1,4-Benzenediamine, 2-methyl-, sulfate: Human health tier II assessment

27 October 2017

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Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
1,4-Benzenediamine, 2-methyl-, sulfate (1:1)	615-50-9
1,4-Benzenediamine, 2-methyl-, sulfate	6369-59-1

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.



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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

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ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemicals are sulfate salts of 1,4-benzenediamine, 2-methyl- (CAS No. 95-70-5) with either a 1:1 or 1:(unspecified) ratio of sulphuric acid to diamine (CAS Nos. 615-50-9 and 6369-59-1, respectively). Both CAS Nos. 615-50-9 and 6369-59-1 have been used to represent the same chemical, 1,4-benzenediamine, 2-methyl-, sulfate (SCCP, 2007; HCIS); hence these chemicals are assessed together for the purposes of this report.

Import, Manufacture and Use

Australian

The chemicals (sulfate salt) are on the 'List of chemicals used as dyes in permanent and semi-permanent hair dyes in Australia' (NICNAS, 2007).

International

The reported international use for the chemicals (sulfate salt) is in cosmetics (SCCP, 2007; CIR, 2010; Galleria Chemica; the Environmental Working Group (EWG) Skin Deep database; the European Union (EU) Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Personal Care Product Council International Cosmetic Ingredients (INCI) Directory; the US Department of Health and Human Services Household Products Database (US HPD)) in the following products:

- oxidative hair dyes (as a precursor), the maximum permitted concentration applied to hair is 4.0 % (calculated as free base), or 7.2 % (calculated as sulfate) after mixing under oxidative conditions; and
- hair bleaches, at concentrations up to 3.0 %.

The chemicals (sulfate salt) are used in 155 cosmetic products in the US (Compilation of Ingredients Used in Cosmetics in the US (CIUCUS), 2011).

Restrictions

Australian

The chemicals (sulfate salt) are not separately listed in the *Poisons Standard* — *the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP). However, the chemical group restrictions for 'toluenediamines' contained in Schedules 6 and 10 (previously called Appendix C) of the SUSMP will apply to the chemicals (SUSMP, 2017).

Schedule 6:

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'TOLUENEDIAMINE not elsewhere specified in these Schedules:

a) in hair dye preparations **except** when the immediate container and primary pack are labelled with the following statements:

KEEP OUT OF REACH OF CHILDREN, and

WARNING – This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.

written in letters not less than 1.5 mm in height; or

b) in eyelash and eyebrow tinting products when the immediate container and primary pack are labelled with the following statement:

WARNING – This product contains ingredients which may cause skin irritation to certain individuals, and when used for eyelash and eyebrow tinting may cause injury to the eye. A preliminary test according to the accompanying directions should be made before use.

written in letters not less than 1.5 mm in height; or

c) in nail polish preparations containing 2,5-toluenediamine except when labelled 'avoid contact with skin'.

Schedule 6 chemicals are labelled 'Poison'. These are substances with a moderate potential for causing harm, the extent of which can be reduced by using distinctive packaging with strong warnings and safety directions on the label (SUSMP, October 2017).

Schedule 10:

TOLUENEDIAMINES in preparations for skin colouration (including tattooing) and dyeing of eyelashes or eyebrows **except** when included in Schedule 6.

Schedule 10 chemicals are 'substances of such danger to health as to warrant prohibition of sale, supply and use — substances which are prohibited for the purpose or purposes listed for each poison' (SUSMP, 2017).

International

The use of the chemicals (sulfate salt) in oxidative hair dye products is restricted by the Association of Southeast Asian Nations (ASEAN), the EU and New Zealand (NZ) as a 'substance which cosmetic products must not contain except subject to the restrictions and conditions laid down' in the following:

- the EU Regulation (EC) No 1223/2009 Annex III (CosIng);
- the NZ Cosmetic Products Group Standard 2006 (Schedule 5) (NZ Environmental Protection Agency (EPA)); and
- the ASEAN Cosmetic Directive Annex III (ASEAN Cosmetics Association).

