Disiloxane, hexamethyl-: Human health tier II assessment

08 March 2019

CAS Number: 107-46-0

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

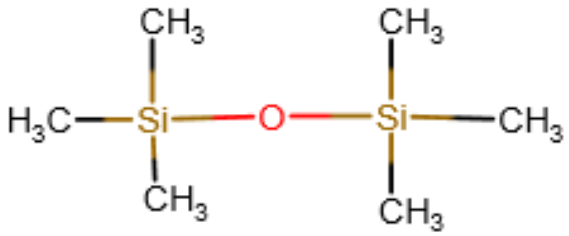
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	hexamethyldisiloxane (L2) oxybis(trimethylsilane) silane, oxybis(trimethyl- bis(trimethylsilyl)oxide disiloxane
Structural Formula	
Molecular Formula	C6H18OSi2
Molecular Weight (g/mol)	162.38
Appearance and Odour (where available)	liquid
SMILES	C[Si](C)(C)O[Si](C)(C)C

Import, Manufacture and Use

Australian

The chemical has reported domestic use in coating products.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; the Organisation for Economic Co-operation and Development (OECD) Screening information data set International Assessment Report (SIAR); Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the United States (US) Department of Health and Human Services, Household Products Database (US HPD); and the Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS).

The chemical has reported cosmetic uses, including:

- in personal care products such as hairspray available in aerosol form at unspecified concentrations as listed on the US HPD; and
- as anti-foaming and (miscellaneous) skin conditioning agents in a wide range of personal care products (colognes and eau de toilettes, tonics, dressings, powders (dusting and talcum excluding aftershave talcs), hair preparations (non-colouring) and conditioners, hairsprays (aerosol fixatives), miscellaneous manicuring preparations and other hair grooming products.

The chemical has reported domestic uses, including:

- in paints, lacquers and varnishes (e.g. in toner for printing inks);
- as coatings (e.g. hydrophilic coating of contact lenses);
- as adhesion promotor-priming agents for photolithography;
- as cleanings and washing agents (e.g. cleaning of optical wear and laundry detergents);
- in the formulation of non-metal surface treatments; and
- in surface-active agents.

The chemical has reported commercial uses, including:

- in solvents;
- in fillers (e.g. in sealant formulations);
- in impregnation materials;
- as anti-foaming agents in aqueous environments;
- in automotive care products (e.g. hydraulic fluid as organosilicate);
- as monomer in the manufacture of polymers used in personal care products;
- in the manufacture of plastics and insulating materials;
- as construction material additives;
- in petroleum processing; and
- in the manufacture of electronic, semiconductors, photovoltaics and optical products.

The chemical has reported site-limited uses, including:

- as an intermediate in the chemical synthesis of silyl ether and benzoyl chloride;
- as an intermediate in the preparation of speciality organic chemicals and polymers (i.e. silicone polymers), resins and other organosilicon compounds (such as octamethylcyclotetrasiloxane) used in a range of industrial, medical and consumer products; and
- as end-blocking agents in the production of fluorosilicone oil.

The chemical has reported non-industrial uses, including:

- as medical adhesives and in coating materials to improve biocompatibility of medical devices; and
- as antiflatulent agents (human and veterinary use).

Restrictions

Australian

No known restrictions have been identified.

International

No known international restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Chemicals Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

- Temporary emergency exposure limit (TEEL) values of 13 (TEEL-1), 140 (TEEL-2), and 150 ppm (TEEL-3) by the US Department of Energy (DOE); and
- TEEL values of 2.0E+03 (TEEL-1), 2.0E+03 (TEEL-2), and 7.5E+02 ppm (TEEL-3) by the USA Air Military.

Health Hazard Information

The chemical hexamethyldisiloxane (also known as L2) is an organosilicon compound, containing a silicon-oxygen backbone and it is a member of the volatile methyl siloxanes group. The chemical is mainly used as an ingredient in the preparation of a wide range of personal care products and polymers (CIUCUS, 2011; Personal Care Products Council; REACH).

Linear siloxanes (L2 to L5) are expected to have similar physico-chemical properties including high log Kow (increasing with chain length) and low water solubility (REACH). Thus, animal and human data for other structurally relevant linear siloxanes including octamethyltrisiloxane (L3) (CAS No. 107-51-7), decamethyltetrasiloxane (L4) (CAS No. 141-62-8), and dodecamethylpentasiloxane (L5) (CAS No. 141-63-9) are considered relevant as analogue data (NICNASa; NICNASb; NICNASc) and will be used for read-across where hazard data for L2 are lacking.

