Sulfuric acid, diethyl ester: Human health tier II assessment

27 November 2014

CAS Number: 64-67-5

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.

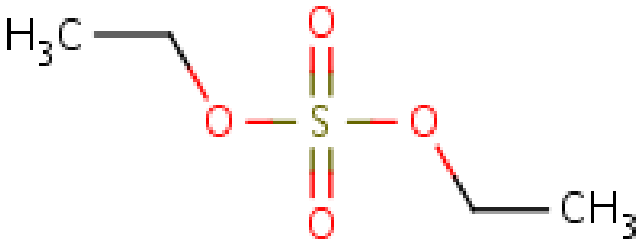
For more detail on this program please visit:www.nicnas.gov.au

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 protection. Use of this information without obtaining the permission from the owner(s) of the respective information might violate the rights of the owner. NICNAS does not take any responsibility whatsoever for any copyright or other infringements that may be caused by using this information.

Acronyms & Abbreviations

Chemical Identity

Synonyms	diethyl sulfate diethyl sulphate
Structural Formula	
Molecular Formula	C4H10O4S
Molecular Weight (g/mol)	154.185
Appearance and Odour (where available)	Colourless and odourless oily liquid
SMILES	C(C)OS(=O)(=O)OCC

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified through: the European Union (EU) Registration, Evaluation and Authorisation of Chemicals (REACH) dossiers; Galleria Chemica; the United States (US) Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR), the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments (IARC 1992; IARC, 1999; SCOEL, 2009).

The chemical has reported site-limited use:

- mostly as an intermediate for manufacturing a wide variety of chemicals including ethylating agents to produce dyes, pigments and textile chemicals;
- as reactants in polymer synthesis;

- as a finishing agent in textile production; and
- as a dye-set agent in carbonless paper.

The chemical also has reported non-industrial applications in agrochemicals and pharmaceuticals through manufacturing quaternary ammonium salts (Dow, 2006; Environment Canada, 2009).

Restrictions

Australian

The chemical is a restricted carcinogen for all uses under the *Work, Health and Safety Act 2011* (WHS, 2011).

International

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

- 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):

- Carc. Cat. 2; R45 (carcinogenicity);
- Muta. Cat. 2; R46 (mutagenicity);
- Xn; R20/21/22 (acute toxicity);
- C; R34 (corrosion).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

- 0.2 mg/m^3 (0.03 ppm) time weighted average (TWA) in Germany and Switzerland;
- 0.32 mg/m^3 (0.05 ppm) TWA in Ireland and United Kingdom.

Health Hazard Information

Toxicokinetics

The chemical is likely to be absorbed through the skin, based on its similarity to dimethyl sulfate (CAS No. 77-78-1). A study in rats showed that the chemical was metabolised via conjugation to glutathione. Ethyl mercapturic acid has been identified as a metabolite of the chemical in urine (SCOEL, 2009).

Acute Toxicity

Oral

The chemical is classified as hazardous with the risk phrase ‘Harmful if swallowed’ (Xn; R22) in the HSIS (Safe Work Australia). The available data support this classification.

The chemical was administered (by gavage) to six male rats at up to 10000 mg/kg bw. The median lethal dose (LD50) was estimated to be 880 mg/kg bw (Smyth et al., 1949, cited in Dow, 2006).

Other data indicate LD50 values of 1410 mg/kg bw for the rat and 650 mg/kg bw for the mouse (REACH).

Dermal

The chemical is classified as hazardous with the risk phrase ‘Harmful in contact with skin’ (Xn; R21) in the HSIS (Safe Work Australia). The available data support this classification.

Following the application of undiluted and diluted solutions (up to 10 %) of the chemical to the skin of albino rabbits, the dermal LD50 was determined to be 706 mg/kg bw (Smyth et al., 1949, cited in Dow, 2006).

Inhalation

The chemical is classified as hazardous with the risk phrase ‘Harmful by inhalation’ (Xn; R20) in the HSIS (Safe Work Australia). The available data support this classification.