The above regulations restrict the maximum concentration applied to hair to 4 % (calculated as free base) after mixing under oxidative conditions.

The chemicals (sulfate salt) are listed in the Health Canada List of restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist") and the US Toxic Substances Control Act (TSCA) — Chemical Substance Inventory (Galleria Chemica).

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals (sulfate salt) are classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

- Acute toxicity category 3, H301 (Toxic if swallowed); category 4, H332 (Harmful if inhaled); category 4, H312 (Harmful in contact with skin); and
- Skin sensitisation category 1, H317 (May cause an allergic skin reaction).

Exposure Standards

Australian

No specific exposure standards are available for the chemicals (sulfate salt).

International

No specific exposure standards are available for the chemicals (sulfate salt).

Health Hazard Information

The chemicals, 1,4-benzenediamine, 2-methyl, sulfate (sulfate salt; CAS Nos. 615-50-9 and 6369-59-1) and 1,4-benzenediamine, 2-methyl (free base; CAS No 95-70-5) are reported to be used in hair dye formulations.

The free base, 1,4-benzenediamine, 2-methyl was previously assessed under the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework (NICNAS) and where data were not available, information on its sulfate salt (CAS Nos. 615-50-9 and 6369-59-1) was used as read across data on several toxicity endpoints. Therefore, the health hazard information for 1,4-benzenediamine, 2-methyl, sulfate (CAS Nos. 615-50-9 and 6369-59-1) was taken primarily from the Tier II IMAP report of the free base, 1,4-benzenediamine, 2-methyl.

The Tier II assessment report for 1,4-benzenediamine, 2-methyl is available at: https://www.nicnas.gov.au/chemical-information/imapassessments/imap-assessment-details?assessment_id=869#cas-A_95-70-5. The assessment report for 1,4-benzenediamine, 2-methyl, sulfate (CAS Nos. 615-50-9 and 6369-59-1) should be read in conjunction with the Tier II assessment report for 1,4-benzenediamine, 2methyl.

Both the free base, 1,4-benzenediamine, 2-methyl (CAS No. 95-70-5) and its sulfate salt (CAS Nos. 615-50-9 and 6369-59-1) are classified as hazardous on the HCIS (Safe Work Australia) for acute toxicity (from oral, dermal and inhalation exposure), and skin sensitisation. The free base, 1,4-benzenediamine, 2-methyl is also classified for eye irritation and specific organ toxicity following repeated oral exposure. Based on the available data, the same classification is recommended for specific organ toxicity following repeated oral exposure for the sulfate salt (CAS Nos. 615-50-9 and 6369-59-1) (see **Recommendation** section).

The following data are available for the chemicals in this group (sulfate salt; CAS Nos. 615-50-9 and 6369-59-1) and confirm the toxicological similarity to the free base (CAS No 95-70-5) (NICNAS).

The sulfate salt has low bioavailability following dermal application. In studies conducted according to Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 417 or 427, the bioavailability of the sulfate salt in Kyoto rats was >90 % after oral administration and 2 % after dermal application. The main metabolite found in the urine and the faeces was N,N-diacetyl-toluene-2,5-diamine. In Sprague Dawley rats, the bioavailability was reported to be 69 % after oral administration and 2 % after dermal application (SCCP, 2007). The sulfate salt has low bioavailability following dermal application. In studies conducted according to Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 417 or 427, the bioavailability of the sulfate salt in Kyoto rats was >90 % after oral administration and 2 % after dermal application. The main metabolite found in the urine and the faeces was N,N-diacetyl-toluene-2,5-diamine. In Sprague Dawley rats, the bioavailability following dermal application. In studies conducted according to Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 417 or 427, the bioavailability of the sulfate salt in Kyoto rats was >90 % after oral administration and 2 % after dermal application. The main metabolite found in the urine and the faeces was N,N-diacetyl-toluene-2,5-diamine. In Sprague Dawley rats, the bioavailability was reported to be 69 % after oral administration and 2 % after dermal application (SCCP, 2007).

