1,3-Benzenediol, 4-hexyl-: Human health tier II assessment

10 March 2017

CAS Number: 136-77-6

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.

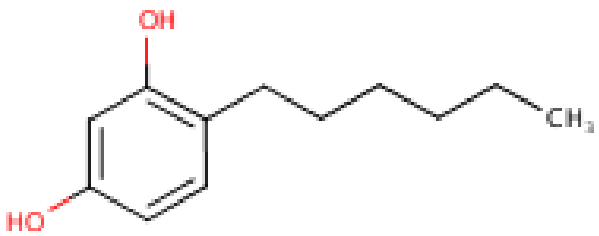
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	hexylresorcinol 1,3-dihydroxy-4-hexylbenzene 4-hexylresorcinol 4-(1-hexyl)resorcinol Antascarin
Structural Formula	
Molecular Formula	C12H18O2
Molecular Weight (g/mol)	194.2
Appearance and Odour (where available)	Pale yellow/peach coloured liquid that solidifies at room temperature. Pungent faintly fatty odour
SMILES	c1(CCCCCC)c(O)cc(O)cc1

Import, Manufacture and Use

Australian

The following non-industrial uses have been identified in Australia:

- used in food as an antioxidant to prevent melanosis in shrimps and related crustacean.

International

The following international uses have been identified through 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's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the European Food Safety Authority Scientific Opinion on 4-hexylresorcinol (EFSA, 2014); World Health Organisation (WHO) Joint Expert Committee on Food Additives (JECFA, 1998) report; and National Toxicology Program (NTP, 1988) Report.

The chemical has reported cosmetic use as an antimicrobial, antioxidant, cosmetic biocidal and oral health care agent.

The chemical has reported non-industrial uses, including as:

- an antioxidant in the processing of seafood (shrimps and related crustaceans) to prevent melanosis;
- an anthelmintic (nematodes); and
- a topical antiseptic agent.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

Oral administration of the chemical as single dose of 1000 mg in male dogs (n=6) resulted in detection of around 29 % of the dose in urine and 67 % in faeces, with 96 % of the total administrated dose being recovered. When administered as crystals in gelatine capsules (3000 mg) in male dogs (n=4), 17 % of the dose was excreted in urine and 73 % in faeces. Excretion was rapid, mainly within the first 6-12 hours for the low dose and 24-36 hours for the high dose (EFSA, 2014; JECFA, 1998; NTP, 1988; HSDB).

The chemical was recovered in the urine (approximately 18 %) in the first 12 hours in two men after administration of 1000 mg of the chemical. Around 64 % of the dose was excreted in the faeces (EFSA, 2014; JECFA, 1998; NTP, 1988; HSDB).

Acute Toxicity

Oral

The chemical has moderate acute toxicity based on results from animal tests following oral exposure. The effects are sufficient to warrant hazard classification (see **Recommendation** section).

The median lethal dose (LD50) in rats is 750 mg/kg bw and 430 mg/kg in guinea pigs (EFSA, 2014; JECFA, 1998; SCF, 2003; HSDB). Observed sub-lethal effects included congestion and necrosis of the gastrointestinal mucosa, occasional congestion of liver, heart and kidneys with focal necrosis and hyaline degeneration of renal tubular epithelium (SCF, 2003).

In an acute oral toxicity study in cats, dosing with the chemical in alcohol or olive oil at doses up to 60 mg/kg bw/day had no effects, although all animals died at 260 mg/kg bw/day. A LD50 of <260 mg/kg bw was reported. No further details were provided (EFSA, 2014; JECFA, 1998; NTP, 1988; SCF, 2003; HSDB).

Dermal

No data are available for the chemical.

Inhalation

No data are available for the chemical.

Corrosion / Irritation

Skin Irritation

No animal data are available for the chemical and Quantitative Structure-Activity Relationship (QSAR) modelling did not provide any evidence for skin irritation for the chemical. Limited data from human case studies have suggested potential skin irritation after topical exposure to high concentrations of the chemical (SCF, 2003; HSDB).

Eye Irritation

Limited data from one study suggested eye irritation potential of the chemical.

In an eye irritation study in rabbits, no signs of irritation were reported with 5 min exposure to the chemical as a 1:10,000 solution. However, diffused oedema of the corneal epithelium was observed with 1-5 min exposure to 1:1,000 solution, which was followed by bluish stromal oedema and hyperaemia of the iris in 2 or 3 hours (HSDB).

Due to the low tested concentrations, the eye irritation potential of the chemical has not been fully characterised.

Observation in humans

Limited data from human case studies suggested there was skin irritation after topical exposure of high concentrations of the chemical (SCF, 2003; HSDB). The data are not sufficient to warrant hazard classification.

Sensitisation

Skin Sensitisation

The chemical was not found to induce delayed contact sensitisation in male Hartley guinea pigs (number of animals not available) after dermal exposure to the chemical either by five daily topical applications or weekly subcutaneous applications of an emulsion in Freund's complete adjuvant (dose or concentration data not available) (EFSA, 2014; JECFA, 1998; SCF, 2003; HSDB).

