



Australian Government
Department of Health and Ageing
NICNAS

INVENTORY MULTI-TIERED ASSESSMENT AND PRIORITISATION (IMAP)



HUMAN HEALTH TIER II ASSESSMENT FOR Methylenediphenyl diisocyanates

Chemical name in AICS	CAS Number
Benzene, 1,1'-methylenebis[4-isocyanato-	101-68-8
Benzene, 1,1'-methylenebis[2-isocyanato-	2536-05-2
Benzene, 1-isocyanato-2-[(4-isocyanatophenyl)methyl]-	5873-54-1
Isocyanic acid, polymethylenepolyphenylene ester	9016-87-9
1,3-Diazetidone-2,4-dione, 1,3-bis[4-[(4-isocyanatophenyl)methyl]phenyl]-	17589-24-1
Benzene, 1,1'-methylenebis[4-isocyanato-, homopolymer	25686-28-6
Benzene, 1,1'-methylenebis[isocyanato-	26447-40-5
1,3-Diazetidone-2-one, 1,3-bis[4-[(4-isocyanatophenyl)methyl]phenyl]-4-[[4-[(4-isocyanatophenyl)methyl]phenyl]imino]-	31107-36-5
Benzene, 1,1'-methylenebis[isocyanato-, homopolymer	39310-05-9

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 three 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

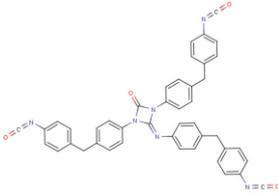
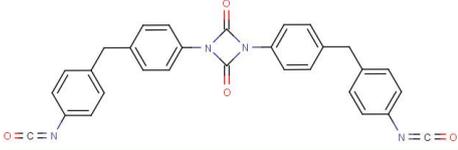
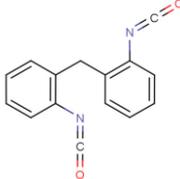
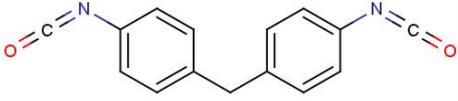
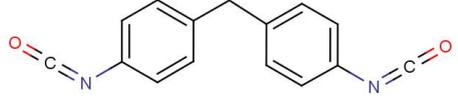
Part 2: IPCS Glossary of Key Exposure Assessment Terminology.

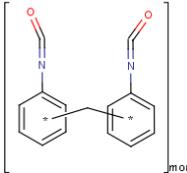
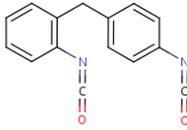
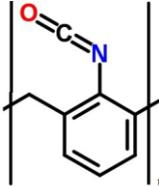
The IPCS Risk Assessment Terminology can be accessed at:

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

*Globally Harmonised 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>

Chemical Name in AICS (Including Synonyms)	CAS Number	Structural Formula	Molecular Formula	Weight (g/mol)
1,3-Diazetid-2-one, 1,3-bis[4-[(4-isocyanatophenyl)methyl]phenyl]-4-[[4-[(4-isocyanatophenyl)methyl]phenyl]imino]- 1,3-Di[4-[(p-isocyanatophenyl)methyl 1,3-Di(4-((p-Isocyanatophenyl)methyl)phenyl)-4-((4-((p-isocyanatophenyl)methyl)phenyl)imino)-2-uretidinone 4,4'-MDI trimer	31107-36-5		C44H30N6O4	706.76
1,3-Diazetidine-2,4-dione, 1,3-bis[4-[(4-isocyanatophenyl)methyl]phenyl]- 1,3-Bis(4-((4-isocyanatophenyl)methyl)phenyl)-1,3-diazetidine-2,4-dione 2,4-Dioxo-1,3-diazetidine-1,3-diylbis(p-phenylenemethylene-p-phenylene) diisocyanate 4,4'-MDI dimer	17589-24-1		C30H20N4O4	500.51
Benzene, 1,1'-methylenebis[2-isocyanato- 2536-05-2 1,1-Methylenebis(2-isocyanatobenzene) 2,2'-Methylenediphenyl diisocyanate Diphenylmethane-2,2'-diisocyanate Benzene, 1,1'-methylenebis(2-isocyanato- 2,2'-MDI	2536-05-2		C15H10N2O2	250.26
Benzene, 1,1'-methylenebis[4-isocyanato- 101-68-8 4,4-Diisocyanatodiphenylmethane 4,4-Diphenylmethane diisocyanate 4,4-Methylenediphenyl diisocyanate Diphenylmethane-4,4'-diisocyanate 4,4'-MDI	101-68-8		C15H10N2O2	250.26
Benzene, 1,1'-methylenebis[4-isocyanato- 25686-28-6 , homopolymer 1,1'-Methylenebis(4-isocyanatobenzene) homopolymer Methylene diphenyl diisocyanate homopolymer Diphenylmethane diisocyanate homopolymer	25686-28-6	No Structure Available	(C15H10N2O2) _x	N/A
Benzene, 1,1'-methylenebis[isocyanato- 26447-40-5 Diphenylmethane diisocyanate Methylenediphenyl diisocyanate 4,4'-,2,4'-,2,2'-Diisocyanatodiphenylmethane MDI Isocyanic acid, methylenediphenylene ester	26447-40-5		C15H10N2O2	250.26

