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

Methanol

CAS Registry Number: 67-56-1

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

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

Methanol

CAS No: 67-56-1

Chemical Identity

Synonyms	Methyl alcohol Methyl hydroxide Monohydroxymethane Carbinol; Methylol Wood alcohol
Structural Formula	
Molecular Formula	CH4O
Molecular Weight (g/mol)	32.04
Appearance and Odour (where available)	Clear colourless liquid
SMILES	CO

Import, Manufacture and Use

Australian

The chemical is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported introduction volume between 10000 and 99999 tonnes (NICNAS, 2006).

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information.

The chemical has reported domestic use including:

- as a solvent; and
- in adhesives as a binding agent.

The chemical has reported commercial use including:

- in fuels as a petrol additive.

The chemical has reported site-limited use including:

- in the manufacture of other chemicals; and
- as an industrial solvent.

International

The following International uses have been identified via European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers; the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR); Galleria Chemica; Substances in Preparations In the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary and eChemPortal: OECD High Production Volume chemical program—OECD HPV, the US Environmental Protection Agency's Aggregated Computer Toxicology Resource—ACToR, and the US National Library of Medicine's Hazardous Substances Data Bank—HSDB.

The chemical has reported cosmetic use including as:
- an ingredient in fragrances; and
- a solvent.

The chemical has reported domestic use including in:
- cleaning agents and de-icers (spray products);
- paint strippers, aerosol and non-aerosol spray paints, sealers and adhesives;
- fuels (indoors: domestic hobby, model engines, fuel cells, fondue sets); and
- fuels (outdoors: gasoline additive).

The chemical has reported commercial use including:
- in manufacturing bulk, large scale chemicals including petroleum products;
- in leather tanning, dye, finishing, impregnation and care products;
- in washing and cleaning products including solvent based products;
- as an ingredient of gasoline;
- in polymer preparations and compounds; and
- as an antifreeze for automotive radiators, diesel oil and air brakes.

The chemical has reported site-limited use including:
- in manufacturing other chemicals;
- as a laboratory reagent in industrial settings;
- in cleaning agents;
- in wastewater treatment processes;
- as a corrosion and scale inhibitor in water-based fracking fluids;
- as an industrial and intermediate pharmaceutical solvent, process aid or intermediate in manufacturing pharmaceuticals;
- in industrial offshore use of chemicals in oil & gas production;
- as a fuel in industrial/professional settings;
- to denature ethanol; and
- as an octane booster in petrol.

Restrictions

Australian

The chemical is listed in the Poisons Standard (the Australian Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)):
- Schedule 5: Methanol (excluding its derivatives) in preparations containing 10 per cent or less of methanol except in preparations containing 2 per cent or less of methanol;
- Schedule 6: Methanol (excluding its derivatives) except: (a) when included in Schedule 5; or (b) in preparations containing 2 per cent or less of methanol.

The Australia New Zealand Food Standards Code's list of contaminants and natural toxicants has maximum levels specified for methanol under non-metal contaminants in food:
- 3 g of methanol per litre of ethanol in red wine, white wine and fortified wine;
- 0.4 g of methanol per litre of ethanol in whisky, rum, gin and vodka; and
- 8 g of methanol per litre of ethanol in other spirits, fruit wine, vegetable wine and mead.

Australia New Zealand Food Standards Code has a maximum permitted level of 5 mg/kg of methanol in all food when it is used as a processing aid (listed under permitted extraction solvents).

International

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: Restriction: Maximum authorized concentration in the finished cosmetic product is 5% calculated as a percentage of ethanol and isopropyl aclohol.

New Zealand Cosmetic Products Group Standard - Schedule 5: Components Cosmetic Products May Contain With Restrictions - Maximum authorised concentration in the finished cosmetic product is 5% calculated as a percentage of ethanol and isopropyl alcohol.

Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex III Part 1: List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down: Restrictions - Maximum authorised concentration in the finished cosmetic product is 5% calculated as a percentage of ethanol and isopropyl alcohol.

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

Existing Worker 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):
T; R23/24/25 (acute toxicity)
T; R39/23/24/25 (irreversible effects from acute exposure)

Exposure standards

Australian

The chemical has an exposure standard of 262 mg/m³ (200 ppm) Time Weighted Average (TWA) and 328 mg/m³ (250 ppm) Short-Term Exposure Limits (STEL) (Safe Work Australia).

