



Australian Government
Department of Health and Ageing
National Industrial Chemicals
Notification and Assessment Scheme

INVENTORY MULTI-TIERED ASSESSMENT AND PRIORITISATION (IMAP)



HUMAN HEALTH TIER II ASSESSMENT FOR
Sulfuric acid, dimethyl ester
CAS Registry Number: 77-78-1

PREFACE

As part of the reform regarding assessment of Existing Chemicals, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) is implementing a new framework to address the human health and environmental impacts of industrial chemicals, not yet assessed, on the Australian Inventory of Chemical Substances (AICS).

The framework provides a more rapid, flexible and transparent approach for the assessment of existing chemicals.

The Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework was developed, with significant input from stakeholders, and will be applied in stages.

Stage One of this program, which will take four years, started 1 July 2012 and is examining 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This includes chemicals for which NICNAS already holds exposure information, chemicals identified as a concern or for which regulatory action has been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

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.

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

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

Disclaimer

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ACRONYMS & ABBREVIATIONS

ACToR	Aggregated Computational Toxicology Resource (US)
AICS	Australian Inventory of Chemical Substances
ASTDR	Agency for Toxic Substances and Disease Registry (US)
bw	bodyweight
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations (US)
CHO	Chinese hamster ovary
CosIng	Cosmetic Ingredients and Substances database (EU)
d	day
DNA	Deoxyribonucleic acid
EC	European Commission
EC3	Estimated concentration three
ECHA	European Chemicals Agency
ESIS	European Chemical Substances Information System
EU	European Union
EU RAR	European Union Risk Assessment Report
FDA	Food and Drug Administration (US)
FSANZ	Food Standards Australia and New Zealand
g	gram
g/mol	grams per mole
GHS	Globally Harmonized System of Classification and Labelling of Chemicals*
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPMT	Guinea Pig Maximisation Test
h	hour
HGPRT	hypoxanthine guanine phosphoribosyltransferase
HPV	high production volume
HSDB	Hazardous Substances Data Bank
HSIS	Hazardous Substances Information System
HVICL	High Volume Industrial Chemicals List
IARC	International Agency for Research on Cancer
INCHEM	International Programme on Chemical Safety (also known as IPCS)
INCI	International Nomenclature of Cosmetic Ingredients
ip	intraperitoneal
IRIS	Integrated Risk Information System (US)
IUCLID	International Uniform Chemical Information Database
iv	intravenous
kg	kilogram
L	litre
LC50	median lethal concentration
LD50	median lethal dose
LCLo	lowest published lethal concentration
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
m ³	cubic metre
mg	milligram
mg/cm ³	milligrams per cubic centimetre
mg/kg bw/d	milligrams per kilogram bodyweight per day
min	minute
mL	millilitre
µg	microgram
µL	microlitre
(m)SDS	(material) Safety Data Sheet

NIOSH	National Institute for Occupational Safety and Health (US)
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOHSC	National Occupational Health and Safety Commission
NTP	National Toxicology Program (US)
OECD	Organisation for Economic Cooperation and Development
OEL	occupational exposure limit
PCBU	person conducting a business or undertaking
PEL	permissible exposure limit
PND	postnatal day
ppb	parts per billion
PPE	personal protective equipment
ppm	parts per million
REACH	Registration Evaluation Authorisation of Chemicals (ECHA)
SD	Sprague Dawley
SIAP	SIDS Initial Assessment Profile (OECD)
SIAR	SIDS Initial Assessment Report (OECD)
SIDS	Screening Information Data Set (OECD)
SMILES	simplified molecular-input line-entry system
SPIN	Substances in Preparations In the Nordic countries
STEL	short-term exposure limits
STV	short-term value
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons (The Poisons Standard**)
TCLo	lowest published toxic concentration
TEEL	temporary emergency exposure limits
TSCA	Toxic Substances Control Act (US EPA)
TG	test guideline
TGA	Therapeutic Goods Administration
TLV	threshold limit values
TWA	time weighted average
UN	United Nations
US	United States of America
US EPA	United States Environmental Protection Agency
WHS	Work, Health and Safety
wt	weight
w/w	weight per weight

Glossary

NICNAS uses the IPCS Risk Assessment Terminology (IPCS, 2004) glossary, which includes:

Part 1: IPCS/OECD Key Generic Terms used in Chemical Hazard/Risk Assessment; and

Part 2: IPCS Glossary of Key Exposure Assessment Terminology.