Toxicokinetics

In vivo toxicokinetic data are available for linear siloxanes including dodecamethylpentasiloxane (L5) and hexamethyldisiloxane (L2). In vitro dermal absorption studies are available for hexamethyldisiloxane (L2) and decamethyltetrasiloxane (L4), showing minimal absorption. L2 is reported to be a volatile liquid (vapour pressure of 5500 Pa at 25 °C), insoluble in water (0.093 mg/L at 23 °C) and highly lipophilic (with a reported octanol-water partition coefficient value of 5.06 at 25 °C). Minimal human exposure is expected through the oral, inhalation or dermal routes. The absorbed fraction of L2 is reported to be effectively metabolised and mainly eliminated as expired volatiles despite its high lipophilicity (OECD 2011; REACH).

Absorption/administration:

Oral

The chemical L2 is expected to have low oral absorption due to its high molecular weight, highly lipophilic nature and low water solubility. A non-guideline in vivo oral toxicokinetics study on L5 reported that absorption following oral administration (single dose) of 600 mg/kg bodyweight (bw) to 2 Sprague-Dawley (SD) male rats was approximately 25 %. Due to its lipophilic nature and low water solubility, oral absorption of L5 from the gastrointestinal tract is expected to occur via micellar solubilisation. In a repeated dose oral study in rats, oral absorption of L2 based on pathological changes in the liver was reported (see **Repeat dose toxicity: Oral** section) (OECD 2011; REACH).

Dermal

The chemical L2 is expected to have low dermal absorption as its insolubility in water reduces its ability to partition from the stratum corneum into the epidermis. There was no evidence of absorption in the acute dermal toxicity and skin irritation studies (see **Acute toxicity: Dermal** and **Skin irritation** sections). In a guideline in vitro dermal penetration study (in accordance with Bronaugh flow through method), the absorption of L2 (as neat ^{14}C-hexamethyldisiloxane) through the human skin was reported to be very low (0.023 %), with the majority of absorbed L2 (75.1 %) found in the skin after 24 hours of exposure. It was reported that 97.5 % of the applied dose of L2 volatised from human skin (OECD, 2011; REACH). An in vitro dermal penetration study (in accordance with Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 428 (skin absorption: in vitro method), using L4 reported almost all (99.9 %) of recovered ^{14}C-decamethyltetrasiloxane volatilised from the surface of human skin while a small amount of the applied dose (0.06 %) was reported to be on the surface of skin 24 hours post-exposure, or remained in the skin after washing and tape stripping (0.03 %). It was estimated that 0.001 % of the applied dose of L4 penetrated through the skin into the receptor fluid and 0.03 % of applied dose was retained in the skin (OECD 2011; NICNASb; REACH).

Inhalation

If inhaled, L2 is expected to be absorbed by micellar solubilisation. Based on 2 in vivo inhalation toxicokinetics studies (in accordance with OECD TG 417 (Toxicokinetics)) on L2, it was reported that 3 or 4 % of the dose was retained in male and female Fischer 344 (F344) rats exposed to L2 vapours (5000 ppm) (single-exposure for 6 hours or repeated exposure over 14 days) (OECD 2011; REACH).

Distribution

Minimal distribution of L2 to tissues and organs is expected, based on both in vivo inhalation toxicokinetics studies (in accordance with OECD TG 417) where the majority of retained dose (3 or 4 %) of L2 was reported to be primarily in the fat,

kidneys and ovaries of F344 rats following exposure (OECD, 2011: REACH). L5 is reported to be rapidly processed through the liver and expired from the lungs based on an oral gavage study in rats where a single dose of L5 (600 mg/kg bw/day) was administered by oral gavage and measurements taken 96 hours post-administration. As a result, minimal concentrations of L5 were detected in the tissues and organs of rats (OECD 2011; NICNASc).