International

The following were identified (Galleria Chemica):
250-270 mg/m³ (200 ppm) TWA in USA, Canada, Denmark, United Kingdom, Germany, France, Estonia, Greece, Hungary, South Africa, Spain, Singapore, Taiwan, Sweden, Malta, Malaysia, Latvia, Japan, Indonesia, India, Iceland, Egypt, Ireland, Mexico, Philippines and Switzerland;
250-350 mg/m³ (250-328 ppm) STEL in USA, Canada, United Kingdom, Greece, South Africa, Singapore, Sweden, India, Egypt and Mexico;
50 mg/m³ TWA in Bulgaria;
100 mg/m³ TWA and 300 mg/m³ STEL in Poland;
133 mg/m³ TWA in Netherlands;
25 mg/m³ TWA and 50 mg/m³ STEL in China;
1300 mg/m³ (1000 ppm) STEL in France; and
1040 mg/m³ STEL in Hungary and Switzerland.

Health Hazard Information

Toxicokinetics

The chemical is readily absorbed by inhalation, ingestion and dermal contact and distributes rapidly throughout the body (organs and tissues). Metabolism in humans, rodents, and monkeys contributes up to 98 % of the clearance, with more than 90 % of the administered dose exhaled as carbon dioxide. Renal and pulmonary excretion contributes only about 2–3 %. The metabolism and toxicokinetics of methanol varies by species and dose. In humans, the half-life is approximately 2.5–3 h at doses lower than 100 mg/kg bw. At higher doses, the half life can be 24 h or more (OECD, 2004).

Studies in humans and monkeys exposed via inhalation to concentrations of 0.26-2.6 mg methanol/L for six to eight hours showed that the chemical reaches approximately 50 mg/L in the blood. Rats had methanol blood levels of approximately 80 mg/L when exposed to 2.6 mg/L, and the level in mice was 400 mg/L. At a higher inhalation dose (6.5 mg/L), humans showed the lowest blood methanol level (140 mg/L), followed by monkeys, rats and mice, with the level in mice being more than 10 times higher than in humans (OECD, 2004).

Species differences in methanol metabolism were reported (NTP, 2003): 'In primates, including humans, methanol is converted to formaldehyde by the enzyme alcohol dehydrogenase. In rodents, this conversion is made by catalase. Metabolism of methanol to formaldehyde and then to formate occurs at similar rates in rodents and conversion of formate to carbon dioxide in primates proceeds at half the rate observed in rats. This indicates that primates accumulate formate at lower doses of methanol than some other species. Studies indicate that formate is the methanol metabolite responsible for methanol toxicity resulting in systemic clinical signs, metabolic acidosis, and ophthalmic effects in primates. Kinetic studies in methanol poisoned patients showed that the half-life of formate in blood is 3.4 hours (Kerns et al., 2002)'.

The metabolism of methanol occurs mainly in the liver in mammals. In humans and monkeys, the conversion to formaldehyde is mediated by alcohol dehydrogenase, and in rodents occurs mainly via a catalase peroxidase pathway, which is rate limiting. Therefore, methanol accumulates in the blood at high doses in rodents. In monkeys, the conversion of formate to carbon dioxide by the formyl-tetrahydrofolate synthetase is rate limiting, leading to a disproportionate increase of formate in the blood and sensitive target tissues such as the central nervous system and retina (OECD, 2004).

The OECD (2004) report states: 'The critical methanol dose that saturates the folate pathway in humans is estimated to be 200 mg/kg bw. Based on data produced in studies of monkeys, metabolic saturation in humans is also less likely to happen during inhalation if the amount is divided over a prolonged time and not incorporated as a bolus'.

Acute Toxicity

Oral

The chemical is classified with the risk phrase 'Toxic if swallowed' (R25) in Australia (Safe Work Australia–HSIS). The chemical was reported to cause low acute oral toxicity in animals (LD50 in rats > 2,000 mg/kg bw). However, human data indicate acute oral toxicity at comparatively lower doses of 300-1000 mg/kg bw (IPCS/WHO, 1997). Therefore, the existing hazard classification is supported.

