Cyclohexasiloxane, dodecamethyl-: Human health tier II assessment

01 July 2016

CAS Number: 540-97-6

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.

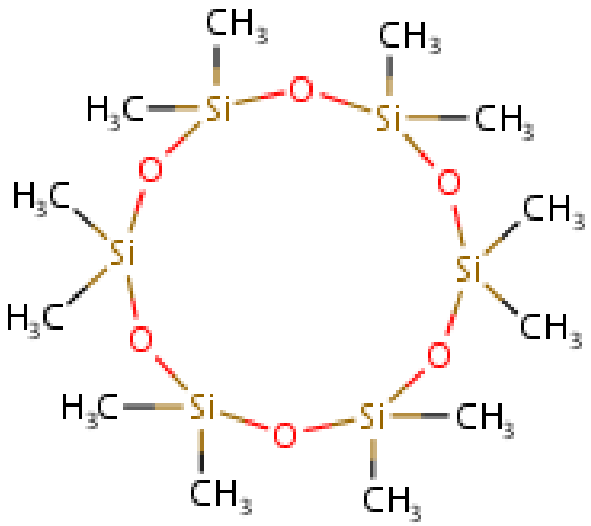
These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time,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

Acronyms & Abbreviations

Chemical Identity

Synonyms	dodecamethylcyclohexasiloxane cyclohexasiloxane, 2,2,4,4,6,6,8,8,10,10,12,12-dodecamethyl- D6
Structural Formula	
Molecular Formula	C12H36O6Si6
Molecular Weight (g/mol)	444.926
Appearance and Odour (where available)	clear, odourless liquid
SMILES	C[Si]1(C)O[Si](C)(C)O[Si](C)(C)O[Si](C)(C)O[Si](C)(C)O[Si](C)(C)O1

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses have been identified through: the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments including from the Organisation for Economic Cooperation and Development (OECD) Screening information data set (SIDS) (OECD, 2009), the Cosmetic Ingredient Review (CIR) (Johnson et al., 2011), Government of Canada (2008) and the European Commission's Scientific Committee for Consumer Safety (SCCS) (SCCP, 2005; SCCS, 2010).

The chemical has reported cosmetic uses, including as:

- an antistatic;
- an emollient;
- a hair conditioning agent;
- a humectant;
- a skin conditioning agent;
- a solvent; and
- a viscosity controlling agent.

The chemical has reported domestic uses, including in:

- cleaning/washing agents;
- paints, lacquers and varnishes;
- surface-active agents (anti-foaming agents); and
- surface treatment (polishing agents).

The chemical has reported commercial uses, including in:

- lubricants and additives (engine and gear oil); and
- reprographic agents (printing inks).

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

The chemical, also referred to as D6 in this assessment, belongs to the group of cyclic dimethyl polysiloxanes compounds. These compounds contain the base unit $[–Si(CH_3)_2O–]_x$ in a cyclic formation. The chemical contains six base units (Johnson et al., 2011).

Dodecamethylcyclohexasiloxane (D6) is a component of cyclomethicone (cyclosiloxanes, dimethyl; CAS No. 69430-24-6), which is a mixture of cyclic dimethyl polysiloxane compounds consisting of 3–7 $[–Si(CH_3)_2O–]_x$ base units. Cyclomethicone is widely used in cosmetics and is predominantly composed of octamethylcyclotetrasiloxane (CAS No. 556-67-2) and decamethylcyclopentasiloxane (CAS No. 541-02-6), also known as D4 and D5, respectively (SCCP, 2005; SCCS, 2010; Johnson et al., 2011).

Toxicokinetics

Based on the available data, the chemical has a low dermal absorption. There is no evidence of toxic metabolites.

The toxicokinetics of D6 were examined in an oral administration study. Ten groups of Fischer 344 (F344) rats (n= 4/sex) were administered a single oral dose of radiolabelled chemical at 1000 mg/kg bw in corn oil and sacrificed for examination 168 hours after dosing. The chemical was absorbed to the extent of 11.88 % in males and 11.83 % in females. In males and females, the majority of the administered dose was excreted within 48 hours in the faeces as the parent chemical. Only a small amount of the administered chemical was systemically available and detected in organs including the liver, fat tissues and bone marrow. Most of the systemically absorbed dose was excreted in expired air (Johnson et al., 2011; OECD, 2009).