Metabolism

Based on a non-guideline in vivo oral toxicokinetics study on L2, linear siloxanes are reported to be extensively metabolised to a number of metabolites following hydroxylation of methyl groups, Si-O hydrolysis and demethylation at the silicon-methyl bond that were distinct from metabolites obtained from cyclic siloxanes. Major metabolites of L2 identified in rat urine were $Me_2Si(OH)_2$, $HOMe_2SiCH_2OH$, $HOCH_2Me_2SiOSiMe_2CH_2OH$ (predominant), $HOCH_2Me2SiOSiMe_3$, $HOMe_2SiOSiMe_3$, Me_3SiOH. The presence of $Me_2Si(OH)_2$ was reported to demonstrate demethylation at the silicon-methyl bonds. In an in vivo inhalation toxicokinetics study (in accordance with OECD TG 417) using L2, the major metabolites reported included 1,3-bis(hydroxymethyl)tetramethyldisiloxane (combined with an unknown metabolite) (61 %), hydroxymethyldimethylsilanol (14 %), dimethylsilanediol (14 %), and trimethylsilanol (6 %) (OECD 2011; REACH).

Excretion

In an in vivo inhalation toxicokinetics study (in accordance with OECD TG 417), the majority of systemically absorbed L2 (3 % of the applied dose) in the blood and tissues of F344 rats was eliminated in urine or as expired volatiles (71 % as mainly L2), while urinary excretion is reported to be of polar metabolites. To a lesser extent (due to low vapour pressure compared to L2), L5 is reported to be expired as volatiles through the lungs, with excretion of metabolites in urine as the major routes of excretion (OECD 2011; REACH).

In a non-guideline in vivo oral toxicokinetics study, L5 was reported to be rapidly eliminated from 2 male rats, where approximately 74 % of the dose was excreted in faeces, 23 % was eliminated in expired air, and 2.2 % was excreted in urine. It was reported that 65 % and 97 % of the applied dose was eliminated within 24 and 48 hours, respectively (OECD 2011; NICNASc; REACH).

Acute Toxicity

Oral

The chemical has low acute oral toxicity based on the results from 2 guideline rat studies (in accordance with OECD TG 401 (acute oral toxicity)) and 1 non-guideline rat study. The oral median lethal doses (LD50s) were reported to be >12160, >3819 and >3200 mg/kg bw in female and male Hilltop-Wistar Albino rats, Wistar rats and male SD rats, respectively. No mortality or significant treatment-related effects were reported in 2 out of 3 studies. In the Hilltop-Wistar rat study, it was reported that 1 animal at the lowest dose of 8 mL/kg (equivalent to 6080 mg/kg bw) exhibited sluggishness and unsteady gait at 4 minutes, and died within 15 minutes (necroscopic findings included darkened-reddish lungs, liver, intestines and kidneys). Treatment-related effects and mortality in the animal were at very high doses (OECD, 2011; REACH).

Dermal

The chemical has low acute dermal toxicity based on the results from 1 guideline rat and 2 guideline rabbit studies (in accordance with OECD TG 402 (acute dermal toxicity)). The dermal LD50s were reported to be >2000 mg/kg bw in female and male SD rats, ≥12160 and >10000 mg/kg bw in male and female New Zealand White (NZW) rabbits, respectively. No mortality or significant treatment-related effects were reported in the rat study. However, mortalities were reported in both the rabbit studies (where 4 out of 16, and 1 out of 6 animals died) at very high doses. Treatment-related effects reported for all animals included oedema, eschar formation and desquamation at the treatment-site, and necroscopy findings included darkened-reddish lungs, kidneys, liver and blood clots around the heart. Clinical signs of toxicity in some animals included prostration, sluggishness and unsteady gait, hyperactivity, decreased activity, ataxia, gasping and paralysis (OECD, 2011; REACH).

Inhalation

The chemical has low acute inhalation toxicity based on the results from a guideline rat study (in accordance with OECD TG 403 (acute inhalation toxicity)). The median lethal concentration (LC50) was reported to be >106000 mg/m^3/4 hours (equivalent to >15956 ppm or >106 mg/L) in female and male F344 rats following whole-body inhalation exposure to the chemical vapour. At the concentrations tested (11000, 14000 and 18000 ppm (73.7, 93.8 and 120.6 mg/L, respectively)), treatment-related effects (including mortalities) were reported at the 2 highest doses (1 male rat and 1 female rat died at 14000 ppm; and 3 male and 3 female rats died at 18000 ppm). At the highest doses, clinical signs of toxicity included prostration and convulsions, ataxia, porphyrin staining of the eyes and face (in some animals). Lung congestion and haemorrhage were reported at necroscopy in the animals that died. Treatment-related effects and mortalities were at very high concentrations (OECD, 2011; REACH).