Oral LD50 (mg/kg bw) = 7300 (mouse), 5628 (rat), 14200 (rabbit), 7000 (monkey) (ChemIDPlus).
Oral LDLo = 7500 mg/kg bw (dog) and 143 - 428 mg/kg bw (humans) (ChemIDPlus).

Rodents, rabbits and dogs suffered from ataxia, narcosis and coma after high methanol doses. However, these animals do not exhibit the acidosis and ophthalmologic changes typically seen in humans at high lethal and sublethal doses. In addition, studies in Rhesus monkeys, 1000-2000 mg/kg bw did not lead to mortality, while animals receiving 3000-8000 mg/kg bw died within two days. Treated animals showed acidosis, and some exhibited semi-coma and ophthalmologic changes (OECD, 2004).

Dermal

The chemical is classified with the risk phrase 'Toxic in contact with skin' (R24) in Australia (Safe Work Australia–HSIS). The rat and rabbit LD50 values available do not support this classification. However, the limited data available on monkeys indicate that the chemical is toxic via the dermal route, and the oral data indicate that humans have higher susceptibility when compared with monkeys. Therefore, the existing hazard classification is not amended.

The LD50 in rabbits ranges from 15800 to 20000 mg/kg bw (OECD, 2004).
The LD50 in rats is >45000 mg/kg bw (OECD, 2004).

In Rhesus monkeys, four daily doses of 400 mg/kg bw caused sickness within 24 hours, and eventually death (OECD, 2004).

Inhalation

The chemical is classified with the risk phrase 'Toxic by inhalation' (R23) in Australia (Safe Work Australia–HSIS). The animal data available do not support this classification. However, data available on humans indicate severe visual disturbances at methanol air levels of about 1.5 mg/L or more (OECD, 2004). The susceptibility of humans to methanol toxicity is higher than that of rodents as evidenced in the oral data. Therefore, the existing hazard classification is not amended.

Rat inhalation LC50 = 67000 mL/m³/6 h (87.5 mg/L) and 98000 mL/m³/4 h (128.2 mg/L) with toxic effects (aqueous secretion of eyes and nose, laboured breathing, staggering, apathy, and narcosis) (OECD, 2004).

Mouse inhalation LC50 = approximately 79 mg/L (2.25 h) with narcotic doses of 40 and 55 mg/L after 2.2 and 7 hours respectively (OECD, 2004).

Cat inhalation LC50 = 26-48 mg/L/6 h and 85.4 mg/L/4.5 h (OECD, 2004).

Monkey inhalation LC50 = 13 mg/L (18 h) and 52 mg/L (1-4 h). Blindness associated with optic atrophy and eventual recovery from it was reported (OECD, 2004).

Observation in humans

The chemical is currently classified with the risk phrase 'Toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed' (T; R39/23/24/25). The minimum acute lethal dose in humans (300-1000 mg/kg bw) and the serious sublethal effects reported, support this classification.

A wide range of human toxic/lethal values have been reported:

- Minimal acute lethal dose in humans = 300-1000 mg/kg bw (OECD, 2004).

- Human oral LDLo (Lowest Lethal Dose) = 143-428 mg/kg bw with toxic effects such as headache, nausea or vomiting and dyspnoea and other changes (ChemIDplus).

- Human (male) oral LDLo = 6422 mg/kg bw. The toxic effects include haemorrhage, thrombosis, nausea or vomiting, dyspnoea and other changes (ChemIDplus).

- Human (male) oral TDLo (Lowest Toxic Dose) = 3.571 mL/kg. Visual field changes and dyspnoea were reported at this dose. At 9.45 mL/kg, mydriasis (pupillary dilation) was reported (ChemIDplus).

- Human (male) oral TDLo = 3429 mg/kg. Visual field changes were reported at this level. At 4000 mg/kg (female), visual field changes, nausea or vomiting, and dyspnoea were reported (ChemIDPlus).

The OECD (2004) report indicates that ingestion is the most frequent route of human poisoning, but dermal contact and inhalation are equally effective in producing acute toxic symptoms. The report further states that a blood level of ≥500 mg/L requires treatment by haemodialysis and that this is equivalent to adult ingestion of 316 mg (0.4 mL). The acute lethal dose in humans is in the range of 300-1000 mg/kg bw, with coma, seizures and prolonged acidosis being the initial observed symptoms.

