Australian Government
Department of Health, Disability and Ageing
Australian Industrial Chemicals Introduction Scheme

1,1'-Biphenyl, 4,4'-diisocyanato-3,3'-dimethyl-

Evaluation statement (EVA00158)

26 June 2025

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AICIS evaluation statement (EVA00158)

Subject of the evaluation

1,1'-Biphenyl, 4,4'-diisocyanato-3,3'-dimethyl-

Chemical in this evaluation

CAS name	CAS number
1,1'-Biphenyl, 4,4'-diisocyanato-3,3'-dimethyl-	91-97-4

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory).

This evaluation statement is a human health risk assessment for all identified industrial uses of the chemical. In this evaluation, the chemical 1,1'-Biphenyl, 4,4'-diisocyanato-3,3'-dimethyl- (CAS No. 91-97-4) will be referred to as tolidine diisocyanate (TODI).

Summary of evaluation

Summary of introduction, use and end use

There is currently no specific information about the introduction, use and end use of TODI in Australia.

Based on international use information, TODI has site-limited application with functional use as an intermediate in the manufacture of polyurethane (including polyurethane adhesives), plastic and rubber products.

Human health

Summary of health hazards

The identified health hazards are based on available data for TODI and close structurally related diisocyanate chemicals:

- 1,6-diisocyanato-hexane (HDI)
- methylene diphenyl diisocyanates (MDI)
- toluene diisocyanates (TDI).

In addition, TODI is hydrolysed to 3,3'-dimethyl- [1,1'-biphenyl]-4,4'-diamine (TODA, CAS No. 119-93-7). Although there is uncertainty whether this metabolite would be sufficiently bioavailable *in vivo*, conclusions on systemic toxicity of TODI have been supported using data from TODA.

Based on the available information on the related diisocyanates, the toxicokinetics of TODI will vary with the route of exposure and is likely to be more complex than simple hydrolysis to TODA. Based on the available data, dermal absorption is expected to be low and oral bioavailability will be limited due to formation of insoluble polyureas in the stomach. Based on the K_{ow} value (> 6) of TODI, the transfer rate between the stratum corneum and the epidermis will be slow and will limit absorption across the skin. The chemical is expected to be completely absorbed following inhalation exposure. There is evidence of metabolism to TODA following oral and dermal exposures, but not inhalation.

Based on the available data, TODI:

- has low acute oral and dermal toxicity
- is at most slightly irritating to the skin and eyes
- is not expected to cause serious systemic health effects following repeated oral exposure
- is not expected to cause specific adverse effects on fertility and foetal development.

Based on the available data, TODI has moderate acute inhalation toxicity with a reported median lethal concentration (LC50) in rats of 2.06 mg/L for males and 4.44 mg/L for females.

The chemical is expected to be an extreme skin sensitiser. In a guinea pig maximisation test (GPMT) a sensitisation rate of ≥ 80% was observed following intradermal induction at ≤ 0.1%.

As a diisocyanate, TODI has structural alerts for protein binding and endpoint specific alerts for respiratory sensitisation. Based on read across data from HDI, MDI and TDI, TODI is expected to be a respiratory sensitiser. These read across chemicals are classified for respiratory sensitisation (SWA n.d.-a) and have been shown to cause respiratory sensitisation in humans. The evidence of respiratory sensitisation is supported by data from several animal studies in which the production of specific antibodies and the impairment of pulmonary function were demonstrated as a consequence of exposure to diisocyanates via inhalation.

Based on information for structurally related diisocyanates, TODI may cause adverse effects in the respiratory tract following repeated inhalation exposure.

The genotoxicity potential of TODI is equivocal based on available data, including data on structurally related diisocyanates. Positive results were seen in *in vitro* genotoxicity studies for TODI, but it is uncertain whether these results were affected by instability in the aprotic polar solvents. Although TODI was negative in *in vivo* studies there was uncertainty whether the chemical had reached the target tissues. Mostly negative results were reported for structurally related diisocyanates in *in vivo* inhalation genotoxicity tests. However, there is uncertainty around sufficient bioavailability *in vivo*. The potential metabolite TODA is classified on the HCIS with the hazard category ‘Germ cell mutagenicity – Category 2’ and ‘hazard statement ‘H341 (Suspected of causing genetic defects).

The structurally related diisocyanates MDI and TDI are suspected human carcinogens on the basis of experimental evidence in animals. MDI and TDI both have the same diisocyanate functionality as TODI and have the potential to metabolise to carcinogenic amines. Based on

read across from MDI and TDI, carcinogenicity hazard classification for TODI is warranted (see **Hazard classifications relevant for worker health and safety** section). Although the potential metabolite, TODA is a known carcinogen there is uncertainty whether this metabolite would be sufficiently bioavailable *in vivo* to cause carcinogenic effects.

For further details of the health hazard information see **Supporting information**.

Hazard classifications relevant for worker health and safety

The chemical satisfies the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for worker health and safety as follows. This evaluation does not consider classification of physical hazards and environmental hazards.

