1,3-Benzenediol, 2-methyl-: Human health tier II assessment

24 April 2015

CAS Number: 608-25-3

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	2-methylresorcinol 2-methyl-1,3-benzenediol 1,3-dihydroxy-2-methylbenzene
Structural Formula	 Structural formula of 1,3-Benzenediol, 2-methyl-
Molecular Formula	C7H8O2
Molecular Weight (g/mol)	124.138
Appearance and Odour (where available)	colourless to light brown crystalline substance
SMILES	c1(O)c(C)c(O)ccc1

Import, Manufacture and Use

Australian

The chemical is on the 'List of chemicals used as dyes in permanent and semi-permanent hair dyes in Australia' with a reported cosmetic use in permanent hair dye preparations (NICNAS, 2007).

International

The following international uses have been identified through:

- the European Union (EU) Registration, Evaluation, Authorization 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 Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary;
- the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and
- various international assessments (Corbett, 1999; SCCS, 2008).

The chemical has reported cosmetic use as a component of hair dyes.

The chemical has reported site-limited use as an intermediate in producing oxidative and non-oxidative hair dye formulations.

Restrictions

Australian

No known restrictions have been identified.

International

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

- EU Cosmetic Directive 76/768/EEC Annex III Part 1: List of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down—maximum concentration in ready to use formulation; 1.8 %;
- ASEAN Cosmetic Directive Annex III—Part 1 List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down;
- New Zealand Cosmetic Products Group Standard—Schedule 5—Table 1: Components cosmetic products must not contain except subject to the restrictions and conditions laid down.

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

The chemical is commonly known as 2-methylresorcinol (CAS No. 608-25-3) and will be referred to as such henceforth.

Toxicokinetics

No in vivo studies are available for the toxicokinetics of the test chemical.

Quantitative Structure Activity Relationship (QSAR) analysis of 2-methylresorcinol indicated an approximate half-life of 0.014 days (REACH).

Dermal absorption

The chemical 2-methylresorcinol was assessed for dermal absorption in an Organisation for Economic Co-operation and Development (OECD) draft Test Guideline (TG) 428 (skin absorption: in vitro method) study. Excised pig skin (dermatomed to a mean thickness of 0.38 mm) was exposed to the test chemical in:

- a cream formulation with hydrogen peroxide;
- a cream formulation without hydrogen peroxide; and
- in aqueous solution,

all at a concentration of 1.8 %, for 30 minutes.

The amount of substance systemically available from the cream formulation with or without hydrogen peroxide was 0.85 ± 0.78 $\mu g/cm^2$ (0.45 %) and 8.38 ± 5.41 $\mu g/cm^2$ (4.48 %), respectively, and 32.2 ± 11.91 $\mu g/cm^2$ (17.18 %) for the aqueous solution. Dermal absorption from the formulation with and without hydrogen peroxide is markedly different from the aqueous solution, which showed the greatest absorption (REACH).

Acute Toxicity

Oral

Based on available studies, the chemical has moderate acute toxicity from oral exposure.

In a non-guideline study, male CF1 mice (10/group) were administered 2-methylresorcinol via oral gavage at 251, 316, 398, 425, 448 or 501 mg/kg bw. No clinical effects were observed in the lowest dose group. A median lethal dose (LD50) of 390 mg/kg bw was reported; although limited experimental details were provided (SCCS, 2008; REACH).

The US Environmental Protection Authority (EPA) used computer modelling to estimate the acute oral toxicity of 2-methylresorcinol in rats, using the Toxicity Estimation Software Tool (T.E.S.T v4.1). The chemical has an estimated oral LD50 of 200 mg/kg bw (REACH).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Respiratory Irritation

No data are available.

Skin Irritation

The chemical is considered to be slightly irritating to skin.

In a study conducted according to OECD TG 404 (acute dermal irritation/corrosion) study, 0.5 g of the test material was moistened and applied to the intact, shaved back skin of New Zealand White rabbits (three males/group) for four hours under semi-occlusive patches. Observations were made at one, 24, 48 and 72 hours post-treatment. Very slight erythema developed in one animal after one hour. The test chemical was concluded to have caused slight and transient skin irritation (SCCS, 2008; REACH).

Eye Irritation

The chemical is a severe eye irritant.