Chemical Name in AICS (Including Synonyms)	CAS Number	Structural Formula	Molecular Formula	Weight (g/mol)
Benzene, 1,1'-methylenebis[isocyanato-, homopolymer	39310-05-9		(C ₁₅ H ₁₀ N ₂ O ₂) _x	252.27
Methylenebis[isocyanatobenzene 1,1'-Methylenebis(isocyanatobenzene) homopolymer Diphenylmethane diisocyanate homopolymer Methylenebis(isocyanatobenzene) polymer				
Benzene, 1-isocyanato-2-[(4-isocyanatophenyl)methyl]-	5873-54-1		C ₁₅ H ₁₀ N ₂ O ₂	250.26
Diphenylmethane-2,4-diisocyanate 2,4'-Diisocyanatodiphenylmethane 2,4'-Diphenylmethanediisocyanate o-(p-Isocyanatobenzyl)phenyl isocyanate 2,4-MDI				
Isocyanic acid, polymethylenepolyphenylene ester	9016-87-9		Unspecified	N/A
Polymethylenepolyphenyl isocyanate Polymethylenepolyphenylene isocyanate polymer Polymeric mdi Polymeric diphenyl methylene diisocyanate				

Grouping Rationale

All chemicals of this group are structurally related with free isocyanate functional groups. Commercially produced methylenediphenyl diisocyanate (CAS No. 26447-40-5) comprises a mixture of benzene, 1,1'-methylenebis[4-isocyanato- (CAS No. 101-68-8), benzene, 1-isocyanato-2-[(4-isocyanatophenyl)methyl]- (CAS No. 5873-54-1) and benzene, 1,1'-methylenebis[2-isocyanato- (CAS No. 2536-05-2) (OECD 2003). All these individual isomers have a similar structure and the same molecular weight.

Most toxicological data are available on the benzene, 1,1'-methylenebis[4-isocyanato- (CAS No. 101-68-8) and assessing these chemicals as a group allows read-across of data from data rich members to data poor members. In certain cases study details do not specify the exact test material used but specifies it as methylenediphenyl diisocyanate.

1,3-Diazetidone-2,4-dione, 1,3-bis[4-[(4-isocyanatophenyl)methyl]phenyl]- (CAS No. 17589-24-1), 1,3-diazetidone-2-one, 1,3-bis[4-[(4-isocyanatophenyl)methyl]phenyl]-4-[[4-[(4-isocyanatophenyl)methyl]phenyl]imino]- (CAS No. 31107-36-5), benzene, 1,1'-methylenebis[isocyanato-, homopolymer (CAS No. 39310-05-9), isocyanic acid, polymethylenepolyphenylene ester (CAS No. 9016-87-9) and benzene, 1,1'-methylenebis[4-isocyanato-, homopolymer (25686-28-6), while being dimers, trimers and polymers, may contain unreacted isocyanate functional groups and also may contain or reversibly form methylenediphenyl diisocyanate and hence exhibit a similar toxicology profile to other chemicals of this group.