Health hazards	Hazard category	Hazard statement
Acute toxicity	Acute Tox. 4	H332: Harmful if inhaled
Skin sensitisation	Skin sens. 1A*	H317: May cause allergic skin reaction
Respiratory sensitisation	Respiratory sens. 1	H334: May cause allergy or asthma or breathing difficulties if inhaled
Carcinogenicity	Carcinogenicity 2	H351: Suspected of causing cancer

*A specific concentration limit of 0.001% is recommended based on the potency observed in animal studies.

Summary of health risk

Public

Based on the available use information, it is unlikely that the public will be exposed to the chemical. Although the public could be exposed to products manufactured using TODI, the chemical is expected to be fully reacted with other components and bound to the matrix of the substrates. Although there may be trace amounts of TODI remaining, exposure is anticipated to be low.

Therefore, there are no identified risks to the public that require management.

Workers

During product formulation and packaging, dermal and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to TODI at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the respiratory and skin sensitisation, and systemic health effects, the chemical could pose a risk to workers. Control measures to minimise dermal and inhalation exposure are

needed to manage the risk to workers (see **Proposed means for managing risk** section). Controls in place due to the sensitisation and carcinogenicity classifications should minimise the potential risks of adverse effects on the respiratory tract.

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety (see **Summary of Health Hazards** section).

A specific concentration limit of 0.001% is recommended based on the potency observed in animal studies.

Information relating to safe introduction and use

The information in this statement including recommended hazard classifications, should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Recommended control measures that could be implemented to manage the risk arising from oral, dermal and inhalation exposure to the chemical include, but are not limited to:

- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

These control measures should be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health.

Measures required to eliminate, or manage risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used.

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.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be

contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

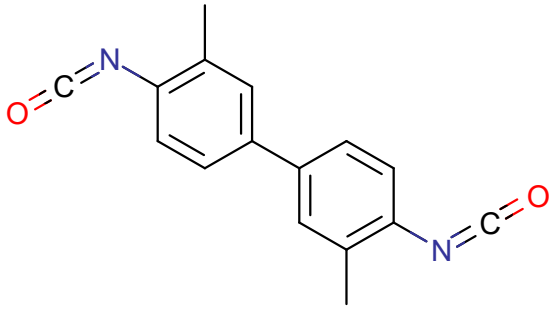
The Executive Director is satisfied that the identified risks to human health from the introduction and use of the industrial chemical can be managed.

Note:

1. Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Chemical identity

CAS number	91-97-4
CAS name	1,1'-Biphenyl, 4,4'-diisocyanato-3,3'-dimethyl-
Molecular formula	$C_{16}H_{12}N_2O_2$
Associated names	Tolidine diisocyanate (TODI)
	3,3'-Dimethylbiphenyl-4,4'-diyl diisocyanate
Molecular weight (g/mol)	264.28
SMILES (canonical)	O=C=NC=1C=CC(=CC1C)C2=CC=C(N=C=O)C(=C2)C
Structural formula	

Relevant physical and chemical properties

Physical form	Solid
Melting point	71.7°C at 101.29 kPa (exp.)
Boiling point	Decomposes before boiling
Vapour pressure	0.0029 Pa (at 25°C) (calc.)
Water solubility	Rapidly hydrolyses. Hydrolysis product (TODA) has solubility of 1.3 g/L at 25°C (exp.)
log K_{ow}	6.052 at 25°C (calculated)

Introduction and use

Australia

No specific information about the introduction, use and end use of TODI in Australia is available.

International

The following international uses have been identified through:

- Registration, Evaluation, Authorisation and Restriction of Chemicals dossier (REACH n.d.)
- Government of Canada Assessment (Government of Canada 2014)
- Substances and Preparations in the Nordic countries (SPIN n.d.)
- United States Environmental Protection Agency (US EPA) Chemical Data Reporting (US EPA 2020).

The chemical has site-limited uses, as an intermediate, including in the manufacture of:

- polyurethane/urethane
- plastic
- rubber products.

As part of the US EPA data reporting, end use in adhesives and sealants was identified. Based on other international sources, this is considered likely to be based on polyurethane adhesives manufactured from the chemical. TODI was identified as a diisocyanate in polyurethane adhesives for use in food packaging laminates (Government of Canada 2014).

Existing Australian regulatory controls

Public

TODI is not individually listed in the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). However, isocyanates are listed in the SUSMP under Schedule 6 (TGA 2024). The Schedule 6 entry states:

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

(a) viscous polyurethane adhesives; or
(b) viscous polyurethane sealants;

containing not more than 0.7% of free organic isocyanates boiling below 300°C.’

Workers

TODI is not listed on the HCIS (SWA n.d.-a).

The following 8-hour time weighted average (TWA) exposure standards are available for isocyanates in Australia (SWA n.d.):

- TWA: 0.02 mg/m^3 and STEL: 0.07 mg/m^3.

International regulatory status

Exposure standards

The following exposure standards were identified for diisocyanates (Chemwatch n.d.):

- TWA: 0.02 mg/m^3 – Canada, Croatia, New Zealand, Norway, South Africa, Switzerland and United Kingdom.