In a subcutaneous study, a mixture of low molecular weight cyclosiloxanes (including D4, D5 and D6) was administered to female CD1 mice (n = 6–8 per group) as a single subcutaneous injection of 250 mg. Mice were then sacrificed and examined at 3, 6, 9 or 52 weeks post-exposure. Similarly to D4 and D5, D6 was detected in all of the organs examined, including brain, heart, kidney, liver, lung, lymph nodes, ovaries, spleen, skeletal muscle and uterus. There was an increase of D6 levels over the early weeks post-exposure, then a decrease after week 9. Throughout the study, the highest levels were measured in the mesenteric lymph nodes, ovaries and uterus. This study showed that cyclosiloxanes could still be detected one year after exposure in the organs of exposed mice. The chemicals D5 and D6 seemed to persist longer than D4 (Johnson et al., 2011).

In an in vitro percutaneous study, epidermis samples from six human donors were exposed to a dose of 6 mg/cm^2 of radiolabelled D6 under semiocclusive conditions, during 24 hours. The majority of the applied dose was measured at the surface of the skin (46.4 % of the applied dose) or had volatilised (40 % of the applied dose). A small amount (3 %) was measured in the skin, but did not penetrate through the skin and into the receptor fluid. This study showed that there was negligible percutaneous absorption of the chemical (Johnson et al., 2011; OECD, 2009).

Acute Toxicity

Oral

The chemical has low acute toxicity following oral exposure.

The median lethal dose (LD50) in Wistar rats is >2000 mg/kg bw. No mortality or sub-lethal effects were observed (Government of Canada, 2008; OECD, 2009).

Dermal

The chemical has low acute toxicity following dermal exposure.

The LD50 in Wistar rats is >2000 mg/kg bw. No mortality or sub-lethal effects were observed (Government of Canada, 2008; OECD, 2009).

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

Based on the available data, the chemical is not a skin irritant.

In a skin irritation study conducted in accordance with OECD Test Guideline (TG) 404 (REACH), three New Zealand White (NZW) rabbits were applied 0.5 mL of the undiluted chemical under semi-occlusive conditions, for four hours. Signs of skin irritation were not observed at one, 24, 48 or 72 hours following exposure. The mean primary dermal irritation index (PDII) was reported to be zero (OECD, 2009; REACH).

Eye Irritation

Based on the available data, the chemical is not an eye irritant.

In an eye irritation study conducted in accordance with OECD TG 405 (REACH), three NZW rabbits were exposed to a volume of 0.1 mL of the undiluted chemical, instilled into one eye, which was observed at one, 24, 48 and 72 hours following exposure. Redness of the conjunctivae was observed but resolved within 24 hours (scores were not provided). The mean overall irritation score was reported to be zero (OECD, 2009; REACH).

Sensitisation

Skin Sensitisation

Based on the available data, the chemical is not expected to be sensitising. The chemical was not found to induce dermal sensitisation when tested according to OECD TG 406.

In a guinea pig maximisation test conducted in accordance with OECD TG 406 (REACH), Himalayan guinea pigs (n = 10) were exposed to three intradermal injections (day 0) and one topical application (day 7) of undiluted chemical (induction phase), two weeks before being exposed to challenge doses. In the first challenge phase (day 22), animals were topically exposed to the chemical at 100 % under semi-occlusive patches. One week later (day 29), a second challenge phase was initiated with topical applications of the chemical at 50 % and 20 % in corn oil on the flank of each animal. Skin reactions were reported after the first challenge, both in treated (2/10 and 3/10 after 24 and 48 hours, respectively) and control animals (1/5 and 1/5, respectively), but not after the second challenge phase. While these results indicated some skin irritation, they did not indicate any potential for sensitisation (OECD, 2009; REACH).

Repeated Dose Toxicity

Oral

Repeated oral exposure to the chemical is not expected to cause serious damage to health.