The OECD (2004) report further states: 'Acute methanol intoxication (including acidosis and visual effects) evolves in a well-defined pattern. First, a mild depression of the CNS occurs and is followed by an asymptomatic latent period commonly lasting 12 to 14 hours. Clinical symptoms include headache, dizziness, nausea, and vomiting, abdominal pain, and laboured, periodic breathing (Kussmaul breathing) and may progress to coma and death from respiratory failure. Methanol exposure results in ocular effects

ranging from mild photophobia, misty or blurred vision to markedly reduced visual acuity and total blindness. Severe visual disturbances have been reported in workers who experienced methanol air levels of about 1.5 mg/L (1200 ml/m^3) or more.'

Corrosion / Irritation

Skin irritation

The chemical is not a skin irritant.

The irritation potential of undiluted methanol (dose not specified) in rabbits was examined under occlusive conditions after exposure intervals of 1, 5, and 15 minutes and 20 hours. According to Draize scoring, no signs of skin irritation were observed at 24 hours or on day eight after treatment, for any of the exposure time periods (OECD, 2004).

Eye irritation

The chemical is a slight eye irritant in rabbits. Eye irritation effects were not sufficient to warrant a hazard classification.

One hour after instillation of 0.05 mL of undiluted methanol into the eyes of two rabbits, slight erythema and corneal opacity, as well as moderate oedema associated with secretion, were observed. After 24 hours, the effects were assessed as mild, and after eight days the animals had no symptoms (OECD, 2004).

In six rabbits, mild to moderate conjunctivitis and oedema as well as mild iritis were produced after instillation of 0.1 mL undiluted methanol into the eyes. Average scores after 24, 48, and 72 h were approximately two for conjunctival redness and less than one for other effects. Primary irritation subsided although redness of the conjunctivae persisted after 72 hours (OECD, 2004).

Respiratory irritation

Limited information is available. However, as saturated atmospheric levels of methanol vapours are unlikely to occur, a hazard classification is not warranted.

Exposure (time not specified) to an atmosphere saturated by methanol vapours at 20 °C produced severe irritation of mucous membranes and milky corneal opacity in rats. The exposure led to mortality of all animals after eight hours (OECD, 2004).

Sensitisation

Skin sensitisation

The chemical is not a skin sensitiser.

A guinea pig maximisation assay gave no evidence of contact sensitisation in 10 female animals after induction and challenge with a 50 % aqueous methanol solution (0.1 mL). In another study using 24 female guinea pigs (two tests with 12 animals each), 1/12 (test 1) and 2/12 (test 2) animals exhibited a slight skin response (score 1) after 24 and 48 hours. Therefore, the chemical is not considered to be a skin sensitiser in guinea pigs (OECD, 2004).

Repeat Dose Toxicity

Oral

Considering the no observed adverse effect level (NOAEL) available from a 90-day rat study (500 mg/kg bw/day), the chemical is not considered to cause serious damage to health by repeated oral exposure.

In a 90-day oral gavage study, Sprague Dawley (SD) rats (n = 30) were administered the chemical at 100, 500 or 2500 mg/kg bw/day. The reported effects were increased liver enzyme levels and reduced brain weights at the highest dose. No effects at other doses were reported. The NOAEL was 500 mg/kg bw/day (OECD, 2004). However, the acute oral data indicate that humans are more sensitive to methanol toxicity than rodents.

No data are available on repeated oral exposure in humans. To infer safe levels for repeated oral exposure, the Australia New Zealand Food Standards Code's list of contaminants and natural toxicants has maximum levels specified for methanol under 'non-metal contaminants in food'. The Australia New Zealand Food Standards Code also has a maximum permitted level of 5 mg/kg of methanol in all foods when it is used as a processing aid (under permitted extraction solvents).

Dermal

No data are available.

Inhalation

Some histological effects were reported in monkeys in the cerebral area after repeated exposure to doses of up to 1.3 mg/L with up to 29 months' exposure. Although a lowest observed adverse effect level (LOAEL) of 0.013 mg/L was established in this study, the effects were generally mild and the statistical significance of these effects were not verified (OECD, 2004). The limited, qualitative information available does not warrant a hazard classification.