Canada

Based on the screening assessment by the Government of Canada (2014), it was concluded that the benzidine-based dyes and related substances, which included TODI, do not meet the criteria under paragraph 64(c) of the *Canadian Environmental Protection Act, 1999* (CEPA), as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

European Union

The chemical is listed in Table 1 of the EU Regulation No. 10/2011 on plastic materials and articles intended to come into contact with food which has a restriction of 1 mg/kg in the final product, expressed as an isocyanate moiety.

United States of America

The Code of Federal Regulations (CFR) Title 21 has listed the chemical for use in food contact surface articles (see CFR 21 Section 177.1680; US FDA 2024).

Health hazard information

The following chemicals and classes of chemicals that contain the same diisocyanate functionality (i.e. they have 2 isocyanate (N=C=O) functional groups) have been used as read across to support hazard conclusions:

- 1,6-diisocyanato-hexane (HDI, CAS No. 822-06-0)
- methylene diphenyl diisocyanates (MDI) (with the majority of toxicological data available for 4,4’-MDI, CAS No. 101-68-8)
- toluene diisocyanates (TDI) (with the majority of toxicological data available for CAS No. 26471-62-5, a reaction product of 2,4-TDI and 2,6-TDI isomers (80/20)).

In addition, TODI is hydrolysed to 3,3'-dimethyl- [1,1'-biphenyl]-4,4'-diamine (TODA, CAS No. 119-93-7). Although there is uncertainty whether this metabolite would be sufficiently bioavailable *in vivo* (see **Toxicokinetics** section), conclusions on systemic toxicity have been supported using data from TODA.

Toxicokinetics

No data are available for TODI.

No toxicokinetic data in mammals are available for the chemical. TODI is highly reactive in water, resulting in hydrolysis to 3,3'-dimethyl- [1,1'-biphenyl]-4,4'-diamine (TODA, CAS No. 119-93-7). In a hydrolysis test, TODI was fully hydrolysed within 30 minutes at 25 and 50°C at both pH of 4 and 9. TODI was fully hydrolysed at a pH 7 within 29 hours at 25°C and within 2.5 hours at 50°C (ECHA RAC 2021a; ECHA 2021b).

Based on the available information on structurally related diisocyanates (summarised below) the toxicokinetics of the chemical will vary with the route of exposure and is likely to be more complex than simple hydrolysis to TODA. Based on the available data, dermal absorption is low and oral bioavailability is limited due to formation of insoluble polyureas in the stomach. Based on the K_{ow} value (> 6) of TODI, the transfer rate between the stratum corneum and the epidermis will be slow and will limit absorption across the skin. The chemical is expected to be completely absorbed following inhalation exposure. There is evidence of metabolism of diisocyanates to the respective amines following oral and dermal exposures but not inhalation.

Absorption

Read across: Structurally related isocyanates

Studies with TDI indicate that the absorption varies with the route of exposure.

Application of a TDI mixture (2,4-TDI and 2,6-TDI) on to the skin resulted in a low percentage (≤ 1%) reaching systemic circulation 8 hours after exposure.

The chemical TDI is not well absorbed after oral administration with the chemical being polymerised in the stomach and excreted in the faeces. Under acidic conditions TDI hydrolyses to toluene diamine (TDA) which reacts with excess TDI to form insoluble polyureas. As the dosage of TDI is decreased, the bioavailability of TDI is increased following oral administration. For example, 3.5% of the applied radioactivity was recovered in urine after gavage with 700 mg/kg, 6.3% after 70 mg/kg and 16% after 7 mg/kg 2,4-TDI. This is because at lower dosages there is reduced TDI for the metabolite to react with (ECHA 2012).

Almost complete absorption of TDI was observed in rats following acute inhalation exposure, where most of the radioactivity was absorbed via the lungs. In controlled studies in human volunteers, HDI was rapidly absorbed via the respiratory tract and up to 39% of the estimated inhaled dose was excreted in the urine (NICNAS 2014a).

Metabolism

Read across: Structurally related isocyanates

Metabolic profiles of orally administered TDI showed similarities with those for TDA. A small percentage (< 10%) of the metabolic products of TDI were identified as 2,4-bis(acetylamino) toluene, while 80% were similar to the metabolites of 2,4-TDA. Urinary metabolites formed following oral administration of 2,4-TDI included acid-labile conjugates (65%) as well as monoacetyl-, diacetyl-, and free TDA.

Application of TDI on the skin resulted in absorption in a dose dependent manner. There was a linear correlation in the amount of hydrolysed urinary TDA with the amount of TDI applied on the skin.

Following inhalation exposure to radiolabelled TDI isomers in rats, a large proportion (90%) of the radiolabelled TDI in the plasma was associated with proteins. Most (97–100%) of the 2,4-TDI administered via inhalation existed in the form of biomolecular conjugates. The authors concluded that conjugation was the predominant reaction and that free TDA was not a primary *in vivo* reaction product following inhalation of 2,4-TDI (ECHA 2012).