Corrosion / Irritation

Skin Irritation

Based on the available animal and human data (see **Irritation: Observation in humans** and **Sensitisation: Observation in humans** sections), the chemical is not considered to be a skin irritant.

In a study conducted similarly to OECD TG 404 (acute dermal irritation/corrosion), 0.5 mL of the undiluted chemical (unspecified purity) was applied to the clipped, intact skin of NZW rabbits (3 animals/group) for 4 hours under occlusive patches with a 7 day observation period (observations were made at 1, 2, 3, and 7 days(s) after patch removal). No treatment-related dermal effects were reported (erythema and oedema mean scores of 0 were noted) (OECD, 2011; REACH).

No skin irritation was reported in a study conducted similary to OECD TG 404 with a semi-occlusive application of 0.5 mL of the chemical (unspecified purity) to the intact skin of 12 NZW male rabbits and observations at 1, 2, 4, 8, 16 or 24 hours (OECD, 2011; REACH).

In a non-guideline dermal irritation study, 0.5 mL of the undiluted chemical (as a liquid (>99.9 % purity)) was applied (10 applications over 14 days) to the intact or abraded skin of 9 NZW rabbits (3 rabbits/dose; sex unspecified) for 24 hours, under occlusive, semi-occlusive and non-occlusive conditions. Animals were observed at 24, 48, and 72 hours after patch removal. No treatment-related effects were reported in animals in the semi-occlusive and non-occlusive groups. In the non-occlusive group, abraded sites in animals had healed by day 4. However, slight (grade 1) to well-defined erythema (grade 2) and exfoliation was reported in the occlusive group by day 4 of application where a difference between intact and abraded skin was observed (exfoliation was observed in days 4 to 6 at the intact sites, and days 4 to 10 at abraded sites). Mean erythema and oedema scores of 0 were reported in all animals (except for the occlusive group, where a mean score of 0.7 was reported). It was concluded by the authors that semi-occluded and non-occluded applications of the chemical did not cause skin irritation but under occlusive applications, an irritation response was reported (OECD, 2011; REACH).

In a supporting non-guideline acute dermal study (similar to the above), 0.5 mL of the undiluted chemical (unspecified purity) was applied to the skin of NZW rabbits (3 males/group) for 24 hours under semi-occlusive, occlusive and non-occlusive conditions and was reported to not produce significant treatment-related skin irritation. No mean erythema and oedema scores were available (OECD, 2011; REACH).

Occlusive application of the undiluted chemical (unspecified volume) was reported to be non-irritating to the intact and abraded skin of 6 rabbits (strain/sex not specified) at 4, 24 or 48 hours after application (OECD, 2011; REACH).

Eye Irritation

Based on the available animal and human data (see **Irritation: Observation in humans** section), the chemical is not considered to be an eye irritant.

In a study conducted similarly to OECD TG 405 (acute eye irritation/corrosion), 0.1 mL of the undiluted chemical (no vehicle; unspecified purity) was instilled into one eye of 6 NZW rabbits (unspecified sex) which were left unwashed for 3 days. Animals were observed at 24, 48, and 72 hours after instillation. No treatment-related effects were noted. Mean Draize scores of 0 (72 hours post-exposure) were reported for corneal opacity, iritis, redness of the conjunctivae and chemosis (OECD 2011; REACH).

In another study conducted similarly to OECD TG 405, 0.1 mL of the undiluted chemical (no vehicle; unspecified purity) was instilled into one eye of 6 female and male NZW rabbits which were left unwashed for 3 days. Animals were observed at 1, 4, 24, 48, and 72 hour(s) after instillation. No significant treatment-related effects were reported; however, transient effects for iritis (in 1 eye), redness of the conjunctivae (in 3 out of 6 eyes) and swelling (in 1 eye) were resolved within 24 hours in affected animals. The maximum mean score at 1 hour was reported to be 1.8/110 (OECD 2011; REACH).

Observation in humans

In a clinical study in humans, exposure to inhalation vapour of the chemical was reported to produce a slight irritation of the lungs, skin and eyes. No further study details were available and the study was considered unreliable (REACH).