In an inhalation study, *Macaca fascicularis* monkeys were exposed (whole body) to the chemical at 0.013, 0.13 or 1.3 mg/L (10, 100 or 1000 mL/m³ respectively), 21 h/d, 7 days per week for 7, 19 or 29 months. Several general clinical signs as well as degenerative effects in the brain (at 0.13 and 1.3 mg/L), slight peripheral nerve damage (at 0.13 and 1.3 mg/L), very slight degeneration of the optic nerve, increased fat granules in the liver (at all doses) with slight fibrosis (at 1.3 mg/L), and sudan positive granules in the kidneys (at 0.13 and 1.3 mg/L) were observed. Some additional effects (hyalinisation of glomeruli) were also observed at 1.3 mg/L. A slight myocardial disorder (at 0.13 and 1.3 mg/L), localised effects in the trachea and possible slight fibrosis in the lungs (dose levels not reported) were also reported. Although the statistical significance of the effects cannot be verified from the study report, the number of effects and systems affected indicate a relationship with methanol exposure. A LOAEL of 0.013 mg/L was determined based on the qualitative effects (OECD, 2004).

Mice (B6C3F1) and rats (Fischer 344) were exposed (whole body) to the chemical at 0.013, 0.13 or 1.3 mg/L (10, 100 or 1000 mL/m³ respectively) for 20 h/d for 12 months. Slight changes in clinical signs, body and organ weights, and some changes in histopathology were observed in mice (details not available). In rats, slight changes in body weight and organ weights were observed at the highest dose. A no observed effect level (NOEL) of 0.13 mg/L was established for both species, as adverse effects were not explicitly reported (OECD, 2004).

In a 28-day study, there was no evidence of adverse effects in SD rats exposed to methanol up to 6.5 mg/L (5000 mL/m³) for 6 h/d over 28 days, except local nasal irritation, ocular discharge and increased relative spleen weights, which were observed only at 2.7 mg/L dose. The NOAEL was 6.5 mg/L and the estimated blood methanol level was about 250 mg/L (OECD, 2004).

Observation in humans

In male and female workers exposed to methanol (0.3-7.8 years), highly exposed workers often complained of blurred vision, headache and nasal irritation during or after work. Workers exposed to methanol at 0.12-3.6 mg/L showed retarded pupil reflex and/or mild mydriasis, but no permanent eye damage occurred (OECD, 2004).

A study published by the National Institute for Occupational Safety and Health (NIOSH) stated that a

group of workers exposed to 0.48-4.0 mg/L (99 % methanol) had increased symptoms relevant to methanol toxicity such as headache, dizziness, and eye irritation compared with a non-exposed control group at the same workplace (OECD, 2004).

Genotoxicity

Considering all available data, the chemical is not considered genotoxic.

Numerous in vitro assays (including seven Ames assays, four micronucleus/cytogenetic assays, a mammalian gene mutation assay, a yeast gene mutation assay, a mouse lymphoma test, three cell transformation assays, and a DNA damage and repair assay) were conducted using methanol (OECD, 2004). The majority of these assays are negative, with the exception of positive results in the mouse lymphoma test and a mitotic recombination assay in *Aspergillus*. Ambiguous results were observed in an Ames assay with *Salmonella typhimurium* strain TA102 and in a DNA damage and repair assay. Only limited details were available for the mouse lymphoma test (OECD, 2004).

Of the 11 in vivo assays (micronucleus and cytogenicity assays and one *Drosophila* sex linked recessive lethal assay), all gave negative results except one cytogenetic assay, which was positive for aneuploidy, sister chromatid exchange and micronuclei (OECD, 2004).

Carcinogenicity

The chemical is not likely to be a carcinogen. There was no evidence of carcinogenic potential in rats and mice that inhaled the chemical at concentrations up to 1.3 mg/L for 24 and 18 months, respectively.

Methanol was tested in two long term inhalation studies (whole body exposure for 24 months in rats and 18 months in mice for 20 and 19 h/d, respectively). Tumour frequencies showed no statistically significant differences between treatment groups and controls in either rats or mice. The biological importance of a non statistically significant increase in the incidence of the phaeochromocytomas (vascular tumours of the adrenal gland) in the high dose, aged female rats is considered to be low (OECD, 2004).