In a study conducted according to OECD TG 405 (acute eye irritation/corrosion) study, 0.1 mL of undiluted 2-methylresorcinol (equivalent to 50.6 mg) was instilled into one eye of one New Zealand White rabbit and left for 24 hours. The animal was observed regularly for 21 days. The test chemical caused corneal opacity (maximum grade 3) and epithelial damage (maximum 100% of the corneal surface). These effects were not fully reversible within the observation period. Neovascularisation of the cornea was apparent seven days after exposure. Iridial irritation (grade 1) was observed for the first seven days of observation. Conjunctival irritation (consisting of erythema and chemosis) was observed. The nictitating membrane and eyelids exhibited white discolouration, consistent with necrosis (SCCS, 2008; REACH).

Sensitisation

Respiratory Sensitisation

No data are available.

Skin Sensitisation

The chemical is considered to be a weak skin sensitiser, based on the positive results seen in a single local lymph node assay (LLNA) the EC3 (estimated concentration needed to produce a stimulation index (SI) of 3) is 50 %).

The sensitising potential of 2-methylresorcinol was assessed in a study conducted in accordance with OECD TG 429 (skin sensitisation: LLNA) in CBA mice (five/group). Animals had 25 µL of the test material (at 1, 10, 25 or 50 %) applied to the dorsal surface of each ear, once daily for three consecutive days. Five days after the first topical application, all mice were administered radiolabelled thymidine (^{3}HTdR), draining lymph nodes were excised and thymidine incorporation into the lymph node cells was assessed. Slight irritation was observed at doses higher than 10 %. SIs of 0.7, 0.6, 1.1 and 3 were calculated for the 1, 10, 25 and 50 % groups, respectively. An EC 3 of 50 % was determined accordingly (SCCS, 2008; REACH).

Repeated Dose Toxicity

Oral

The available data suggest that the chemical has low repeated dose toxicity following oral exposure.

An oral repeated dose toxicity study was conducted in compliance with OECD TG 408 (repeated dose 90-day oral toxicity in rodents). Wistar rats of both sexes were administered the test chemical by oral gavage at 0, 100, 200 or 450 mg/kg bw/day for 90 days. A minimum of 12 animals per sex, per group were used in this study. Animals in the two highest dose groups exhibited clonic spasms, salivation and scratching movements from week four. Body weight gain in the high dose males was reduced from week four onwards. Glucose levels were increased in males at 450 mg/kg bw/day. Liver function (as determined by transaminase enzyme levels) was impaired in some of the animals in the two highest dose groups. All adverse effects were reversible during the recovery period. On the basis of these results, a no observed adverse effect level (NOAEL) of 100 mg/kg bw/day was determined based on clonic spasms, salivation and scratching movements at the lowest observed adverse effect level (LOAEL) of 250 mg/kg bw/day (SCCS, 2008; REACH).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the weight of evidence from the available well-conducted in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic.

In vitro

The chemical 2-methylresorcinol was assessed for its potential to cause genotoxicity in an Ames study conducted in compliance with OECD TG 471 (bacterial reverse mutation assay). The test chemical was incubated with *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537, in the presence or absence of a metabolic activation system, at concentrations up to 5000 µg/plate. No statistically significant increase in the number of revertant colonies was observed in any of the tester strains, at any dose, either in the presence or absence of metabolic activation. Under these experimental conditions, the test chemical was not considered to be genotoxic (SCCS, 2008; REACH).

The chemical was assessed for genotoxicity in a study conducted in accordance with OECD TG 473 (in vitro mammalian chromosome aberration test) study. Chinese hamster lung fibroblast (V79) cells were incubated with the test chemical at concentrations ranging from 80–500 µg/mL, in the presence or absence of metabolic activation. Cells were treated for four hours and harvested for assessment 18 hours post-treatment. No clear toxic effects were observed up to the highest concentration tested. There were statistically significant increases in the number of cells exhibiting structural chromosome aberrations in the absence of metabolic activation (starting from 400 µg/mL) or presence of metabolic activation (starting from 80 µg/mL). On the basis of this effect, the test chemical was considered to be clastogenic in vitro (SCCS, 2008; REACH).