In a combined repeated dose and reproductive/developmental toxicity study, conducted in accordance with OECD TG 422 (REACH), the chemical was administered to Crl:CD rats (n = 10/sex/dose) at oral doses of 0, 100, 330 or 1000 mg/kg bw/day, for 28 days. There were no effects observed on mortality, body weight and weight gain, food consumption, clinical chemistry and gross pathology. Reported effects included: relative organ weight increases in the liver and kidneys of both sexes and in the adrenals of females at all doses and a dose-related increase in the liver weights of females. However, these increases were reported to be within the historical control values. In males, prothrombin time (measuring the time blood takes to clot) was prolonged at the two highest doses, suggesting impaired liver function. There was an increase in periportal lipidosis (accumulation of lipids due to abnormal lipid metabolism) in the liver of females at all doses. A lowest observed adverse effect level (LOAEL) of 100 mg/kg bw/day was determined based on the increased liver weight and periportal lipidosis (OECD, 2009; REACH).

Dermal

No data are available. However, given the low dermal absorption of the chemical and the absence of serious systemic effects (see **Repeat Dose Toxicity: Oral** section), repeated dermal exposure to the chemical is not expected to cause serious damage to health.

Inhalation

Repeated inhalation exposure to the chemical is not expected to cause serious damage to health.

In a subchronic toxicity study conducted in accordance with OECD TG 413 (REACH), groups of Sprague Dawley (SD) rats (n = 10/sex/dose) were exposed (whole body) to vapours of the chemical at concentrations of 0, 1, 10 or 30 ppm (equivalent to 0, 18.2, 182 and 546 mg/m^3, respectively), six hours per day, seven days per week, for 13 weeks. Additional groups of rats were treated similarly and given another 28 days without treatment before sacrifice. There were no effects observed on mortality, body weight and weight gain, food consumption, clinical chemistry, organ weights, haematology or gross pathology. Microscopic findings were observed at 10 and 30 ppm in nasal tissues, liver and lung. At the mid and high doses, males and females exhibited increased incidence and severity of subacute inflammation and hyperplasia of nasal tissues, along with increased mucous cell hyperplasia. Slight increased incidence of periportal vacuolation in the liver was observed in the high-dose female group. Minimally increased incidence of alveolar macrophages in the lung was seen in the mid- and high-dose female groups. While the effects in the liver and the lung resolved within 28 days post-exposure, effects persisted in the nasal tissues. Based on the local effects seen in nasal tissues, a NOAEC of 1 ppm (18.2 mg/m^3) was determined (REACH).

Genotoxicity

Based on the negative results observed in both in vitro and in vivo assays, the chemical is not expected to be genotoxic.

Two in vitro studies were conducted using the chemical (OECD, 2009):

- a bacterial gene mutation test (in accordance with OECD TG 471) on *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA 1537 and *Escherichia coli* strain WP2uvrA, gave negative results at concentrations up to 1000 µg/plate, with and without metabolic activation; and
- a mammalian cell chromosome aberration test (in accordance with OECD TG 473) on Chinese hamster ovary (CHO) cells exposed to 25, 50, 500, 1000, 2500 or 4450 µg/mL, gave negative results; a statistically significant increase in the percentage of cells with structural aberrations was seen at 500 and 4450 µg/mL, without metabolic activation, but was not considered to be biologically significant.

In an in vivo micronucleus assay, conducted in accordance with OECD TG 474, the chemical was intraperitoneally (i.p.) injected to ICR mice at single doses of 500, 1000 or 2000 mg/kg bw. There was no statistically significant increase in the number of micronucleated polychromatic erythrocytes in the bone marrow (OECD, 2009).

Carcinogenicity

No animal data are available for the chemical. Based on the information available from the genotoxicity (see **Genotoxicity**) and Quantitative Structure Activity Relationship (QSAR) modelling, the chemical is not expected to be carcinogenic.

The chemical has no structural alerts for either genotoxicity or carcinogenicity based on the profilers of the OECD QSAR Application Toolbox v3.3.