Sensitisation

Skin Sensitisation

Based on the available animal and human data (see **Sensitisation: Observation in Humans** section), the chemical is not considered to be a skin sensitiser.

In a guinea pig maximisation test conducted in accordance with the OECD TG 406 (skin sensitisation), male Hartley guinea pigs (10/dose; 5 controls) were intradermally induced at 10 % and topically induced with the undiluted chemical. The undiluted chemical (0.3 mL) was used in the topical challenge phase, (occlusive epicutaneous application for 24 hours) 2 weeks after topical induction. No animals had adverse reactions at 24 and 48 hours post-challenge. A positive control was not included in this study (OECD 2011; REACH).

The chemical structures did not give protein binding alerts for skin sensitisation or respiratory sensitisation as profiled by the OECD Quantitative Structure–Activity Relationship (QSAR) Toolbox v3.4 (OECD Toolbox).

Observation in humans

No evidence of skin sensitisation in human volunteers was reported in a human patch test where 100 subjects were exposed to an induction and challenge dose of 0.2 mL of the undiluted hexamethyldisiloxane (L2) under semi-occlusive conditions. There was no evidence of skin sensitisation under the conditions of this study. Superficial epidermal erosion in a significant number of subjects, indicating irritation, was observed, but this was attributed to the occlusive conditions of the preliminary study (patch conditions were changed to semi-occlusive thereafter) (OECD, 2011; REACH).

In a human patch test, 103 subjects of both sexes were exposed to octamethyltrisiloxane (L3) on the infrascapular region of the back under semi-occlusive conditions. The induction phase consisted of 9 consecutive patch applications of 0.2 mL of undiluted L3 (unspecified purity) at the same site every 48 hours. Patches were removed 24 hours after application. After a 12 to 14 day rest period, the subjects were then challenged, using the same method described for the induction phase, on previously unexposed sites. At 24 and 48 hours following removal of patches, no dermal responses were observed (OECD, 2011; NICNASa).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical is not expected to cause severe adverse health effects following repeated oral exposure.

In a repeated dose 28-day oral gavage rodent study (in accordance with OECD TG 407), the chemical did not produce severe systemic toxicity in male and female SD rats (n=6/sex/dose) following repeated oral exposure at doses of 8, 40, 160 or 640

mg/kg bw/day. No mortality or changes to clinical parameters were reported. Treatment-related effects in males at the highest dose were reported at high doses, including decreased body weight and food consumption, increased organ weights (liver, spleen and brain), and changes to haematological, urinary and histopathological parameters. A no observed adverse effect level (NOAEL) of 160 mg/kg bw/day was reported for males, based on reduced food consumption, increased organ weights and changes to white cell count and haematological parameters. Kidney effects (alpha-2µ-globulin nephropathy) observed in male rats were reported to be species-specific and not considered relevant to humans. An NOAEL for female rats was not determined (REACH).

A non-guideline repeated dose 28-day oral gavage (mechanistic) study in F344 rats (30 males/dose; 10 females/dose), it was reported that alpha-2µ-globulin nephropathy increased in a dose-dependent manner (10, 100 to 1000 mg/kg bw/day). It was concluded that the mechanism of kidney tumour formation in male rats following oral administration is not of human relevance. An NOAEL of ≥ 1000 mg/kg bw/day was reported (REACH).

In a repeated dose 28-day oral gavage rodent study (in accordance with OECD TG 407 with restrictions), the lowest observed adverse effect level (LOAEL) was reported to be <1500 mg/kg bw/day (single dosed tested) for male and female SD rats (n=6/sex/dose) based on bile duct protoporphyrin accumulation at this dose. No other data are available (REACH).

No adverse effects were reported in several non-guideline repeated dose oral studies wherein mice, rats, rabbits and dogs were orally administered the chemical in diet containing up to 2.5 % of the chemical for up to 80 weeks. An NOAEL of ≥2.5 % was reported. No further details on methods were available and the study was not considered reliable (REACH).

Dermal

Based on the available data, the chemical is not expected to cause severe adverse health effects following repeated dermal exposure.