In the OECD TG 476 (in vitro mammalian cell gene mutation test) study, 2-methylresorcinol was incubated with mouse lymphoma L5178Y cells, in the presence or absence of a metabolic activation system, at concentrations ranging from 25–1000 µg/mL. Mutations in the target gene, thymidine kinase, were assessed as a marker of genotoxicity. The test chemical failed to induce mutations at the target locus and, therefore, the chemical was not considered to be mutagenic in this mouse lymphoma assay (SCCS, 2008; REACH.

In vivo

2-Methylresorcinol was assessed for genotoxicity in a study conducted in compliance with OECD TG 474 (mammalian erythrocyte micronucleus test). Male and female NMRI mice were administered the test chemical via a single intraperitoneal

injection at 12.5, 25 or 50 mg/kg bw. Cells were harvested from bone marrow to assess cytotoxicity and genotoxicity. A 24-hour sampling time was used for all concentrations. In addition, a 48-hour sampling time was used for the highest dose. No cytotoxic effects were observed on bone marrow cells. There were no statistically significant or biologically relevant increases in the frequency of micronuclei formation in harvested bone marrow cells at any sampling time, at any dose tested. On the basis of this finding, the test chemical was considered not to be genotoxic (SCCS, 2008; REACH).

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

Based on the data available, 2-methylresorcinol is not a reproductive or developmental toxicant.

The chemical was assessed in a study conducted in compliance with OECD TG 414 (prenatal developmental toxicity study). Female Wistar rats were administered the test chemical via oral gavage at 0, 40, 200 or 400 mg/kg bw/day on days 0–20 post-coitum. Dams were euthanised and necropsied on post-coitum day 21. No maternal mortalities occurred and the clinical appearance, body weight, food consumption and macroscopic evaluation revealed no evidence of maternal toxicity. No effects were observed on pregnancy outcome, post-implantation loss, litter size or sex distribution. No significant effects were observed on foetal body weights, placental weights or external, visceral and skeletal malformations. On the basis of these findings, a NOAEL of 400 mg/kg bw/day was determined for all three toxicological endpoints (maternal, reproductive and developmental toxicity) (SCCS, 2008; REACH).

Gestating female Sprague Dawley rats (25 /dose) were fed diets containing 2-methylresorcinol at 0, 0.1, 0.4 or 1.5 % during the period of major organogenesis. Clinical analysis was conducted on day 20 of gestation. At the two highest doses, slight increases (not statistically significant) were observed in the mean post-implantation loss with corresponding decreases in the number of viable foetuses and implantation sites. No significant effects were observed; therefore, a NOAEL of 1.5 % in feed (equivalent to approximately 900 mg/kg bw) was determined (Re et al., 1986; SCCS, 2008).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic acute effects (acute toxicity from oral exposure) and local effects (severe eye damage, skin sensitisation).

Public Risk Characterisation

The chemical was reported to be used in permanent hair dye preparations in Australia (NICNAS, 2007).

The EU has restricted the use of these chemicals in hair dye preparations to a maximum of 1.8 % concentration in ready-to-use hair dye formulations (see **International restrictions**) .

Currently, there are no restrictions in Australia on using these chemicals in hair dyes. The eye irritation and skin sensitisation risk could be mitigated by implementing concentration limits for use in hair dyes.

Occupational Risk Characterisation

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

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of the chemical in cosmetics and/or domestic products be managed through changes to poisons scheduling, and risks for workplace health and safety be managed through changes to classification and labelling.

Assessment of the chemical is considered to be sufficient, provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Given the risk characterisation, it is recommended that the chemicals should be included in Schedule 6 of the *Poisons Standard* (the *Standard for the Uniform Scheduling of Medicines and Poisons*—SUSMP) with an appropriate concentration cut-off (exemption) for hair dye use.

Consideration should be given to the following:

- the chemical has moderate acute oral toxicity;
- the chemical is a severe eye irritant;
- the chemical is a skin sensitiser; and
- overseas restrictions for use of these chemicals in hair dyes. The maximum concentration allowed on hair is 1.8 % (SCCS, 2008).

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]
Acute Toxicity	Harmful if swallowed (Xn; R22)	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Risk of serious eye damage (Xi; R41)	Causes serious eye damage - Cat. 1 (H318)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)	May cause an allergic skin reaction - Cat. 1 (H317)

[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 chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal or ocular 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;
- 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;
- 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 chemicals.

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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