The sulfate salt has an oral median lethal dose (LD50) and median lethal concentration (LC50) of 98 mg/kg and 1.77 mg/L (calculated) in rats, respectively (CIR, 2010). These data support the current classification of the sulfate salt. A dermal LD50 of 3519 mg/kg bw in rats was reported for the free base. While the data do not support a classification, in the absence of more comprehensive information, there is insufficient evidence to support a recommendation to amend the current classification of the sulfate salt for acute dermal toxicity.

The sulfate salt tested positive for skin sensitisation in one local lymph node assay (LLNA) tested in aqua/acetone/olive oil (2:2:1), and produced equivocal results in another LLNA study tested in dimethyl sulfoxide (DMSO) vehicle (SCCP, 2007; CIR, 2010). The estimated concentration needed to produce a three-fold increase in lymphocyte proliferation (EC3) was calculated to be 0.31 % for the first study. The data support the current classification of the sulfate salt.

In an in vitro Hen's Egg Test – Chorioallantoic Membrane (HET-CAM) ocular irritation assay that has not been validated, the sulfate salt was found to be slightly irritating to eyes (SCCP, 2007). The limited information available is not sufficient to warrant classification.

The free base is classified for specific organ toxicity based on data available for its sulfate salt from various 90-day oral studies in rats. A lowest no observed adverse effect level (NOAEL) of 2.5 mg/kg bw/day was reported. The release of aspartate aminotransferase (AST) observed in these studies is reported to be closely related to myotoxicity. Therefore, the increased AST levels in plasma in treated rats indicates that the chemicals are capable of inducing myodegenerative changes (SCCP, 2007). Based on the available information, the free base and its sulfate salt are considered to cause serious damage to health from repeated oral exposure and warrant classification (see **Recommendation** section).

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Based on data available for the free base and/or the sulfate salt, the other toxicity endpoints for CAS Nos. 615-50-9 and 6369-59-1 can be summarised as follows:

- the chemicals are not considered to be genotoxic;
- data available are insufficient to conclude carcinogenicity, although the chemicals are not genotoxic compared to other members of the toluenediamine group (e.g. 2,4-toluenediamine); and
- the chemicals are not expected to cause reproductive or developmental toxicity.

Risk Characterisation

Critical Health Effects

The chemicals (sulfate salt) are considered to have the following critical health effects for risk characterisation:

- skin sensitisation;
- systemic acute effects (by oral, dermal and inhalation routes of exposure); and
- may cause harmful health effects following repeated oral exposure.

Public Risk Characterisation

The chemicals (sulfate salt) are reported to be used in permanent hair dye preparations in Australia and overseas.

The ASEAN, Canada, NZ and the EU have restricted the use of the chemical (sulfate salt) in cosmetics. In Australia, the 'TOLUENEDIAMINE' chemical group, which includes CAS Nos. 615-50-9 and 6369-59-1 is listed on Schedules 6 and 10 of the SUSMP, with restrictions and prohibitions on their use in specific cosmetic products. The Schedule 6 entry in the SUSMP allows toluenediamines to be included in hair dye preparations, in eyelash and eyebrow tinting products, and nail polish with specific requirements. The current controls are considered adequate to minimise the risk to public health posed by hair dyes containing the chemicals. Therefore, the chemicals (sulfate salt) are not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

Given the critical acute and long-term systemic effects, the chemicals (sulfate salt) could pose an unreasonable risk to workers unless adequate control measures to minimise oral exposure are implemented. Oral exposure can be prevented by good hygiene practices. The chemicals (sulfate salt) 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 data available support an amendment to the hazard classification in HCIS (Safe Work Australia) (see Recommendation section).

NICNAS Recommendation

Assessment of the chemicals (sulfate salt) is considered to be sufficient provided that existing risk management is implemented, recommended amendment to the classification is adopted, and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

Products containing the chemicals (sulfate salt) should be labelled in accordance with state and territory legislation (SUSMP, 2017).