The median lethal concentration (LC50) was estimated to be between 250 and 500 ppm (1.57 and 3.15 mg/L/4-hour, respectively) in rats exposed to vapours of the chemical. No deaths were reported at 250 ppm, but there was 100 % mortality at 500 ppm (Smyth et al., 1949 cited in Dow, 2006).

Corrosion / Irritation

Corrosivity

The chemical is classified as corrosive with the risk phrase ‘Causes burns’ (C; R34) in the HSIS (Safe Work Australia). The available data support this classification.

The chemical produced necrosis of the dorsal skin and erythema and swelling on abdominal skin of rabbits comparable to 'mild first degree burns' (Smyth et al., 1949, cited in MAK, 2012). An overall irritation score of 6/10 was reported, based on the necrosis observed 24 hours after application (Smyth et al., 1949, cited in REACH).

A 40 % solution of the chemical caused severe corrosion and necrosis of the rabbit eye (Smyth et al., 1949 cited in MAK, 2012).

Sensitisation

Skin Sensitisation

The chemical at a 10 % concentration produced positive results for skin sensitisation in a mouse local lymph node assay (LLNA) (Ashby et al., 1995 cited in REACH). However, considering the corrosive nature of the chemical and possibility of generating false positive results for corrosive chemicals in the LLNA (Basketter & Kimber, 2007), it is not considered appropriate to classify the chemical as a skin sensitiser.

Repeated Dose Toxicity

Oral

No data are available.

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

The chemical is classified as hazardous—Category 2 mutagenic substance—with the risk phrase ‘May cause heritable genetic damage’ (T; R46) in the HSIS (Safe Work Australia). The available data support this classification.

As an alkylating agent, the chemical reacts with the RNA and DNA bases of the cell nucleus, causing alkylation of oxygen sites, including the O6-position of guanine 'which is considered to play a special role in the mutagenic and carcinogenic activity' (Hoffman, 1980 cited in MAK, 2012).

As a result of the alkylation mechanism, the chemical produced positive results in the following in vitro assays (IARC, 1992; IARC, 1999):

- forward and reverse mutations in bacterial systems (e.g. strains of *Salmonella typhymurium*);
- unscheduled DNA synthesis (UDS) in rat hepatocytes;
- mutations at the *hprt* locus in Chinese hamster ovary (CHO) and V79 lung cells;
- sister chromatid exchange in V79 cells; and
- micronuclei in cultured human lymphocytes.

The chemical induced genotoxic effects in vivo, including in germ cells (IARC, 1992; IARC, 1999):

- micronucleated erythrocytes in larvae of newts exposed to the chemical;
- DNA fragmentation in brain cells of male rats treated intraperitoneally (i.p.) with the chemical;
- micronuclei in mouse peripheral reticulocytes;
- specific locus mutations in mouse germ-line cells;
- DNA alkylation in mice, producing N7-ethylguanine in germ cells, bone marrow and liver;
- dominant lethal mutations (chromatid breaks and gaps) in mouse embryonal cells after transplacental treatment; and
- sex-linked recessive lethal mutations in *Drosophila melanogaster* fed or injected with the chemical.

Carcinogenicity

The chemical is currently classified as a Category 2 carcinogen with the risk phrase ‘May cause cancer’ (T; R45) in the HSIS (Safe Work Australia). The available data support this classification.

The International Agency for Research on Cancer (IARC) has classified the chemical as ‘Probably carcinogenic to humans’ (Group 2A) (IARC, 1992; IARC, 1999).

Increased mortality from upper respiratory tract cancers associated with exposure to high concentrations of the chemical was reported in workers in an ethanol manufacturing plant (Lynch et al., 1979 cited in IARC, 1992). Cohort studies suggested that exposure to the chemical increased the risk of cancers in the larynx, buccal cavity, pharynx and in the brain (IARC, 1992).

Two groups of rats (n = 12/group) received the chemical orally at 25 or 50 mg/kg bw/week for 81 weeks and observed until death. One rat with squamous cell carcinoma of the forestomach was found in each group and 6/24 rats exhibited a number of benign papillomas of the forestomach (group unspecified). No control group was included in the original study (Druckrey et al., 1970 cited in IARC, 1992).