Import, Manufacture and Use

Australian

Three chemicals of this group are listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume between 1000 and 10000 tonnes. These chemicals are benzene, 1,1'-methylenebis[4-isocyanato- (CAS No. 101-68-8), benzene, 1-isocyanato-2-[(4-isocyanatophenyl)methyl]- (CAS No. 5873-54-1) and isocyanic acid, polymethylenepolyphenylene ester (CAS No. 9016-87-9).

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

information for benzene, 1,1'-methylenebis[isocyanato- (CAS No. 26447-40-5), benzene, 1,1'-methylenebis[isocyanato-, homopolymer (CAS No. 39310-05-9) and the above mentioned chemicals.

Benzene, 1,1'-methylenebis[4-isocyanato- (CAS No. 101-68-8) has reported potential domestic use including:

- adhesives - binding agents.

The chemicals have reported commercial use including:

Benzene, 1,1'-methylenebis[4-isocyanato- (CAS No. 101-68-8)

- construction materials additives;
- foaming agents;
- process regulators;
- in fluids/pastes used for repair of metal, rubber and concrete; and
- in manufacture of polyurethane foam, resins, adhesives, sealants, adduct mouldings, binders, fabric and coatings.

Benzene, 1-isocyanato-2-[(4-isocyanatophenyl)methyl]- (CAS No. 5873-54-1)

- used in polyurethane foam, resin and coatings manufacture.

Benzene, 1,1'-methylenebis[isocyanato- (CAS No. 26447-40-5)

- foaming agents; and
- process regulators.

Isocyanic acid, polymethylenepolyphenylene ester (CAS No. 9016-87-9)

- construction materials additives;
- insulating agents;
- polyurethane elastomers and insulating foam;
- polyurethane compounds used in electrical insulation;
- adhesives for rubber and laminates;
- automotive paints;
- foam systems; and
- curing compounds.

Benzene, 1,1'-methylenebis[isocyanato-, homopolymer (CAS No. 39310-05-9)

- construction materials additives;

No specific Australian use, import, or manufacture information has been identified for benzene, 1,1'-methylenebis[2-isocyanato- (CAS No. 2536-05-2), 1,3-diazetidione-2,4-dione, 1,3-bis[4-[(4-isocyanatophenyl)methyl]phenyl]- (CAS No. 17589-24-1), 1,3-diazetidin-2-one, 1,3-bis[4-[(4-isocyanatophenyl)methyl]phenyl]-4-[[4-[(4- (CAS No. 31107-36-5) and benzene, 1,1'-methylenebis[4-isocyanato-, homopolymer (CAS No. 25686-28-6).

International

The following international uses have been identified through the 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 Chimica, Substances and Preparations in the Nordic countries (SPIN) database, the European Commission Cosmetic Substances and Ingredients (CosIng) database, United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) directory and other data sources via eChemPortal, US Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR), US Environment Protection Agency Action Plan on methylenediphenyl diisocyanate and the US National Library of Medicine's Hazardous Substances Data Bank (HSDB):

The majority of the chemicals of this group have the following reported uses which may include domestic applications including:

- adhesives and sealants;
- paints, lacquers and varnishes; and
- one component foam.

The majority of the chemicals of this group have the following reported commercial uses including:

- construction materials;
- foaming agents;
- process regulators;
- insulating materials;
- manufacture of polyurethane resins, foams, mastics, coatings, Spandex fibres;
- manufacture of particle board; and
- used in bonding rubber to plastics and metals.

The majority of the chemicals of this group have the following reported site-limited uses including intermediates.

Some chemicals of the group have the following reported uses including:

- solvents;
- laboratory chemicals; and
- vulcanising agents.

Restrictions

Australian

Chemicals of this group, belonging to the group 'Isocyanates', are listed in the Poisons Standard (Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)) in Schedule 6 with the below entry:

"ISOCYANATES, free organic, boiling below 300° C, **except in:**

(a) viscous polyurethane adhesives; or

(b) viscous polyurethane sealants;

containing not more than 0.7 per cent of free organic isocyanates boiling below 300°C."

Schedule 6 chemicals are labelled as a '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.

Chemicals of this group, belong to the group 'Isocyanates', are listed in the Safe Work Australia, Model Work Health and Safety Regulations, Hazardous chemicals (other than lead) requiring health monitoring (Safe Work Australia 2011).