In biomonitoring studies, haemoglobin adducts and urine metabolites of MDI were determined. Toxicokinetic results indicated that a proportion of MDI dose is converted to metabolites via the intermediary formation of an amine group which was rapidly acetylated (ECB 2005).

Excretion

Read across: Structurally related isocyanates

An inhaled dose of TDI was excreted mostly in the faeces (> 50%), suggesting transportation into the gastrointestinal tract via biliary excretion. Excretion in the urine accounted approximately 20–24% of the recovered radioactivity. The urinary elimination half-life following dermal and inhalation exposure was similar at 20 hours but differed from oral administration (3–5 hours), indicating that the dermal and inhalation routes have similar distribution and excretion (ECHA 2012).

Acute toxicity

Oral

Based on the available data, TODI has low acute oral toxicity.

In a GLP compliant acute oral toxicity study conducted in accordance with the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401, Sprague Dawley (SD) rats (n = 5/sex/dose) were treated with a single dose of the chemical at 2000 mg/kg bw in both sexes. The median lethal dose (LD50) was > 2000 mg/kg bw. No sublethal signs of toxicity were reported (REACH n.d.).

Dermal

Based on the available data, TODI has low acute dermal toxicity.

In a GLP compliant acute dermal toxicity study conducted in accordance with OECD TG 402, SD rats (n = 5/sex/dose) were treated in a semi-occlusive manner with a single dose of the chemical at 2000 mg/kg bw in both sexes. The LD50 was > 2000 mg/kg bw. Very slight well defined erythema at the site of application was reported within a day of dosing (REACH n.d.).

Inhalation

Based on the available data, TODI has moderate acute inhalation toxicity, warranting hazard classification (see **Hazard classifications relevant for worker health and safety** section).

In a GLP compliant acute inhalation toxicity study conducted in accordance with OECD TG 403, SD rats (n = 5/sex/dose) were exposed to the chemical as a dust, with a mass median aerodynamic diameter (MMAD) of up to 10 µm nose-only for 4 hours at concentrations of 0.98, 3.78 or 5.09 mg/L. Median lethal concentration (LC50) values of

2.06 mg/L for males and 4.44 mg/L for females were determined. Mortalities were reported at concentrations of 3.78 mg/L (3 males and 1 female) and 5.09 mg/L (5 males and 3 females). Clinical signs of toxicity were reported at 5.09 mg/L including wet fur, decreased respiratory rate, laboured respiration and extreme lethargy. In animals sacrificed or found deceased, necropsy findings included enlargement of the lungs, haemorrhagic patches and abnormally dark or reddened appearance of the lungs, dark liver, pale kidneys and gaseous distention of the gastrointestinal tract (REACH n.d.).

Corrosion/Irritation

Skin irritation

Based on the available data, TODI is not considered to be a skin irritant.

In a GLP compliant skin irritation study conducted in accordance with OECD TG 404, 3 New Zealand white (NZW) rabbits (1 female, 2 males) were treated with the chemical on abraded skin for 3 minutes, 1 and 4 hours under semi-occlusive conditions. Observations were recorded at 1, 24, 48 and 72 hours after patch removal. Mean scores (based on observations at 24, 48 and 72 hours) for erythema and oedema were 0 for each animal. Very slight erythema (score of 1) and very slight oedema (score of 1) were observed at 2 treated skin sites 1 hour after patch removal, which were fully reversible within 24 hours (REACH n.d.).

Eye irritation

Based on the available data, TODI is slightly irritating to the eye.

In a GLP compliant eye irritation study conducted in accordance with OECD TG 405, the chemical was instilled into one eye of 3 NZW rabbits. Effects were observed at 1, 24, 48 and 72 hours after treatment. Mean scores for individual animals based on observations at 24, 48 and 72 hours were:

- corneal opacity 0.3/4, iritis 0/2, conjunctival redness 1/3 and chemosis 1/4 (animal 1)
- corneal opacity 0/4, iritis 0/2, conjunctival redness 0.7/3 and chemosis 0/4 (animal 2)
- corneal opacity 0/4, iritis 0.3/2, conjunctival redness 1/3 and chemosis 1/4 (animal 3).

Iritis was observed in 2 treated eyes. Minimal conjunctival irritation was observed in all treated eyes one hour after treatment. Transient diffuse corneal opacity was observed in one treated eye 24 hours after treatment. The observed effects were reversible within 72 hours (REACH n.d.).

Sensitisation

Skin sensitisation

Based on the available data, TODI is considered to be a skin sensitiser, warranting hazard classification.

Based on a sensitisation rate of ≥ 80% following intradermal induction at ≤ 0.1%, the chemical is considered to have extreme potency supporting sub-classification and a specific concentration limit (SCL) of 0.001% (ECETOC 2003; ECHA RAC 2021a; ECHA RAC 2021b) (see **Hazard classifications relevant for worker health and safety** section).