Reproductive and Developmental Toxicity

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

In a combined repeated dose and reproductive/developmental toxicity study conducted in accordance with OECD TG 422, rats (n = 10/sex/dose) were orally administered the chemical at doses of 0, 100, 330 or 1000 mg/kg bw/day for 14 days prior to and during mating, and through gestation and postpartum for the females (for a total of 45 days of exposure). Apart from a non-statistically significant increase in the number of sperm-positive non-gravid females at the highest dose, there were no effects on the reproductive parameters for either sex. Signs of developmental toxicity were not observed. A no observed adverse effect level (NOAEL) for reproductive and developmental toxicity was determined to be 1000 mg/kg bw/day. Based on the results from repeated exposure (see **Repeat Dose Toxicity: Oral** section), a LOAEL of 100 mg/kg bw/day was considered relevant for maternal toxicity (OECD, 2009).

In a developmental toxicity study conducted in accordance with OECD TG 414, the chemical was orally administered to pregnant female rats (n = 22/dose) at doses of 0, 100, 330 or 1000 mg/kg bw/day, on days 6–20 post-coitum. There were no effects on mortality, clinical signs, body weights, food consumption and macroscopic examination up to the highest dose, leading to a NOAEL of 1000 mg/kg bw/day for maternal toxicity. There were no effects either reported on the number of resorptions, viable foetuses, pre- and post-implantation loss, corpora lutea or implantation sites at any dose. All treated and control animals were gravid. Teratogenic effects were seen at the highest dose, consisting of increased incidence of skeletal malformations (severely malaligned and fused sternebrae) in four foetuses (one foetus from each of four litters) (REACH).

Risk Characterisation

Critical Health Effects

There are no critical health effects for the chemical.

Public Risk Characterisation

Considering the range of domestic, cosmetic and personal care products that may contain the chemical, the main route of public exposure is expected to be through the skin, inhalation from products applied as aerosols, and incidental oral exposure.

However, given the low bioavailability and low toxicity of the chemical, significant public risk is not expected. Hence, the public risk from use of the chemical is not considered to be unreasonable.

Occupational Risk Characterisation

Based on the available data, the chemical is not likely to be hazardous to human health. Hence the risk of workers from use of the chemical is not considered to be unreasonable.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Regulatory Control

Work Health and Safety

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.

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 chemicals has not been undertaken as part of this assessment.

References

Approved Criteria for Classifying Hazardous Substances [NOHSC: 1008(2004)] Third edition. Accessed at http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf

Cosmetic Ingredients and Substances database (CosIng). Accessed at http://ec.europa.eu/consumers/cosmetics/cosing/

European Chemicals Agency (ECHA). Available at http://echa.europa.eu/information-on-chemicals

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

Government of Canada 2008. Screening Assessment for the Challenge Dodecamethylcyclohexasiloxane (D6) CAS No. 540-97-6. November 2008. Available at: https://www.ec.gc.ca/ese-ees/FC0D11E7-DB34-41AA-B1B3-E66EFD8813F1/batch2_540-97-6_en.pdf

Johnson W, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks JG, Shank RC, Slaga TJ, Snyder PW, Andersen FA. 2011. Safety assessment of cyclomethicone, cyclotetrasiloxane, cyclopentasiloxane, cyclohexasiloxane, and cycloheptasiloxane. International Journal of Toxicology, 30(3):149S-227S.

Organisation for Economic Co-operation and Development Screening Information Dataset (OECD SIDS) 2009. Dodecamethylcyclohexasiloxane (D6) (CAS No. 540-97-6)SIDS Initial Assessment Report For SIAM 29. Available at: http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id=1C5E76D1-5DB7-4F54-AD4C-2C173B5F5B99

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossiers. Available: http://echa.europa.eu/information-on-chemicals/registered-substances

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

Scientific Committee on Consumer Products (SCCP) 2005. Opinion on Octamethylcyclotetrasiloxane (D4). SCCP/0893/05. Accessed March 2016 at http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_035.pdf

Scientific Committee on Consumer Safety (SCCS) 2010. Opinion on Cyclomethicone: Octamethylcyclotetrasiloxane (Cyclotetrasiloxane, D4) and Decamethylcyclopentasiloxane (Cyclopentasiloxane, D5). SCCS/1241/10. Accessed April 2016 at http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_029.pdf

Substances in Preparations in Nordic Countries (SPIN). Accessed at http://188.183.47.4/dotnetnuke/Home/tabid/58/Default.aspx

United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary. Accessed March 2016 at http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp

Last update 01 July 2016