International

International restrictions on chemicals of this group include:

European Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food - Annex I: Substances. Restriction imposed at 1 mg/kg in final product expressed as isocyanate moiety.

Existing Hazard Classification for Worker Health and Safety

Some of the chemicals (CAS No. 101-68-8, 2536-05-2, 5873-54-1 and 26447-40-5) of this group are classified as hazardous with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Xn; R40 (Carcinogenicity Cat. 3)

Xn; R20 (Acute toxicity)

R48/20 (Repeat dose toxicity)

Xi; R36/37/38 (Irritation)
Xn; R42/43 (Sensitisation)

Exposure Standards

Australian

The chemicals of this group have exposure standards of 0.02 mg/m³ time weighted average (TWA) and 0.07 mg/m³ short term exposure limit (STEL) as isocyanates, all (as-NCO).

International

The following exposure standards are identified (Galleria Chemica):

An exposure limit (STEL) of 0.02 – 0.1 mg/m³ in countries such as Switzerland, United Kingdom, Hungary, China and Poland.

An exposure limit (TWA) of 0.02 – 0.052 mg/m³ in countries such as Spain, United Kingdom, Poland, Ireland and China.

Health Hazard Information

Toxicokinetics

Toxicokinetics data on methylenediphenyl diisocyanate are quite limited (OECD 2003, ECB 2005). No animal studies are available on toxicokinetics through the oral route. However, methylenediphenyl diisocyanate is expected to rapidly breakdown to methylenedianiline (MDA) in contact with water.

A dermal absorption rate of 1% was considered to be the reasonable worst case estimate (OECD 2003, ECB 2005). Toxicokinetics studies through the inhalation route indicate that a proportion of methylenediphenyl diisocyanate is converted to metabolites via formation of an amine group that is rapidly acetylated (OECD 2003).

Acute Toxicity

Oral

The chemicals of this group have low acute toxicity in animal tests as evidenced by reported oral median lethal dose (LD50) in rat studies. The LD50 for several chemicals of this group was >2000 mg/kg bw (OECD 2003, REACH Dossier 2011a). Observed sub-lethal effects included salivation, nasal discharge and abnormal yellow urine excretion.

Dermal

The chemicals of this group have low acute toxicity in animal tests as evidenced by reported dermal median lethal dose (LD50) in rat studies. The LD50 for isocyanic acid, polymethylenepolyphenylene ester (CAS No. 9016-87-9) was >9400 mg/kg bw (REACH Dossier 2011a). Observed sub-lethal effects included dermal irritation in one study.

Inhalation

The chemical is currently classified as hazardous with the risk phrase 'Harmful by inhalation' (Xn; R20) in HSIS (Safe Work Australia). The data available support an amendment to this classification (refer to **recommendation section**) to reflect the findings reported below.

An acute inhalation toxicity study using isocyanic acid, polymethylenepolyphenylene ester (CAS No. 9016-87-9) reported a median lethal concentration (LC50) of 490 mg/m³ for a four hour exposure in rats (OECD 2003, ECB 2005, REACH Dossier 2011a). Reported signs of toxicity include laboured breathing and some haemorrhages in the lungs (REACH Dossier 2011a). Given the vapour pressure of methylenediphenyl diisocyanate is low and since the technique used in the study created an aerosol rather than a vapour this has been taken into consideration in the classification for acute toxicity. It is, however, appreciated that the high concentrations achieved in this study may not occur under current industry processes and existing restrictions (ECB 2005). The LC50 value meets the classification criteria for 'Toxic by inhalation' (T; R23).

Irritation / Corrosivity

Skin Irritation

The chemicals of this group are classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in HSIS (Safe Work Australia). The available data support this classification.

In a well conducted study benzene, 1,1'-methylenebis[isocyanato- (CAS No. 26447-40-5) on unabrased rabbit skin produced erythema and oedema after a four hour semi-occlusive exposure (REACH Dossier 2011a). The mean erythema and oedema scores over the reading times (24, 48 and 72 hours) were 2.03 and 1.43, respectively. After 14 days, the exposed areas had effects which were not completely reversed.

ECB (2005) reported that according to case studies and workplace surveys, occupational exposure to methylenediphenyl diisocyanate had resulted in skin effects. However, there was some uncertainty whether the effects were due to irritation or skin sensitisation.