In a repeated dose 28-day dermal toxicity rodent study (in accordance with OECD TG 410), the chemical did not produce severe systemic toxicity in male and female SD rats (n=10/sex/dose) following repeated dermal exposures at doses of 100, 500 or 1000 mg/kg bw/day. No mortalities and changes to clinical, haematological and histopathological parameters were reported. The NOAEL was reported to be 500 mg/kg bw/day for males based on reduced kidney and liver weights at the highest dose. However, as effects on kidney and liver weights were not accompanied by histopathological findings (or observed in female rats) these effects were not considered to be adverse. An NOAEL of 1000 mg/kg bw/day was determined for females, based on no treatment-related effects reported at any dose (OECD 2011; REACH).

No adverse effects were reported in 4 non-guideline repeated dose dermal toxicity studies in rabbits (unspecified strain) that were dermally administered the chemical over 21 (under occlusive conditions) or 28 days (under unspecified conditions) at doses of up to 1000 mg/kg bw/day. Local irritation was noted at the highest dose but no mortalities, adverse effects on body or organ weights, clinical and histopathological parameters were reported. An NOAEL of 200 mg/kg bw/day was reported based on histopathological examination of pitted kidneys observed in animals at the highest dose. No further details on the studies were available and these studies were not considered reliable (REACH).

In a non-guideline repeated dose dermal toxicity study in female NZW rabbits, no adverse effects were reported. The animals were dermally administered the chemical over 21 days (under unspecified conditions) at a single dose of 1000 mg/kg bw/day. No mortality, adverse effects on body or organ weights, clinical and histopathological parameters were reported. Local irritation was noted at this dose. A NOAEL of 1000 mg/kg bw/day for systemic effects was reported. No further study details on methods were available and the study was not considered reliable (REACH).

Inhalation

Based on the available data, the chemical is not expected to cause severe adverse health effects following repeated inhalation exposure.

In a 2-generation reproductive and developmental inhalation toxicity study (in accordance with OECD TG 416) in male and female SD rats (see **Reproductive & Developmental Toxicity** section), no treatment-related mortality or effects on body weight, food consumption or motor activity were reported. The no observed adverse effect concentration (NOAEC) for systemic

toxicity for the chemical was reported to be 400 ppm (2657 mg/m^3) for both sexes (based on microscopic liver findings: golden-brown pigment in the periportal areas at higher concentrations) (OECD, 2011; REACH).

In 2 90-day subchronic inhalation studies (in accordance with OECD TG 413) in F344 rats, the NOAEC and lowest observed adverse effect level (LOAEC) for systemic toxicity were reported to be 5000 ppm (equivalent to 33.1 mg/L) and 21 ppm (equivalent to 0.14 mg/L), respectively for both sexes (OECD, 2011; REACH).

In a 90-day subchronic inhalation study (in accordance with OECD TG 413), male and female F344 rats were exposed (whole-body) to the chemical vapour for 6 hours/day, 5 days/week for 13 weeks at concentrations of 0, 50, 200, 600, 1500 or 5000 ppm (0.34, 1.3, 4.0, 10.0, and 33.1 mg/L). No treatment-related deaths or significant alterations in body weight, food consumption, and clinical and ophthalmologic parameters were reported. Although not toxicologically significant, changes to some haematological and clinical chemistry parameters were reported including increased haemoglobin, urea and bilirubin levels in males exposed to 600, 1500 or 5000 ppm. Increased kidney and testes weights were reported in males at the highest concentration. Changes to histopathological parameters were reported in the kidneys of male rats (increased incidence and severity of tubular degeneration at concentrations between 600 to 5000 ppm with interstitial fibrosis and tubular hyaline casts in some animals at concentrations of 1500 and 5000 ppm). At the highest concentration, increased incidence and severity of tubular granular casts and of papillary mineralisation were reported in male rats. These kidney effects (alpha-2μ-globulin nephropathy) observed in male rats were reported to be species-specific and not considered relevant to humans as there were no changes to histopathological parameters in females rats at any concentration. A NOAEC for systemic toxicity was reported to be 5000 ppm (equivalent to 33.1 mg/L) for both sexes as effects reported at 200 ppm (1.3 mg/L) were not considered relevant due to species-specific effects (OECD, 2011; REACH).