The IPCS Risk Assessment Terminology can be accessed at:

<http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf>

*Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009.

Third edition. Can be accessed at: http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

**The Poisons Standard (the SUSMP) can be accessed at: <http://www.tga.gov.au/industry/scheduling-poisons-standard.htm>

Sulfuric acid, dimethyl ester

CAS No: 77-78-1

Chemical Identity

Synonyms	Dimethyl sulfate Dimethyl monosulfate
Structural Formula	
Molecular Formula	C ₂ H ₆ O ₄ S
Molecular Weight (g/mol)	126.1
Appearance and Odour (where available)	Colourless, oily liquid with a faint onion-like odour at room temperature
SMILES	COS(=O)(=O)OC

Import, Manufacture and Use

Australian

No specific Australian use, import or manufacture information have been identified.

International

The following International uses have been identified via the European Union Registration Evaluation Authorisation of Chemicals (EU REACH) Dossiers, Galleria Chemica, the Substances and Preparations In the Nordic countries (SPIN) database, the Cosmetic Ingredients and Substances (CosIng) database, Canadian Assessments, the Department of Health and Human Services (DHHS), and through eChemPortal (the Organisation for Economic Cooperation and Development (OECD), the International Programme on Chemical Safety (INCHEM), the Aggregated Computer Toxicology Resource (ACToR) and the Hazardous Substances Data Bank (HSDB)):

The chemical has reported commercial use including:

- methylating agent for organic chemicals, such as amines, carbon acids, thiols and phenols for automobile fluid analysis;
- an agent for sulfonation, as a solvent, a stabiliser, or a catalyst for the production of other organic chemicals and used with boron compounds to stabilise liquid sulfur trioxide; and
- as a solvent, e.g. in the separation of mineral oils.

The chemical has reported site-limited use including:

- synthesis of photographic chemicals from alkylation reaction with nitrogen, oxygen or sulfur.

Restrictions

Australian

Work Health and Safety Regulations 2011 - Restricted Carcinogens: and

New South Wales Notifiable Carcinogens.

This chemical is listed in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) in Schedule 7 (Dangerous poison - Substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use).

International

EU Cosmetic Directive 76/768/EEC Annex II: List of Substances which must not form part of the Composition of Cosmetic Products.

Canada List of Prohibited and Restricted Cosmetic Ingredients (The Cosmetic Ingredient "Hotlist").

New Zealand Cosmetic Products Group Standard - Schedule 4: Components Cosmetic Products Must Not Contain.

ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

The International Air Transport Association (IATA) Dangerous Goods Regulations (UN No: 1595, Class 6.1) - Prohibited List Passenger and Cargo Aircraft (forbidden substances).

European Union (EU) Transport of Dangerous Goods by Road - Dangerous Goods List (UN No: 1595, Class 6.1).

US Consolidated List of Chemicals Subject to the Emergency Planning and Community Right-to-Know Act (EPCRA), and the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and Section 112 (r) of the Clean Air Act.

Existing Worker Health And Safety Controls

Hazard classification

The chemical is currently classified on the Hazardous Substances Information System (HSIS) (may be accessed at <http://hsis.safeworkaustralia.gov.au/HazardousSubstance>) with following:

T; R45 (Carcinogenicity Cat. 2)
Xn; R68 (Mutagenicity Cat. 3)
T+; R26 (Acute toxicity)
T; R25 (Acute toxicity)
C; R34 (Corrosive)
Xi; R43 (Sensitisation)

Exposure standards

Australian

The chemical has an 8 hour Time Weighted Average (TWA) exposure standard of 0.52 mg/m³ (0.1 ppm).