In vivo

In a GPMT conducted according to OECD TG 406, intradermal induction was performed on female Dunkin Hartley guinea pigs (10/dose) using 0.1% of the chemical in arachis oil and topical induction with 50% of the chemical in acetone. The animals were challenged with 25 and 50% of the chemical in acetone. In the first reading (24 hours after challenge), reactions were reported in 8/10 animals at 25% challenge, and in 9/10 animals at 50% challenge during the first reading. In the second reading (48 hours after challenge), reactions were reported in 9/10 animals at 25% challenge, and in 8/10 animals at 50% challenge. In the third reading (72 hours after challenge), reactions were reported in 9/10 animals at 25% challenge, and in 9/10 animals at 50% challenge (REACH n.d.).

In silico

TODI has structural alerts for protein binding and endpoint specific alerts for skin sensitisation based on the mechanistic profiling functionality of the OECD Quantitative Structure Activity Relationship (QSAR) Toolbox (OECD QSAR Toolbox v4.5). The alert indicated that the chemical could interact with proteins via isothiocyanate-protein acyl transfer.

The knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 6.0.1 was utilised to estimate the skin sensitisation potential of TODI (Lhasa Limited 2018). The chemical was predicted positive with an alert for skin sensitisation for isocyanates. The alerting group is electrophilic and may react with skin proteins by carbamylating their sulphydryl group at physiological conditions. The prediction was considered plausible. The predicted effective concentration for a 3 fold increase in lymphocyte proliferation in local lymph node assay (LLNA EC3) for the chemical was 0.053% indicating extreme skin sensitisation potential.

Respiratory sensitisation

Based on read across from HDI, MDI and TDI and *in silico* predictions, the chemical is expected to be a respiratory sensitiser, which warrants hazard classification (see **Hazard classifications relevant for worker health and safety** section).

Read across: Structurally related isocyanates

The chemical TODI belongs to a group with a diisocyanate moiety. The three chemicals HDI, MDI, and TDI have been shown to cause respiratory sensitisation in humans. The evidence of respiratory sensitisation is supported by data from several animal studies in which the production of specific antibodies and the impairment of pulmonary function as a consequence of exposure to diisocyanates via inhalation was demonstrated. HDI, MDI and TDI have been classified as respiratory sensitisation – Category 1 (ECHA RAC 2021a; NICNAS 2013a; NICNAS 2013b; NICNAS 2014a; SWA n.d.). The isocyanate functional group is a common alert in respiratory sensitisation prediction tools. The molecular initiating event for respiratory sensitisation is hypothesised to begin with the covalent binding of electrophiles to proteins in the lungs. This event involves the iso(thio)cyanate functional group undergoing an acylation reaction between the electrophilic functional group and nucleophilic protein moieties, such as amino or sulfhydryl groups, producing protein adducts (ECHA RAC 2021a). It is considered that the respiratory sensitisation potential of TODI will be inferred from the collective respiratory sensitisation data of HDI, MDI, and TDI.

Animal data

Common findings in various guinea pig respiratory sensitisation studies with HDI, MDI or TDI include increased production of antibodies (IgG and/or IgE) specific to these chemicals, increased respiratory rate, production of inflammatory markers, and histopathological changes reflecting inflammatory response in the respiratory tract. Similar histological changes were reported in the airways of mice and rats exposed via inhalation to either HDI, MDI or TDI (ECHA RAC 2021a).

In silico

The chemical has structural alerts for protein binding and endpoint specific alerts for respiratory sensitisation based on the mechanistic profiling functionality of OECD QSAR Toolbox v4.5. Isocyanates have been suggested to be capable of reacting with proteins in the lung via a direct acylation mechanism.

DEREK Nexus version 6.0.1 was utilised to estimate the respiratory sensitisation potential of TODI (Lhasa Limited 2018). The chemical had a positive prediction with an alert for respiratory sensitisation by isocyanates. The prediction was considered plausible. Chronic inhalation exposure to isocyanates as vapours or particulates, e.g. in the workplace, may result in occupational asthma and respiratory sensitisation. Diisocyanates are likely to be more potent respiratory sensitisers, although details of the human respiratory tract toxicity of monoisocyanates are sparse (Lhasa Limited 2018).

Observation in humans

In case reports and systematic examinations, workers with occupational exposure to HDI through spray applications of polyurethane coatings based on prepolymers including HDI showed clinical asthmatic reactions, bronchial hyperreactivity, alveolitis, changes in lung functions and occurrence of IgG or IgE antibodies against the chemical bound to human serum albumin (NICNAS 2014a).

The European Chemicals Bureau (ECB 2005) reviewed a range of animal studies, human case reports, and workplace studies and confirmed respiratory sensitisation with methylenediphenyl diisocyanate (CAS No. 26447-40-5). 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 (NICNAS 2013a).

In humans, inhalation exposure results in toluene diisocyanate induced asthma, which may continue for several years after the removal from exposure. It has been reported that a challenge at 1 ppb (0.007 mg/m^3) toluene diisocyanate induces asthma in previously sensitised subjects. In participants not suffering from occupational asthma, in controlled experiments, sensitisation occurred at 10 ppb (0.07 mg/m^3) (NICNAS 2013b).