Eye Irritation

The chemicals of this group are classified as hazardous with the risk phrase 'Irritating to eyes' (Xi; R36) in HSIS (Safe Work Australia). The available human data support this classification.

While methylenediphenyl diisocyanate is considered a known eye irritant (OECD 2003), the majority of the publicly available animal studies (reviewed in ECB 2005, REACH Dossier 2011a,b,c & d), including some recent well-conducted studies, indicate that the chemicals of this group are not irritating to eyes. However, eye irritation in workers due to methylenediphenyl diisocyanate has been reported (WHO 2000, ECB 2005).

Respiratory Irritation

The chemicals of this group are classified as hazardous with the risk phrase 'Irritating to respiratory system' (Xi; R37) in HSIS (Safe Work Australia). The available data support this classification.

OECD (2003) reported that toxicity studies, human data and mechanistic studies show that chemicals of this group are irritants to the respiratory tract. In one mouse study using benzene, 1,1'-methylenebis[4-isocyanato- (CAS No. 101-68-8) a RD50 (concentration causing a 50% respiratory rate decrease) value of 32 mg/m³ was derived demonstrating respiratory tract irritation (ECB 2005).

Sensitisation

Respiratory sensitisation

The chemicals of this group are classified as hazardous with the risk phrase 'May cause sensitisation by inhalation' (Xn; R42) in HSIS (Safe Work Australia). The available data support this classification.

ECB (2005) reviewed a range of animal studies and human case reports and workplace studies and confirmed respiratory sensitisation with methylenediphenyl diisocyanate. Human case reports and workplace studies reported occupational asthma as a consequence of workplace exposure to methylenediphenyl diisocyanate. A threshold level for respiratory sensitisation could not be determined (OECD 2003).

Studies in animals have shown that respiratory sensitisation to methylenediphenyl diisocyanate can be induced through skin contact (ECB 2005).

Skin sensitisation

The chemicals of this group are classified as hazardous with the risk phrase 'May cause sensitisation by skin contact' (Xi; R43) in HSIS (Safe Work Australia). The positive results, reported for several members of this group, in two guinea pig maximisation tests (ECB 2005, REACH dossier 2011d), three well-conducted Mouse Ear Swelling Tests (ECB 2005) and several local lymph node assays (REACH dossier 2011a,b) support this classification. In one local lymph node assay the concentration of the the test substance needed to produce a stimulation index of three (EC3) was estimated to be approximately 0.03% (REACH dossier 2011a).

A range of case reports/workplace studies also suggest that methylenediphenyl diisocyanate is a skin sensitiser

in humans (OECD 2003, ECB 2005).

Repeat dose toxicity

Oral

There are no data available.

Dermal

There are no data available.

Inhalation

The chemicals of this group are classified as hazardous with the risk phrase 'Danger of serious damage to health by prolonged exposure through inhalation' (Xn; R48/20) in HSIS (Safe Work Australia). A two-year rat study showed adverse effects in the lungs with a NOAEC of 0.2 mg/m³ following inhalation exposure to methylenediphenyl diisocyanate. The data available support an amendment to this classification (refer to **recommendation section**) to reflect the findings reported below.

The respiratory tract is the target organ following inhalation exposure to methylenediphenyl diisocyanate in short term and long term animal studies (OECD 2003). In one combined chronic toxicity/carcinogenicity study, Wistar rats were exposed to isocyanic acid, polymethylenepolyphenylene ester (CAS No. 9016-87-9) aerosol concentrations of 0, 0.2, 1.0 or 6.0 mg/m³ six hours/day for five days/week for up to 2 years (REACH dossier 2011a). A NOAEC of 0.2 mg/m³ and LOAEC of 1.0 mg/m³ were derived based on macrophages with yellow pigment, increased localised fibrosis and alveolar duct epithelialisation in lungs. Other effects observed at higher doses (1 and 6 mg/m³) were increase in lung weights, histopathological changes in lungs, mediastinal lymph nodes and nasal cavity. Similar effects were found at similar doses in another long term study with benzene, 1,1'-methylenebis[4-isocyanato- (CAS No. 101-68-8) (REACH dossier 2011a).