International

UK workplace long-term exposure limit of 0.26 mg/m³;
US National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Limit (REL) of 0.5 mg/m³ (0.1 ppm) TWA;
US Washington Permissible exposure limits of air contaminants: 0.1 ppm TWA and 0.3 ppm STEL
Canada - Saskatchewan Occupational Health and Safety Regulations - contamination Limits: 0.1 ppm for 8 hr and 0.3 ppm for 15 minutes;
US Department of Energy (US DOE) Temporary Emergency Exposure Limits (TEELs) 0.024 to 1.6 ppm;
Argentina (TWA), China (TWA) and Japan - Occupational Exposure Limit 0.52 mg/m³;
South Korea and Vietnam 0.5 mg/m³; and
Brazil occupational exposure limit 0.4 mg/m³.

Health Hazard Information

Acute Toxicity

Oral

The chemical is currently classified with the risk phrase 'Toxic if swallowed' (R25) in Australia. The data available support this classification.

Mouse median lethal dose (LD50) = 140 mg/kg bw (ChemIDPlus).

Rat LD50 = 205 mg/kg bw (ChemIDPlus).

Dermal

No data are available.

Inhalation

The chemical is currently classified with the risk phrase 'Very toxic by inhalation' (R26) in Australia. The data available support this classification.

Mouse LC50 = 280 mg/m³. The effects reported were respiratory depression and depressed activity (ChemIDPlus).

Rat LC50 = 45 mg/m³/4 h. The effects reported were haemorrhaging, laboured breathing (dyspnoea) and cyanosis (ChemIDPlus).

Observation in humans

Lowest published lethal concentration in humans is 97 ppm/10 minute (Galleria Chemica).

Corrosion / Irritation

Corrosivity

The chemical is currently classified with the risk phrase 'Causes burns' (R34) in Australia. The data available support this classification.

The chemical belongs to the alkylsulfuric group where liquids may cause a corrosive effect on the skin. Three eye irritation tests in rabbits reported the chemical as a severe eye irritant (Galleria Chemica).

Sensitisation

Skin sensitisation

The chemical is currently classified with the risk phrase 'May cause sensitisation by skin contact' (R43) in Australia. The data available support this classification.

Mouse LLNA gave positive results for skin sensitisation (Galleria Chemica).

Repeat Dose Toxicity

Oral

No data are available.

Dermal

No data are available.

Inhalation

There are two repeat dose inhalation studies in rats. One reported inflammation (sites not specified) with inhalation of 0.7 ppm intermittently for 2 weeks. The other reported decreased weight gain in rats with exposure to 1.5 ppm intermittently for 5 days (Galleria Chemica). Study details are not available.

Genotoxicity

The chemical is currently classified as a Category 3 Mutagenic Substance with the risk phrase 'Possible risk of irreversible effect' (R68) in Australia. The data available support this classification.

There are several in vitro genotoxicity studies showing DNA damage and/or mutations in bacteria, yeast or human cell lines and in vivo rodent studies (with oral, inhalation or intraperitoneal administration) showing genotoxicity (Galleria Chemica). There are no in vitro studies conducted using germ cells.

Carcinogenicity

The chemical is currently classified as a Category 2 Carcinogen with the risk phrase 'May cause cancer' (R45) in Australia. The data available support this classification.

The chemical is listed on the European Union (EU) Annex I to Directive 67/548/EEC on Classification and Labelling of Dangerous Substances (updated by ATP: 31) - Carcinogenic Substances (Galleria Chemica).

The IARC has classified dimethyl sulfate as '*Probably carcinogenic to humans*' (Group 2A), based on inadequate evidence for the carcinogenicity in humans, but sufficient evidence for the carcinogenicity in experimental animals.

There are three studies reporting tumors in rats with inhalation of 17 mg/m³ intermittently for 19 weeks, intravenous exposure to 20 mg/kg and subcutaneous exposure to 50 mg/kg (Galleria Chemica).

Reproductive and developmental toxicity

Intravenous exposure to 100 mg/kg on day 15 after conception resulted in foetal deaths in rats (Galleria Chemica). No other information on reproductive/developmental toxicity is available.

