENG/Monographs/vol76/mono76.pdf.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) Chemical Gazette. March 2000. Table 18.1 Summary of information provided on chemicals nominated for inclusion on the NICNAS Candidate List for Priority Existing Chemicals, Chemical Gazette, No. C3, 7 March, p93. Australian Government.

National Toxicology Program (NTP) 1996. Toxicology and carcinogenesis studies of phenolphthalein (CAS No. 77-09-8) in F344/N Rats and B6C3F1 Mice (Feed Studies). Accessed September 2016 at https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr465.pdf.

National Toxicology Program (NTP) 2007. Toxicology and carcinogenesis study of phenolphthalein (CAS No. 77-09-8) in genetically modified haploinsufficient p16Ink4a/p19Arf mice (Feed Study). Accessed September 2016 at https://ntp.niehs.nih.gov/ntp/htdocs/gmm_rpts/gmm12.pdf.

National Toxicology Program (NTP) Report on Carcinogens (RoC) (2014). Thirteenth Edition. Phenolphthalein (CAS No. 77-09-8). Accessed September 2016 at https://ntp.niehs.nih.gov/ntp/roc/content/profiles/phenolphthalein.pdf.

Ravdin RM, van Beurden M and Jordan VC (1987). Estrogenic effects of phenolphthalein on human breast cancer cells in vitro. Breast Cancer Research and Treatment, 9(2): 151–154.

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier. Phenolphthalein (77-09-8). Accessed September 2016 at https://echa.europa.eu/registration-dossier/-/registered-dossier/2203/7/5/2.

Registry of Toxic Effects of Chemical Substances (RTECS). Phenolphthalein (CAS No. 77-09-8). Accessed September 2016 at http://ccinfoweb.ccohs.ca/rtecs/search.html

Safe Work Australia (SWA) (2013). Guidance on the interpretation of workplace exposure standards for airborne contaminants. Accessed September 2016 at http://www.safeworkaustralia.gov.au/sites/swa/about/publications/pages/workplace-exposure-standards-airborne-contaminants.

Safe Work Australia. Hazardous Substances Information System (HSIS). Accessed September 2016 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance

Sipe HJ, Corbett Jt and Mason RP (1997). In vitro free radical metabolism of phenolphthalein by peroxidases. Drug Metabolism and Disposition, 25(4): 468–480.

Substances in Preparations in Nordic Countries (SPIN). Accessed September 2016 at http://195.215.202.233/DotNetNuke/default.aspx.

The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) 2016. Accessed September 2016 at https://www.comlaw.gov.au/Details/F2016L00036.

The US Environmental Protection Agency (EPA) Agency Aggregated Computer Toxicology Resource (ACToR), CAS No. 77-09-8. Accessed September 2016 at http://actor.epa.gov/actor/faces/ACToRHome.jsp

United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary. Accessed September 2016 at http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp

United States Environmental Protection Agency (US EPA) Chemical and Product Categories (CPCat) database. Accessed September 2016 at https://actor.epa.gov/cpcat/faces/home.xhtml.

US National Library of Medicine Hazardous Substances Data Bank (HSDB). Accessed September 2016 at http://toxnet.nlm.nih.gov.

Last update 25 November 2016

Share this page