Repeat dose toxicity

Oral

Limited data are available. Based on the available data, including consideration of toxicokinetics, the chemical is not expected to cause serious systemic health effects following repeated oral exposure.

In a GLP compliant 28 day repeat dose toxicity study conducted in accordance with OECD TG 407, SD rats (5/sex/dose) were administered the chemical (in arachis oil) by gavage at doses of 0, 15, 150 or 1000 mg/kg bw/day. Clinical signs of toxicity observed at 1000 mg/kg bw/day included increased salivation, hunched posture, piloerection, noisy respiration, dehydration and red/brown staining around the mouth and snout. Reduced bodyweight gain, dietary intake and food efficiency were observed in males in the 1000 mg/kg bw/day dose group. Food efficiency was also reduced in females in the highest dose group. Treatment related changes in the forestomach of animals such as hyperkeratosis (thickening of the stratum corneum) and acanthosis (thickening of the epidermis) were observed in the highest dose group. A no observed effect level (NOEL) of 150 mg/kg bw/day was reported based on the lack of changes in bodyweight gain, clinical signs and histopathology in the forestomach at this dose (REACH n.d.).

The toxicology of the potential metabolite TODA was investigated in both 2 and 13 week drinking water studies in rats. Non-cancer effects were reported in the liver, kidneys, bone marrow and lymphoid organs. The actual dose received was not calculated in these studies. However, the dose conversions (ppm in drinking water to mg/kg/bw/day) in longer term studies indicated the lowest observed adverse effect levels (LOAELs) based on changes in thyroid hormones to be approximately 20–30 mg/kg bw/day (NICNAS 2014b). TODI and TODA are expected to have limited oral bioavailability based formation of insoluble polyureas in the stomach (see **Toxicokinetics** section).

Dermal

No data are available.

Inhalation

No data are available. Based on information on structurally related diisocyanates, the chemical may cause adverse effects in the respiratory tract following repeated inhalation exposure. The respiratory tract is the target organ following inhalation exposure to MDI, TDI and HDI in short term and long term animal studies (NICNAS 2013a; NICNAS 2013b; NICNAS 2014a).

Genotoxicity

Based on the available data, including on structurally related diisocyanates, the genotoxicity potential is equivocal.

The chemical TODI was reported to be positive in *in vitro* genotoxicity studies but it is uncertain whether these results were affected by instability in the aprotic polar solvents. Although TODI was reported to be negative in *in vivo* studies there was uncertainty whether the chemical had reached the target tissues in these studies. Mostly negative results were reported for structurally related diisocyanates in *in vivo* inhalation genotoxicity tests.

The potential metabolite TODA is classified on the HCIS with the hazard category ‘Germ cell mutagenicity – Category 2’ and ‘hazard statement ‘H341 (Suspected of causing genetic defects) (SWA n.d.). However, there is uncertainty whether this chemical would be sufficiently bioavailable *in vivo*.

In vitro

TODI

The following results were reported for the chemical (REACH n.d.; ECHA RAC 2021b):

- Positive results in a bacterial reverse mutation assay in *Salmonella typhimurium* (*S. typhimurium)* TA 98 and TA 1538 with metabolic activation at concentrations up to 1000 µg/plate and negative without metabolic activation.
- Negative results in a bacterial reverse mutation assay in *S. typhimurium* TA 100, TA 102, TA 104, TA1535, TA 1537, *Escherichia coli* (*E. coli*) wp2 uvr A pKM 101, and *E. coli* wp2 uvr A with and without metabolic activation at concentrations up to 2000 µg/plate.
- Slight positive results in an *in vitro* mammalian chromosome aberration assay in Chinese hamster lung cells with metabolic activation at concentrations up to 0.6 mg/mL.
- Positive results (small but statistically significant increases in mutant frequency) were reported in a mammalian gene mutation assay (OECD TG 476) in the thymidine kinase (TK) locus in mouse lymphoma cells L5178Y with and without metabolic activation at concentrations up to 24 µg/mL (3 independent experiments).

There is uncertainty regarding the positive results from the *in vitro* genotoxicity studies as diisocyanates have been shown to be unstable in the aprotic polar solvents used in the studies. Therefore, degradation of TODI to TODA cannot be excluded and it cannot be determined whether TODI or TODA caused the positive results (ECHA RAC 2021a; ECHA RAC 2021b).

Read across: Structurally related isocyanates

Similar to TODI, the genotoxicity data of structurally similar isocyanates MDI and TDI show positive *in vitro* results: however, it is unclear whether the *in vitro* positive responses were due to hydrolysis to the related aromatic amine chemicals which are known mutagens (ECHA RAC 2021b; NICNAS 2013a; NICNAS 2013b).

Supporting data: TODA

TODA (and/or its hydrochloride salts) was positive in bacterial reverse mutation assay in *S. typhimurium* with metabolic activation and in chromosome aberration tests in CHO cells (NICNAS 2014b).