Work Health and Safety

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The chemicals (sulfate salt) are 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.

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	Toxic if swallowed - Cat. 3 (H301)* Harmful in contact with skin - Cat. 4 (H312)* Harmful if inhaled - Cat. 4 (H332)*
Sensitisation	Not Applicable	May cause an allergic skin reaction - Cat. 1 (H317)*
Repeat Dose Toxicity	Not Applicable	May cause damage to organs through prolonged or repeated exposure - Cat. 2 (H373)

^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 (sulfate salt) 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 exposures to the chemicals 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 chemicals are used.

Examples of control measures which could minimise the risk include, but are not limited to:

- 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 is 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/NZ 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 chemicals 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 these chemicals has not been undertaken as part of this assessment.

References

Association of South East Asian Nations (ASEAN) Cosmetic Directive. Government of Singapore Health Sciences Authority. Health Products Regulation for Cosmetic Products. Accessed at

http://www.hsa.gov.sg/content/dam/HSA/HPRG/Cosmetic_Products/Annexes%20of%20the%20ASEAN%20Cosmetic%20Directive.pdf

Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS), 2011. Washington DC: Personal Care Products Council.

CosIng. Cosmetic Ingredients and Substances. Accessed September 2017 at http://ec.europa.eu/growth/tools-databases/cosing/

Cosmetic Ingredient Review Expert Panel (CIR, 2010). Final amended report of the safety assessment of toluene-2,5-diamine, toluene-2,5-diamine sulfate, and toluene-3,4-diamine as used in cosmetics. Accessed September 2017 at http://gov.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR534.pdf

Environmental Working Group (EWG). Skin Deep Cosmetics Database. Accessed September 2017 at http://www.ewg.org/skindeep/

Galleria Chemica. Accessed September 2017 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

Health Canada. Cosmetic Ingredient Hotlist – Prohibited and Restricted Ingredients. Ottawa: Health Canada. Available: http://www.hc-sc.gc.ca/cps-spc/cosmet-person/hot-list-critique/index-eng.php

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) 2007. List of chemicals used as dyes in permanent and semipermanent hair dyes in Australia. Unpublished internal document.

New Zealand Environmental Protection Authority (NZ EPA) Cosmetic Products Group Standard. Accessed August 2017 at http://www.epa.govt.nz/Publications/Cosmetic%20Products%20Group%20Standard.pdf

NICNAS. Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II Assessment for 1,4-Benzenediamine, 2-methyl-(CAS No. 95-70-5). Available at http://www.nicnas.gov.au

Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary. Accessed September 2017 at http://www.ctfa-gov.org/jsp/gov/GovHomePage.jsp

Safe Work Australia (SWA). Hazardous Chemicals Information System (HCIS). Accessed September 2017 at http://hcis.safeworkaustralia.gov.au/HazardousChemical

Scientific Committee on Consumer Products (SCCP) 2007. Opinion on toluene-2,5-diamine COLIPA No. A5. Adopted at its13th plenary meeting on 2 October 2007. Accessed at https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_108.pdf

The Poisons Standard, October 2017. The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) No. 18. Accessed at https://www.legislation.gov.au/Details/F2017L01285

United States (US) Department of Health and Human Services Household Product Database. Accessed September 2017 at https://householdproducts.nlm.nih.gov/about.htm

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Chemical Identities

Chemical Name in the Inventory and Synonyms	1,4-Benzenediamine, 2-methyl-, sulfate (1:1) toluene-2,5-diamine, sulfate p-toluenediamine sulfate 2-methyl-p-phenylenediamine sulphate C.I. Oxidation Base 4 C.I. 76043
CAS Number	615-50-9
Structural Formula	H_3C H_2 H_3C HO HO S OH HO HO HO HO HO HO HO
Molecular Formula	C7H10N2.H2O4S
Molecular Weight	220.25

Chemical Name in the Inventory and Synonyms	1,4-Benzenediamine, 2-methyl-, sulfate C.I. Oxidation Base 4
CAS Number	6369-59-1
Structural Formula	



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