Continuous inhalation exposure of monkeys to the chemical at 0.013 mg/L for 29 months and at 0.13 and 1.3 mg/L for ≥7 months, led to an increased diffuse hyperplastic responsiveness of the astroglia (tissue consisting of large stellate neuroglial cells) in some parts of the cerebral white substance, without histological signs of degeneration. This effect was absent in recovery groups after one and six months respectively. The chemical related proliferative effects on the astroglia cells observed in monkeys were transient and not associated with cellular neoplastic transformation. The weight of evidence suggests that methanol is not carcinogenic (OECD, 2004).

Reproductive and developmental toxicity

Based on the data available, the chemical is not considered to have reproductive or developmental toxicity in humans.

The data available in rodent studies indicate the chemical has developmental toxicity effects. The NTP report (2003) stated that rodent data on reproductive and developmental toxicity are relevant for humans despite the known differences in methanol metabolism between the two species. However, rodents are adequate models for humans only at levels where formate does not accumulate. In the developmental toxicity studies available, the blood methanol levels associated with serious developmental effects in rodents are in the range associated with formate accumulation (1000-2000 mg methanol per litre of blood) (OECD, 2004). Therefore, despite the developmental effects observed in rodent studies, methanol is not considered to have developmental toxicity in humans.

No impairment of fertility or reproductive performance was reported in male and female rats exposed to the chemical, unless at very high doses. Male mice had morphological anomalies in spermatozoa after repeated oral dosing at 1000 mg/kg bw/day (blood level >500-1000 mg/L in mice) (OECD, 2004).

Several inhalation studies in rats observed a variety of effects in the offspring due to prenatal and/or postnatal dosing:

- A two-generation reproductive study in rats (exposure to doses of 0.013, 0.13 or 1.3 mg/L for 19-20 h/d, 7 d/week during pre-mating, mating, gestation, lactation), showed decreased brain weights in the first (F1) and second (F2) generation offspring. The developmental NOAEL was 0.13 mg/L. The study was of limited value due to absence of quantitative data and statistical analysis (OECD, 2004);
- A developmental study in rats (whole body inhalation exposure on gestation days (GD) 1 to 19 at doses of 6.5 or 13 mg/L, or GD 7-15 at 26 mg/L), showed malformations and foetal weight changes resulting in a developmental NOAEL of 6.5 mg/L (corresponds to maternal blood level of 1000 to 2170 mg/L). The maternal NOAEL was 13 mg/L based on slight, unsteady gait at this dose (OECD, 2004);
- In another developmental study in rats (whole-body inhalation eposure on GD 7-17 for 23 h/d), malformations, increased foetal resorptions, and decreased numbers of live foetuses were observed, resulting in a developmental NOAEL of 1.3 mg/L (the corresponding maternal blood methanol level is ~ 100 mg/L) (OECD, 2004).
- An inhalation study in mice (exposed for 7 h/d on GD 6-15 at doses of 1.3, 2.6, 6.5, 9.75, 13 or 19.5 mg/L), resulted in developmental effects including increased extra cervical ribs or ossifications at $\geq$2.6 mg/L, malformations (such as cleft palate) at 6.5 mg/L, fully resorbed foetuses at 13 mg/L, and dose related significant decrease in the number of live pups per litter at $\geq$9.75 mg/L. This study established a developmental NOAEL of 1.3 mg/L based on the cervical rib defect. There was no maternal toxicity (OECD, 2004).

Oral studies in mice with a single treatment on day seven of gestation resulted in various malformations in foetuses at 4000 mg/kg bw and above. A NOAEL could not be established due to the very high doses used in the study (OECD, 2004).

Blood methanol concentrations associated with serious teratogenic effects and reproductive toxicity are in the range associated with formate accumulation, which is likely to result in metabolic acidosis, and visual and clinical effects in humans (NTP, 2003). Other effects (such as subtle, not yet definitive neurological effects observed in primates) may be exhibited at lower inhalation doses and lower methanol blood levels (OECD, 2004).

The limited data available in humans do not show an association of reproductive and developmental toxicity with methanol (NTP, 2003). Based on the studies reviewed by the NTP (2003), it concluded that there is evidence to suggest that women with low folate levels may be more susceptible to the adverse developmental effects of methanol, but more information is necessary to clarify this issue.

Risk Characterisation

Critical Health Effects

The main critical effects to human health are acute toxicity from inhalation, in contact with skin and if swallowed, and possible irreversible effects from acute exposure.