In vivo

TODI

In a GLP compliant mammalian erythrocyte micronucleus test conducted in accordance with OECD TG 474, albino Crl:CD-1TM (ICR) BR mice (5/sex/dose) were treated with TODI (in arachis oil) by intraperitoneal injection at single doses of 0, 125, 250 or 500 mg/kg bw/day. The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups, indicating a lack of clastogenicity (REACH n.d.).

In a GLP compliant unscheduled DNA synthesis (UDS) test conducted in accordance with OECD TG 486, the chemical (in arachis oil) was administered as a single dose by gavage to male Crj:CD rats (4/dose) at 0, 700 or 2000 mg/kg bw. There were no signs of DNA damage in liver cells at any of the doses tested (REACH n.d.).

There is uncertainty whether the chemical reached the target tissues in these studies (ECHA RAC 2021a; ECHA RAC 2021b).

Read across: Structurally related isocyanates

Mostly negative results have been reported in well conducted *in vivo* inhalation studies including in micronucleus assays in rats and mice (MDI and TDI) and an *in vivo* Comet assay in rats assessing DNA damage to lungs, stomach and liver (MDI) (ECHA RAC 2021b; NICNAS 2013a; NICNAS 2013b; NICNAS 2014a).

Supporting data: TODA

Lethal mutations were observed in the germ cells of *Drosophila melanogaster* following exposure to TODA HCl in the feed or by injection (NICNAS 2014b).

In silico

TODI has structural alerts for DNA binding via acylation and endpoint specific alerts for *in vitro* mutagenicity, *in vivo* micronucleus and *in vivo* chromosomal aberrations based on the mechanistic profiling functionality of the OECD QSAR Toolbox (OECD 2022). Isocyanates can bind to both DNA and proteins via acylation. Isocyanate adducts may result from electrophilic reaction of the N=C=O group with the nucleophilic atoms of DNA and protein. Aromatic isocyanates may also undergo hydrolysis to the carbamic acid and subsequent decarboxylation to the corresponding aromatic amine, giving further arylamine adducts with DNA.

The knowledge based expert system DEREK Nexus version 6.0.1 (Lhasa Limited 2018) was utilised to estimate the genotoxic potential of the chemical. The chemical is predicted positive with an alert for mutagenicity and chromosome damage *in vitro* based on data for isocyanate or isothiocyanate. Isocyanates have the potential to interact with the exocyclic amino group of the DNA bases deoxyadenosine, deoxyguanosine and in particular, deoxycytidine. Conflicting Ames assay results have been reported for isocyanates. The conflicting results may be due to the aqueous instability and high bacterial toxicity associated with these classes of compounds. The presence of S9 mix was found to be necessary in the observation of the mutagenicity of aromatic isocyanates in the Ames test in strains TA 98 and TA 100.

The QSAR modelling using OASIS-TIMES (Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator) version 2.28 predicted that the chemical induced chromosomal aberrations *in vitro* (OASIS LMC n.d.). The predictions were within the applicability domain of the genotoxicity models and based on alerts for isocyanates and diisocyanates. The chemical is predicted to be negative for Ames mutagenicity (80% in domain) using OASIS–TIMES 2.28.

Carcinogenicity

No data are available for TODI. MDI and TDI are suspected human carcinogens on the basis of experimental evidence in animals. MDI and TDI both have the same diisocyanate functionality as TODI and have potential to metabolise to carcinogenic amines. Based on read across from MDI and TDI, hazard classification for carcinogenicity for TODI is warranted (see **Hazard classifications relevant for worker health and safety** section). Although the potential metabolite, TODA is a known carcinogen, there is uncertainty whether this metabolite would be sufficiently bioavailable *in vivo* to cause carcinogenic effects.

Read across: Structurally related isocyanates

Read across: TDI

The HCIS classification for TDI is Category 2 with the hazard statement ‘Suspected of causing cancer’ (SWA n.d.-a).

The International Agency of Research on Cancer (IARC) classification for TDI is Category 2B – Possibly carcinogenic to humans, based on inadequate evidence for carcinogenicity in humans, but sufficient evidence in experimental animals (IARC 1999). TDI is listed in the National Toxicology Program (NTP) Report on Carcinogens as 'reasonably anticipated to be human carcinogens' (NTP 2021).

In oral carcinogenicity studies, TDI was reported to cause:

- subcutaneous fibromas and fibrosarcomas (combined), pancreatic acinar cell adenomas, and pancreatic islet cell adenomas, neoplastic nodules of the liver, and mammary gland fibroadenomas in F344/N rats
- haemangiomas or haemangiosarcomas (combined), as well as hepatocellular adenomas in B6C3F1 mice (NTP 1986).

It is unclear whether the TDA was present in the test sample used in these studies due to degradation (ECHA 2012). No treatment related tumours were seen in animal studies where the inhalation route of exposure was used, although some deficiencies were noted in these studies (NICNAS 2013b).

Read across: MDI

The HCIS classification for MDI is Category 2 with the hazard statement ‘Suspected of causing cancer’ (SWA n.d.-a).