Observation in humans

Based on the limited available human studies, the chemical may have potential to cause contact dermatitis in humans.

In a patch test, a female worker with contact dermatitis reacted strongly to the 0.1 % of the chemical, 48 and 72 hours after coming in contact with the chemical. No cross-reactivity was reported with resorcinol (EFSA, 2014; SCF, 2003).

In a patch test, 2/8 dermatitis subjects known to be sensitised to resorcinol reacted positively to the chemical, while three patients had slight irritation and three patients gave negative results (EFSA, 2014; JECFA, 1998; SCF, 2003; HSDB).

Repeated Dose Toxicity

Oral

Based on the treatment-related effects reported in repeated dose toxicity studies, the chemical is not considered to cause serious damage to health from repeated oral exposure.

The chemical in corn oil was administered to groups of Fisher 344 (F344/N) rats (n=5/sex/ dose group) at doses of 0, 31.3, 62.5, 125, 250 or 500 mg/kg bw/day, five days per week for 16 days. No mortalities were reported. Hyperexcitability in male rats at 500 mg/kg bw/day and slight reductions of mean body weights in males at 250 mg/kg bw/day (8 %) and 500 mg/kg bw/day (16 %) were reported. A no observable adverse effect level (NOAEL) of 125 mg/kg bw/day was established based on reduced body weight (EFSA, 2014; JECFA, 1998; NTP, 1988; SCF, 2003; HSDB).

In a 13-week oral study, F344/N rats (n=5/sex/ dose group) were administered the chemical in corn oil by gavage, at 0, 63, 125, 250, 500 or 1000 mg/kg bw/day, five days/week. Mortality was reported for all rats at 1000 mg/kg bw/day. Mean body weight reduction was seen at 250 mg/kg bw/day (22 % for males and 8 % for females) and at 500 mg/kg bw/day (38 % in males and 16% in females). Observed clinical signs included nasal discharge, ocular irritation, alopecia, diarrhoea and cachexia. Additional effects reported at necropsy were reduction in the size of seminal vesicles in males at 250 mg/kg bw/day (1/10), at 500 mg/kg bw/day (6/10) and 1000 mg/kg bw/day (4/10); hypoplasia of seminal vesicles in males at 500 (3/10) and 1000 (5/10) mg/kg bw/day and hypospermatogenesis in 5/10 males at 1000 mg/kg bw/day. A NOAEL of 125 mg/kg bw/day, based on reduced body weight, was reported (EFSA, 2014; JECFA, 1998; NTP, 1988; SCF, 2003; HSDB).

In a 16-day oral gavage study, B6C3F1 mice (n=5/sex/group) were administered 4-hexylresorcinol by gavage in corn oil at doses of 0, 31.3, 62.5, 125, 250 or 500 mg/kg bw/day, five days per week. No treatment-related effects were reported (EFSA, 2014; JECFA, 1998; NTP, 1988; SCF, 2003; HSDB).

In a 13-week oral study, 4-hexylresorcinol was administered to groups of 10 B6C3F1 mice of both sex by gavage in corn oil at 0, 62.5, 125, 250, 500 or 1000 mg/kg bw/day, five days/week. Mortality was recorded in all male mice and 9/10 female mice at 1000 mg kg/bw/day. No treatment-related clinical signs were reported in other surviving mice. Slight reduction in the mean body weights of male mice at 250 mg/kg bw/day (6 %) and 500 mg/kg bw/day (5 %) were observed. Incidence of mild to moderate nephropathy were observed in 1/10, 4/10, 8/10 and 7/10 in males and 0/10, 1/10, 7/10 and 10/10 in females at doses of 62.5, 125, 250 and 500 mg/kg bw, respectively. A NOAEL was not identified and the calculated benchmark dose level ($BMDL_{10}$) values ranged from 7 to 21 mg/kg bw/day for males and 20 to 90 mg/kg bw/day for females (EFSA, 2014; JECFA, 1998; NTP, 1988; SCF, 2003; HSDB).

In a mouse study, the chemical in corn oil (10 mL/kg bw) was administered to B6C3F1 mice (50/sex/group) by gavage at 0, 63 or 125 mg/kg bw/day, five days/week for 102 weeks. Treatment-related reductions in mean body weight were reported in male mice from the high-dose group (9-11 %) after week 67 and in low-dose females (4-10 %) after week 88. Non-neoplastic lesions such as osteosclerosis (increased incidence in high dose males and females) and nephropathy were observed in both sexes. Nephropathy was reported in 39/50 control males; 43/50 low dose males and 47/50 high dose males) and 7/50 control females; 40/49 low dose females and 47/50 high dose females. Increased incidence of focal medullary hyperplasia of the adrenal gland were seen in treated male mice (5/50 control; 16/50 low dose and 10/49 high dose). A marginal upward trend in the incidence of phaeochromocytomas and slight increases in the incidence of neoplasms of the Harderian gland in males were reported. A no observed effect level (NOEL) of 63 mg/kg bw/day for osteocsclerosis and nephropathy in male mice and osteosclerosis in female mice was reported (NTP, 1988; JECFA, 1998; SCF, 2003; EFSA, 2014; HSDB).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the available in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic. The majority of in vivo tests for gene mutations and clastogenicity gave negative results (EFSA, 2014; JECFA, 1998; NTP, 1988; HSDB).