Public Risk Characterisation

The chemical is reported to be used in cosmetic/domestic products. Characterised hazards have the potential to pose an unreasonable risk under the uses identified. However, products/mixtures containing over 5 % or 2 % of the chemical are scheduled (on SUSMP) with product labelling requirements. There are concentration limits overseas for use of this chemical in cosmetics. Public risks could be further mitigated by revision of the concentration limits.

Occupational Risk Characterisation

Given the critical health effects, the risk to workers from this chemical is considered high if adequate control measures to minimise occupational exposure to the chemical are not implemented. The chemical

should be appropriately classified and labelled to ensure that a person conducting a business, or an employee at a workplace, has adequate information to determine appropriate controls.

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 domestic products be managed through changes to poisons scheduling.

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

The use of this chemical in domestic or cosmetic products is currently controlled by scheduling. The chemical is listed in the SUSMP under Schedule 5 or 6 based on its concentration in products/mixtures:
1) The chemical in preparations for domestic use is in Schedule 5 of the SUSMP if the concentration of methanol is over 2 % and equal to or less than 5 % (packaging with signal heading 'Warning'); and
2) Preparations containing over 5 % methanol is in Schedule 6 (packaging with signal heading 'Poison').
Preparations containing 2 % or less methanol for domestic or cosmetic use are not scheduled.

For the purpose of revising concentration limits for scheduling, the delegate may wish to consider the form of restriction which exists in the EU Cosmetic Directive—'Maximum authorised concentration in the finished cosmetic product is 5% calculated as a percentage of ethanol and isopropyl alcohol'.

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 hazards and environmental hazards.

	Approved Criteria (HSIS)[a]	*GHS Classification*
Acute Toxicity	Toxic if swallowed (T; R25)* Toxic in contact with skin (T; R24)* Danger of very serious irreversible effects (T; R39)* Toxic by inhalation (T; R23)*	Toxic if swallowed - Cat. 3 (H301) Toxic in contact with skin - Cat. 3 (H311) Causes damage to organs - Specific target organ tox, single exp Cat. 1 (H370) Toxic if inhaled - Cat. 3 (H331)

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

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

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal 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 may 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;
- 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 assist with meeting 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.

References

ChemIDPlus Advanced. Methanol (67-56-1). Accessed November 2012 at http://chem.sis.nlm.nih.gov/chemidplus/

Cosmetics Directive (CosIng). Methanol (67-56-1). Accessed November 2012 at http://ec.europa.eu/consumers/cosmetics/cosing/

eChemPortal. Accessed November 2012 at http://www.echemportal.org/echemportal/substancesearch/substancesearchlink.action

Galleria Chemica. Accessed November 2012 at http://jr.chemwatch.net/galleria/

Kerns et al. 2002. Formate kinetics in methanol poisoning. Clinical Toxicology 40:137-143. (Cited in the National Toxicology Program (NTP) report 2003).

National Toxicology Program (NTP) 2003. Monograph on the potential human reproductive and developmental effects of methanol. Center for the evaluation of risks to human reproduction (CERHR), US Department of Health and Human services. September 2003.

NICNAS 2006. Australian High Volume Industrial Chemicals List (AHVICL). Accessed November 2012 at http://www.nicnas.gov.au/Industry/Australian_High_Volume_Industrial_Chemicals/NICNAS_AHVICL_2006_PDF.pdf

NOHSC 2004. Approved Criteria for Classifying Hazardous Substances, 3rd edition [NOHSC:1008(2004)]. National Occupational Health and Safety Commission, Canberra, AusInfo

OECD 2004. SIDS (Screening Information Dataset) Initial Assessment Report (SIAR) on Methanol (67-56-1). Accessed November 2012 at http://webnet.oecd.org/hpv/ui/SIDS_Details.aspx?id=39b5d34a-2f5d-4d53-b000-e497b3a3ee89

Personal Care Product Council, International Nomenclature of Cosmetic Ingredients (INCI). Accessed November 2012 at http://www.ctfa-gov.org/jsp/gov/GovHomePage.jsp

REACH Dossier. Methanol (67-56-1). Accessed November 2012 at http://www.echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Safe Work Australia (SWA). Hazardous Substances Information system (HSIS). Accessed November 2012 at http://hsis.safeworkaustralia.gov.au/HazardousSubstance