In short-term studies, a NOAEC of 0.5 mg/m³ was reported by OECD (2003) based on a transient dysfunction of the pulmonary epithelial barrier in the rat.

These studies have shown that severe effects in the lung occur below the threshold concentration of that leads to classification with R48/23.

Observation in humans

In humans, long term exposure to methylenediphenyl diisocyanate causes "asthma, hypersensitivity pneumonitis, pleuritis, and progressive fibrosing alveolitis" (OECD 2003).

Genotoxicity

The genotoxicity potential of chemicals of this group is equivocal, based on the available data. However, potential breakdown of methylenediphenyl diisocyanate to methylenedianiline (MDA) in the stomach could suggest potential for genotoxicity through the oral route, depending on the metabolic fate of methylenediphenyl diisocyanate and the degree of MDA formation.

Methylenediphenyl diisocyanate gave positive results in several in vitro genotoxicity studies (Bolognesi et al., 2001, ECB 2005, REACH dossier 2011a). The in vitro studies are difficult to interpret given that methylenediphenyl diisocyanate degrades to MDA in the presence of vehicles such as dimethylsulfoxide (DMSO), and ethyleneglycol dimethylether (EDGE) to a lesser extent (Bolognesi et al., 2001). MDA is a well known mutagen.

In a well conducted in vivo micronucleus test, aerosolised methylenediphenyl diisocyanate did not induce cytogenetic damage even at high concentrations (118 mg/m³). OECD (2003) reported that based on the available data, chemicals of this group are not genotoxic.

Carcinogenicity

The chemical of this group are currently classified as hazardous as a Category 3 carcinogen with the risk phrase

'Limited evidence of carcinogenic effect' (Xn; R40 in HSIS (Safe Work Australia). The available data support this classification.

There are no carcinogenicity studies available via the oral and dermal routes of exposure. The International Agency for Research on Cancer (IARC) reported that there is inadequate evidence for carcinogenicity in humans and there is limited evidence in experimental animals (IARC 1999).

In a combined chronic toxicity/carcinogenicity study, Wistar rats were exposed to isocyanic acid, polymethylenepolyphenylene ester (CAS No. 9016-87-9) aerosol concentrations of 0, 0.2, 1.0 or 6.0 mg/m³ six hours/day for five days/week for up to two years (REACH dossier 2011a). Only at the highest dose tested (6.0 mg/m³), six adenomas and one adenocarcinoma were observed in the lungs of males and two adenomas were observed in the lungs of females. Based on lung tumours, a NOAEC of 1.0 mg/m³ was derived for carcinogenicity (REACH dossier 2011a).

In another chronic toxicity/carcinogenicity study, female Wistar rats were exposed to benzene, 1,1'-methylenebis[4-isocyanato- (CAS No. 101-68-8) aerosol concentrations of 0, 0.23, 0.7 or 2.05 mg/m³ 17 hours/day for five days/week for up to two years (REACH dossier 2011a). In this study, only one adenoma was seen in the lungs at the highest dose tested (2.05 mg/m³), hence, this was considered not treatment related.

Reproductive and developmental toxicity

Reproductive toxicity

There are no available fertility or multi-generation studies on chemicals of this group. Developmental effects were only observed secondary to maternal toxicity. Therefore, chemicals of this group are not considered to be specific developmental toxins.

There were no adverse effects on the reproductive organs in the studies mentioned under "Repeated Dose Toxicity". However, it is not possible to derive a NOAEC for fertility based on these studies (OECD 2003).

There are three prenatal developmental toxicity studies on chemicals of this group. The OECD (2003) reported that methylenediphenyl diisocyanate is not a developmental toxin as there were no specific developmental effects at exposures below those causing maternal toxicity. The lowest NOAEC for developmental toxicity was 3 mg/m³ based on a significant increase in the incidence of asymmetric sternbrae at the treatment dose of 9 mg/m³ in Wistar rats (OECD 2003, ECB 2005). In another study, a NOAEC of 4 mg/m³ was established for developmental toxicity based on increased incidence of skeletal variations and retardations, and reduced placental and foetal body weights at the treatment dose of 12 mg/m³ (REACH dossier 2011a). Maternal toxicity was demonstrated at these levels by mortality, respiratory tract damage, reduced body and gravid uterus weights.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation is respiratory sensitisation. Other health effects include a systemic long-term effect (carcinogenicity), a systemic acute effect (acute toxicity by the inhalation route of exposure) and local effects (skin sensitisation and respiratory irritation). The chemicals of this group may also cause toxic effects following repeated exposure by the inhalation route, and skin and eye irritation.