Risk Characterisation

Critical Health Effects

The chemical is carcinogenic, mutagenic, corrosive and a skin sensitiser. It is very toxic by inhalation and toxic by ingestion.

Public Risk Characterisation

No public health risks are expected as the chemical is only expected to be used as a process intermediate in manufacturing facilities.

Occupational Risk Characterisation

In Australia, the chemical is a restricted carcinogen under Work health and Safety (WHS) Regulations (2011). A person conducting a business, or undertaking at a workplace, must apply in writing to the regulator for authorisation to use, handle or store a restricted carcinogen at the workplace.

It is also listed on Schedule 7 of the SUSMP (requiring a label heading, 'Dangerous Poison'). Schedule 7 substances should be available only to specialised or authorised users who have skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply.

The chemical is classified as a hazardous substance for workplace use (on HSIS) and is a dangerous good under transport regulations.

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

NICNAS Recommendation

This chemical is a restricted carcinogen in Australia under the WHS Regulations 2011. There are specific obligations to suppliers of this chemical and obligations to persons conducting business or undertaking (PCBU) to protect the safety of workers using/handling/storing the chemical (Work Health and Safety Regulations 2011).

The information about the status of the chemical as a restricted carcinogen under the WHS 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.

Regulatory Control

Public Health

The chemical is on Schedule 7 of the SUSMP and therefore, not expected to be present in consumer products. As it is only expected to be used as an intermediate in the manufacture of other chemicals, the existing regulatory controls are adequate.

Work Health and Safety

The existing regulatory controls are adequate to protect workers from risks during handling. The chemical is recommended for classification and labelling under the current Approved Criteria and the adopted Globally Harmonised System (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

	<i>Approved Criteria (HSIS)^a</i>	<i>GHS Classification</i>
Acute Toxicity	Toxic if swallowed (T; R25)* Very toxic by inhalation (T+; R26)*	Toxic if swallowed - Cat. 3 (H301) Fatal if inhaled - Cat. 1 (H330)
Irritation / Corrosivity	Causes burns (C; R34)*	Causes severe skin burns and eye damage - Cat. 1 (H314)
Sensitisation	May cause sensitisation by skin contact (Xi; R43)*	May cause an allergic skin reaction - Cat. 1 (H317)
Genotoxicity	Muta. Cat 3 - Possible risk of irreversible effects (Xn; R68)*	Suspected of causing genetic defects - Cat. 2
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)].

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

Advice for industry

Work Health and Safety (WHS) legislation in each Australian state and territory imposes obligations on manufacturers and importers of hazardous chemicals to ensure that the chemicals are correctly classified, correctly labelled and (material) safety data sheets ((m)SDS) are prepared for those chemicals. These include:

- the (m)SDS for the chemical, or products and mixtures containing the chemical, must contain accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of a chemical, as well as instructions on the safe storage, handling, use and disposal of the chemical (a review of physical hazards of the chemical has not been undertaken as part of this assessment); and
- a copy of the (m)SDS must be easily accessible to employees.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals to meet duties under the WHS Regulations are provided in the *Preparation of Safety Data Sheets for Hazardous*

Chemicals—Code of Practice and *Labelling of Workplace Hazardous Chemicals—Code of Practice*, respectively.

To comply with the WHS legislation, a person conducting a business or undertaking (PCBU) at a workplace must manage risks arising from storage, handling and use of a hazardous chemical. Other duties may apply to a PCBU involved in the storage, handling and use of hazardous chemicals at a workplace. Refer to the WHS legislation in the relevant jurisdiction for further information.

Guidance on managing risks from hazardous chemicals are provided in the *Managing Risks of Hazardous Chemicals in the Workplace—Code of Practice*.

It is recommended that a PCBU should ensure that:

- equipment be designed, constructed, and operated so that, the person handling the chemical does not come into contact with the chemical and is not exposed to a concentration of the chemical that is greater than the workplace exposure standard for the chemical;
- equipment used to handle the chemical retains the chemical, without leakage, at all temperatures and pressures for which the equipment is intended to be used and dispenses or applies the substance, without leakage, at a rate and in a manner for which the equipment is designed.

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