The IARC classification for MDI is Category 3 – Not classifiable for carcinogenicity to humans, based on inadequate evidence for carcinogenicity in humans and limited evidence in experimental animals (IARC 1999).

In a chronic inhalation study, polymeric MDI was reported to cause lung tumours in Wistar rats exposed for 2 years (aerosol concentrations of 0, 0.2, 1.0 or 6.0 mg/m³, 6 hours/day). At the highest dose tested (6.0 mg/m³), 6 adenomas and one adenocarcinoma were observed in the lungs of males and 2 adenomas were observed in the lungs of females (ECHA RAC 2021a; ECHA RAC 2021b; IARC 1999; Reuzel et al. 1994). An increase in regenerative proliferation of type-II cells leading to pre-neoplastic changes was proposed as a mechanism for the lung tumours (ECHA RAC 2021a). This would be a non-genotoxic carcinogenic mechanism through compensatory response of the lung to maintain homeostasis. The following statistically significant concentration related pulmonary lesions were observed in a chronic inhalation study with MDI (aerosol concentrations of 0, 0.23, 0.7 or 2.05 mg/m³ 17 hours/day):

- an increase in focal/multifocal alveolar and bronchioalveolar hyperplasia
- interstitial fibrosis
- accumulation of particle laden and pigmented macrophages.

In this study, only one adenoma was seen in the lungs at the highest dose tested (2.05 mg/m³) (NICNAS 2013a; ECHA 2021b).

Supporting data: TODA

The HCIS classification for TODA (CAS No. 119-93-7) is Category 1B with the risk phrase 'May cause cancer' (SWA n.d.-a).

The IARC classification for TODA is Category 2B – Possibly carcinogenic to humans, based on sufficient evidence of carcinogenicity of benzidine in humans, and sufficient evidence in experimental animals (IARC 2010). The chemical is listed in the NTP Report on Carcinogens as 'reasonably anticipated to be human carcinogens' (NTP 2021).

In animal studies TODA caused various types of tumours in rats and by two different routes of exposure. Oral administration of its dihydrochloride salt caused benign and/or malignant tumours of the Zymbal gland (adenoma or carcinoma), liver (hepatocellular adenoma or carcinoma), skin (basal-cell adenoma or squamous-cell papilloma or carcinoma), preputial and clitoral glands (adenoma or carcinoma), and large intestine (adenomatous polyps) in rats. In males, it also caused cancer of the small intestine (adenocarcinoma) and benign lung tumours (adenoma). In females, it also caused mammary gland cancer (adenocarcinoma) and benign or malignant oral-cavity tumours (squamous-cell papilloma or carcinoma). Subcutaneous injection of TODA in rats was reported to cause Zymbal-gland cancer (NICNAS 2014b; NTP 2021).

Reproductive and development toxicity

Based on the available data, including consideration of toxicokinetics, the chemical is not expected to cause specific adverse effects on fertility and foetal development following oral exposure.

TODI

In a GLP compliant combined reproduction/developmental toxicity screening test conducted in accordance with OECD TG 421, Wistar rats (n = 12/sex/dose) were administered TODI (in peanut oil) by gavage at doses of 0, 15, 150 or 1000 mg/kg bw/day for a total of 28 days for males including 14 days before mating, or a total of approximately 47 days for females including 14 days before mating up to day 3 post-partum.

Mortalities and clinical signs of toxicity were reported in one female each in the low and high dose groups. One female was euthanised due to their moribund condition, and the other female was deceased after parturition due to post-partum haemorrhage. All 4 pups of the deceased female did not survive. Parental animals in the high dose group had slightly lower body weight and body weight gain. Changes in the number of corpora lutea, implantations, intrauterine mortality, and postnatal mortality were minimal and not considered to be related to treatment. In the high dose group, the number of pups born was statistically lower than the controls; however, the number of pups were within the normal control range. Therefore, these minor changes were not considered treatment related. Other changes including pup body weights and body weight gains were within the expected range and not considered to be biologically significant. The NOAEL for maternal toxicity was 150 mg/kg bw/day based on the lack of body weight changes and clinical signs of toxicity. The NOAEL for reproductive and developmental toxicity was 1000 mg/kg bw/day based on the absence of adverse effects (REACH n.d.).

Read across: Structurally related isocyanates

There are a number of studies available for structurally similar isocyanates that investigate reproductive and developmental effects following inhalation exposure. In prenatal studies with MDI, developmental effects were only observed secondary to maternal toxicity (NICNAS 2013a). No effects on any reproductive/developmental or neurological parameters were observed at any dose level in a combined reproductive/developmental/neurotoxicity study (OECD TG 422) with HDI (NICNAS 2014b). No treatment related effects on reproductive parameters in any generation were observed in a two generation reproductive toxicity study (OECD TG 416) with TDI and effects in a developmental study (OECD TG 414) were secondary to maternal toxicity.

Supporting data: TODA

The available information on the reproductive and developmental toxicity of the potential metabolite TODA are limited. No malformations were observed in available non-guideline developmental studies (NICNAS 2014b).

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