Public Risk Characterisation

Benzene, 1,1'-methylenebis[4-isocyanato- (CAS No. 101-68-8) has reported potential domestic use in Australia as adhesives – binding agents. Internationally chemicals of this group are known to be used in product types with potential domestic use (eg. adhesives, binding agents, surface coatings and surface treatment). Inhalation and dermal routes are the likely routes of exposure for the public through the consumer use of products containing chemicals of this group. When completely cured, free isocyanate functional groups are not available for reaction. Articles, such as polyurethane products, manufactured from methylenediphenyl diisocyanate are considered to be completely cured, hence they are considered non-toxic (US EPA 2011).

In Australia, the chemicals of this group are currently listed on Schedule 6 of the SUSMP. Strong warning statements, safety directions and first aid instructions apply to any domestic products containing chemicals of this group. The current controls are considered adequate to minimise the risk to public health posed by any domestic use of these chemicals. Therefore, the risk to public health is not considered to be unreasonable.

Occupational Risk Characterisation

During formulation of products, dermal, ocular and inhalation exposure of workers to chemicals of this group may occur, particularly if manual or open processes are used. These may include transfer and blending activities, quality control analysis and cleaning and maintenance of equipment. Worker exposure to these chemicals at lower concentrations may also occur during use of formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical health effects of the chemicals of this group, the chemicals may pose an unreasonable risk to workers if adequate control measures to minimise inhalation exposure are not implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace has adequate information to determine appropriate controls. The data available support an amendment to the hazard classification in HSIS (refer to **recommendation section**).

NICNAS Recommendation

Assessment of chemicals of this group is considered to be sufficient provided that the recommendation is adopted for the amendment of the classification and labelling of the chemicals 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

Products containing the chemicals of this group should be labelled in accordance with state and territory legislation (The Poisons Standard).

Occupational Health and Safety

All the chemicals of this group are recommended for classification and labelling under the current approved criteria and adopted Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

It is noted that the high concentrations achieved in the study leading to the higher classification for acute toxicity may not occur under current industry processes.

	<i>Approved Criteria (HSIS)^a</i>	<i>GHS Classification</i>
Acute Toxicity	Toxic by inhalation (T; R23)	Fatal if inhaled - Cat. 2 (H330)
Irritation / Corrosivity	Irritating to eyes (Xi; R36)* Irritating to skin (Xi; R38)* Irritating to respiratory system (Xi; R37)*	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)
Sensitisation	May cause sensitisation by inhalation (Xn, R42)* May cause sensitisation by skin contact (Xi; R43)*	May cause allergy or asthma symptoms or breathing difficulties if inhaled - Cat. 1 (H334) May cause an allergic skin reaction - Cat. 1 (H317)
Repeat Dose Toxicity	Toxic: danger of serious damage to health by prolonged exposure through inhalation (T; R48/23)	Causes damage to organs through prolonged or repeated exposure through inhalation - Cat. 1 (H372)
Carcinogenicity	Carc. Cat 3 - Limited evidence of a carcinogenic effect (Xn; R40)*	Suspected of causing cancer - Cat. 2 (H351)

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

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

Advice for consumers

Products containing chemicals of this group should be used according to label instructions.

Advice for industry

Control measures

Control measures to minimise the risk from dermal, ocular and inhalation exposure to chemicals of this group 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 storage, handling and use of a hazardous chemical are dependent 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:

- use of closed systems or isolation of operations;
- use of 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;
- minimisation of manual processes and work tasks through automation of processes;
- work procedures that minimise splashes and spills;
- regular cleaning of equipment and work areas; and
- use of 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 be relied upon on its own to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selection of 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 hazardous chemical are prepared; and
- management of risks arising from storage, handling and use of 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 a (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 physical hazards of chemicals of this group has not been undertaken as part of this assessment.

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