In the above mentioned study (Druckrey et al., 1970), two other groups of rats (n = 12/group) were subcutaneously injected with the chemical at 25 or 50 mg/kg bw/week for 49 weeks and observed until death. In the high dose group, local tumours (three spindle-cell sarcomas, three fibrosarcomas, three myosarcomas, one polymorphocellular sarcoma and one glandular carcinoma of unknown origin) were reported at the site of injection in 11 surviving rats, during a mean survival time of 350 days. Two cases of metastasis to the lungs were reported. In the low dose group, local tumours were also

reported, including three fibrosarcomas, two spindle-cell sarcomas and one myosarcoma in 6/12 rats during a mean survival time of 415 days. No control group was included in the study (Druckrey et al., 1970 cited in IARC, 1992).

Three pregnant female rats were exposed to the chemical (by a single injection) at 85 mg/kg bw on gestation day (GD) 15. One of the rats died with multiple mammary gland carcinomas at the age of 742 days. Out of 30 offspring, two developed malignant neurinomas (at the end of the spinal cord and on the lumbal nerve) (Druckrey et al., 1970 cited in IARC, 1992). Based on these results, the chemical was reported to be carcinogenic locally and systemically (SCOEL, 2009).

Reproductive and Developmental Toxicity

Only limited data are available.

Groups of adult female mice were treated with the chemical at 150 mg/kg bw, via a single i.p. injection either four days before mating or at one, six, nine or 25 hours after mating with untreated males. Resorptions increased significantly in mice that received the chemical at one, six or nine hours after mating (30 %, 24 % and 14 %, respectively). Mid and late gestational deaths were increased significantly in the mice receiving the chemical one hour after mating (15 % and 14 %, respectively) and six hours after mating (16 % and 21 % respectively). The observed effects were reported to be due to 'altered programming of gene expression during embryogenesis' (Generoso et al., 1991 cited in IARC, 1999).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include:

- local effects—corrosivity;
- systemic long-term effects—carcinogenicity and mutagenicity; and
- systemic acute effects from oral, dermal and inhalation exposure.

Public Risk Characterisation

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

Occupational Risk Characterisation

The chemical is a restricted carcinogen in Australia, which means a person conducting a business or undertaking (PCBU) at a workplace must apply in writing to the regulator for authorisation to use, handle or store the chemical at the workplace.

The above existing control measures are adequate to protect workers from risks during handling of the chemical.

Based on the available data, the hazard classification in the HSIS (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

This chemical is a restricted carcinogen in Australia under the Work Health and Safety Regulations 2011. Suppliers of this chemical and PCBU using this chemical have specific obligations to protect the safety of workers using, handling and/or storing the chemical (WHS, 2011).

The information about the status of the chemical as a restricted carcinogen under the Work Health and Safety Regulations 2011 should be included in the Australian Inventory of Chemical Substances (AICS) according to section 13(1)(b) of the *Industrial Chemicals (Notification and Assessment) Act 1989*.

No further assessment is required.

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]
Acute Toxicity	Harmful if swallowed (Xn; R22)* Harmful in contact with skin (Xn; R21)* Harmful by inhalation (Xn; R20)*	Harmful if swallowed - Cat. 4 (H302) Toxic in contact with skin - Cat. 3 (H311) Toxic if inhaled - Cat. 3 (H331)
Irritation / Corrosivity	Causes burns (C; R34)*	Causes severe skin burns and eye damage - Cat. 1B (H314)
Genotoxicity	Muta. Cat 2 - May cause heritable genetic damage (T; R46)*	May cause genetic defects - Cat. 1B (H340)
Carcinogenicity	Carc. Cat 2 - May cause cancer (T; R45)*	May cause cancer - Cat. 1B (H350)

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

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

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

Advice for industry

Control measures

Control measures to minimise the risk from 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 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;
- 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.

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