In a 90-day subchronic inhalation study (in accordance with OECD TG 413), male and female F344 rats were exposed (whole-body) to the chemical vapour for 6 hours/day, 5 days/week for 3 months at concentrations of 21, 110, 515, or 2054 ppm (0, 0.14, 0.73, 3.41 and 13.64 mg/L). No mortality and treatment-related effects related to clinical, haematological and ophthalmic parameters, including body weights or food consumption. At the 2 highest concentrations, an increased incidence of occult blood in urine of males was reported at 1 month of exposure and at the top concentration group at 3 months of exposure but was reversible within the recovery period. At necropsy, decreased testes weights, increased lung and adrenal weights (absolute weight, relative to body weight, and relative to brain weight) were reported in males at the highest concentration but these effects were reversible within the recovery period. Decreased testes size of 2 rats in the control group and 5 to 11 rats at each concentration group were reported. Of these animals, 4 still exhibited similar findings at the end of the recovery period. Histopathological findings reported increased incidence and severity of multifocal, subpleural, subacute to chronic interstitial inflammation in the lungs in both sexes at all concentrations, where severity of effects was dose-dependent in males but not in females. These effects were reported in the 1-month recovery period in exposed animals where tubular atrophy of the testes in males (particularly at the highest concentration) and mucification of the vaginal mucosa in females were reported. A NOAEC was not determined. The LOAEC for systemic toxicity was reported to be 21 ppm (equivalent to 0.14 mg/L) for both sexes, based on the organ weight and histopathological changes in the lungs and testes (OECD, 2011; REACH).

In a 28-day subchronic inhalation study (in accordance with OECD TG 412), male and female F344 rats (10/sex/dose group) were exposed (nose-only) to the chemical vapour for 6 hours/day, 5 days/week for 4 weeks at concentrations of 0, 100, 500, 2000 or 10000 ppm (0, 0.67, 3.3, 13.3, and 66.3 mg/L, nominal). After the 20th exposure, one mortality was reported in a female from the highest concentration group (with signs of rapid breathing, hunched posture and a drooping head). Two more females in the same group exhibited similar signs but no further mortalities were reported. No changes to ophthalmic parameters were reported. Slight haematological differences were reported in both sexes at the highest concentration. Clinical findings included elevated levels of serum cholesterol in females at 500 ppm and both sexes at the 2 highest concentrations. Increased levels of triglycerides, phospholipids, phosphorous were reported in some animals and decreased calcium levels were reported for both sexes at the higher doses. At necropsy, it was reported that a slight increase in the lung weights of both sexes at the highest concentration, increase in liver weights of the males at all concentrations, and the females of the 2 highest concentrations and decreases in the thymus weights, and the ovaries of the females of the highest concentration. Gross examination of tissues/organs did not show treatment-related effects. Histopathological findings reported an increase in incidence and severity of local inflammatory lesions in the lungs (interstitial inflammation, alveolar macrophage accumulation and leukocyte infiltration) at the highest concentration but was not dose-dependent. There was also an increase in the incidence and severity of renal tubule degeneration in male rats at the highest concentrations (including hyaline droplet accumulation, protein casts and granular casts). Minimal hepatocellular hypertrophy was evident in males, and in one female at the highest concentration; there was increased pigment accumulation in the bile ducts of males in the highest concentration. A NOAEC could not be determined as minor clinical chemistry and pathologic changes in the lungs occurred at all concentrations from 100 to 10000 ppm (nominal) (136 to 8939 ppm; measured). A LOAEC for systemic toxicity of 100 ppm (0.67 mg/L) or 136 ppm (0.91 mg/L) (measured concentration) was reported based on increased phosphorus levels in females (OECD, 2011; REACH).

Genotoxicity

Based on the available data, the chemical is not expected to be genotoxic.

Several in vitro assays with the chemical gave negative results in (OECD, 2011; REACH):

- bacterial reverse mutation assays (in accordance with OECD TG 471) in *Salmonella typhimurium* strains TA 98, TA 100, TA1535, 1537 and 1538 with or without metabolic activation with S9, at concentrations up to 12500 µg/plate;
- bacterial reverse mutation assays (in accordance with OECD TG 471) in *Escherichia coli* WP2 uvr A strain, with or without metabolic activation with S9, at concentrations up to 10000 µg/plate;
- DNA damage/gene conversion assays (in accordance with OECD 480) in *Saccharomyces cerevisiae* strain D4, with or without metabolic activation with S9, at concentrations up to 3950 µg/mL.
- chromosomal aberration assays (in accordance with OECD TG 473) in Chinese hamster lung fibroblasts V79 cells, with or without metabolic activation with S9, at concentrations up to 300 and 100 µg/mL, respectively; and
- a mammalian cell gene mutation assay (study in accordance with OECD TG 476) in mouse lymphoma L5178Y (TK+/TK-) cells, with or without metabolic activation with S9, at concentrations up to 200 µg/mL.