In vitro studies

- Two Ames tests in five strains of *Salmonella typhimurium* at doses up to 333 µg/plate of 4-hexylresorcinol gave negative results, both in presence and absence of metabolic activation;
- *Escherichia coli* strains WP A+ and A- gave positive results in absence of metabolic activation at concentrations in the range of 4–16 µg/plate; and

- Mouse lymphoma assay (L5178Y cells) gave positive results in the presence of metabolic activation with the chemical at doses of 1.25–40 µg/mL.

In vivo studies

- A chromosome aberration assay in Chinese hamster ovary cells at 5–50 µ/mL gave negative results;
- Sister chromatid exchange (SCE) assay in Chinese hamster ovary cells gave positive results with the chemical in dimethyl sulfoxide (DMSO) at doses of 16, 18 and 20 µg/mL in absence of metabolic activation;
- A cell transformation assay in A31-1-13 clone of BALB/c-3T3 cells was negative, both in presence and absence of metabolic activation with the chemical at dose range of 7–31 µg/mL in DMSO; and
- In a rat liver unscheduled DNA synthesis (UDS) assay conducted according to OECD Test Guideline (TG) 486, the chemical in corn oil administered to male rats at 600 or 2000 mg/kg bw/day gave negative results.

Carcinogenicity

The available information indicate that the chemical is not likely to be carcinogenic.

In a carcinogenicity study, the chemical in corn oil was administered to F344/N rats (50/sex/group) by gavage at 0, 63 or 125 mg/kg bw/day, five days per week for 103 weeks. Males at 125 mg/kg bw/day showed body weight reduction by 7-11 % compared to the controls. Mortality observed during the first year of treatment in females (3 control, 8 mid-dose and 14 high-dose), was not considered to be significant by the author, as the animals died before they were at risk of developing tumours. Two males at 125 mg/kg bw/day were reported with statistically non-significant astrocytomas and one with oligodendroglioma. One male at 63 mg/kg bw/day had glioma and one control male had oligodendroglioma. No other neoplastic and non-neoplastic changes were observed in rats of either sex (NTP, 1988; JECFA, 1998; SCF, 2003; EFSA, 2014; HSDB).

In a 102-week repeat dose study in mice, a marginal upward trend in the incidence of phaeochromocytomas and slight increases in the incidence of neoplasms of the Harderian gland in males were reported. A NOEL of 63 mg/kg bw/day was reported (see **Repeated dose toxicity: Oral** section).

Based on the NTP report the chemical is not carcinogenic in male and female F344/N rats and female B6C3F1 mice. There is equivocal evidence of carcinogenicity in male B6C3F1 mice as shown by the marginal increase in the incidence of pheochromocytomas of the adrenal medulla and of Harderian gland neoplasms (NTP, 1988; JECFA, 1998).

Reproductive and Developmental Toxicity

Based on the available data, the chemical is considered to have reproductive toxicity at high doses. Hazard classifiction is warranted (see **Recommendation** section).

The chemical, 4-hexylresorcinol, has been used as a spermicidal agent by local application in contraceptive preparations and has been characterised as a potent spermicide in an cytoplasmic stripping titration assay against human spermatozoa. Repeaed dose animal studies showed effects on the testes consistent with reduction in male fertility; but only at high exposure levels (NTP, 1988; JECFA, 1998; SCF, 2003; EFSA, 2014). Effects on the male reproductive system were seen at high doses in one repeat dose study (see **Repeated Dose Toxicity**).

Other Health Effects

Endocrine Disruption

The structure of the chemical has raised an alert for possible endocrine disruptor activity. The chemical, 4-hexylresorcinol was found to be a potent transactivator, without binding to the oestrogen receptor alpha (ERa) in an in vitro competition assay in MCF-7 human breast cancer cells transfected with a construct encoding luciferase reporter gene under control of an oestrogen-

responsive promoter. It is hypothesised that 4-hexylresorcinol had an indirect effect on the oestrogen receptor and facilitated the interaction between the ERa and coactivators (EFSA, 2014). However, the SCF stated only branched chain octyl and nonyl phenols have shown endocrine disruptor activity so far and 4-hexylresorcinol is a shorter straight chain, hexyl derivative (SCF, 2003).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity from oral exposure) and effects on male fertility at high doses.

Public Risk Characterisation

Although the public could be exposed to the chemical through potential cosmetic and domestic uses, given the low exposure to the chemical, the chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

Given the critical systemic acute health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalation exposure are implemented. The chemical 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.

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 aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302)
Reproductive and Developmental Toxicity	Not Applicable	May damage fertility - Cat. 1B (H360F)

[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 oral 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 local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- 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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