L3, L4 and L5 are reported to be non-genotoxic based on in vitro and in vivo studies (NICNASa; NICNASb; NICNASc).

The chemical L2 was negative in an in vivo genotoxicity assay (in accordance with OECD TG 475 (mammalian bone marrow chromosomal aberration test) for inducing chromosomal aberrations in bone marrow of male SD rats administered the chemical through intraperitoneal injection at doses up to 1030 mg/kg bw (OECD, 2011; REACH).

The chemical structures did not give DNA binding alerts for genotoxicity as profiled by the QSAR Toolbox v3.4 (OECD Toolbox).

Carcinogenicity

Based on the available data, the chemical is not considered likely to be carcinogenic.

In a 2-year combined chronic toxicity/carcinogenicity study (in accordance with OECD TG 453), F344 rats were exposed to the chemical vapour by whole-body inhalation at concentrations of 700, 2700, 10600 or 33200 mg/m^3 for 6 hours/day, 5 days/week. No treatment-related mortality, or effects on body weight, food consumption or motor activity were reported. Treatment-related effects reported neoplastic histopathology findings which included renal tubular adenomas and carcinomas in some males. Nephropathy and kidney neoplasia were attributed to alpha-2µ-globulin nephropathy (an effect not considered not relevant to humans). The increase in Leydig cell tumours in the testes of males at all concentrations was distinguished to be species-specific to Fischer 344 rats. Irritation effects in the nasal cavity were reported. A NOAEC for carcinogenicity, excluding the effects not relevant to humans, was reported to be 33200 mg/m^3 (equivalent to ≥5000 ppm or 33.2 mg/L) (OECD 2011; REACH).

Reproductive and Developmental Toxicity

Based on the available data, the chemical is not expected to cause reproductive or developmental toxicity.

In a 2-generation reproductive and developmental inhalation toxicity study (in accordance with OECD TG 416), SD rats (n=30/sex/dose) were exposed to the chemical vapour by whole-body inhalation at concentrations of 100, 400, 1600 or 5000 ppm for 6 hours/day, 7 days/week. No significant treatment-related adverse effects on reproductive or developmental parameters were reported at these concentrations when compared to controls. Parental, reproductive and developmental NOAECs of ≥400 ppm (equivalent to ≥2657 mg/m^3 or 33.1 mg/L) were reported (OECD, 2011; REACH).

In a 1-generation reproductive and developmental inhalation toxicity study (in accordance with OECD TG 415), SD rats (n=24/sex/dose) were exposed to the chemical vapour by whole-body inhalation at concentrations of up to 5000 ppm (equivalent

to 5083 mg/m^3 or 33.1 mg/L) for 6 hours/day, 7 days/week. No significant treatment-related effects on reproductive parameters were reported when compared to controls. Parental, reproductive and developmental NOAECs of 5000 ppm (equivalent to 5083 mg/m^3 or 33.1 mg/L) were reported (OECD, 2011; REACH).

Risk Characterisation

Critical Health Effects

The chemical does not have any critical health hazards giving rise to potential health risks under any expected exposure scenarios.

Public Risk Characterisation

The chemical has reported domestic use in coating products in Australia. International information also indicates potential cosmetic and domestic uses (see **Import, manufacture and use** section). However, based on its hazard profile, the chemical is unlikely to pose a risk to the public.

Occupational Risk Characterisation

During product formulation, exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and while cleaning and maintaining equipment. Worker exposure to the chemical at low 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.

Based on its hazard profile, the chemical is unlikely to pose a risk to workers. Information in this report can be used by a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) to determine the appropriate controls.

NICNAS Recommendation

The risk to workers and public from this chemical is not considered to be unreasonable. No recommendations or further assessment is required.

Regulatory Control

Public Health

No specific controls are required.

Work Health and Safety

The chemical is not recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Advice for industry

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical is prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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