Cyclotetrasiloxane, octamethyl-: Human health tier II assessment

01 July 2016

CAS Number: 556-67-2

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.

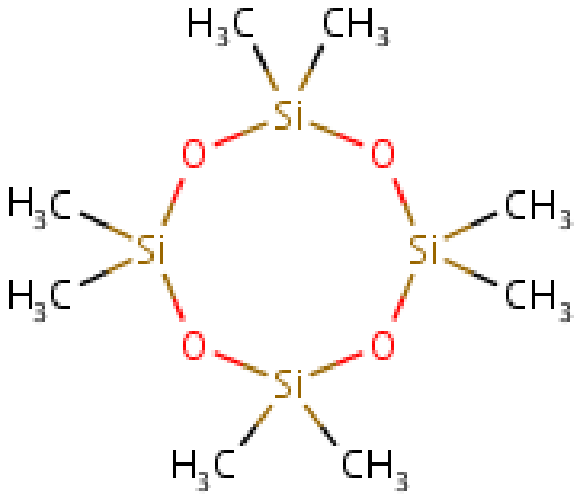
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	octamethylcyclotetrasiloxane D4
Structural Formula	
Molecular Formula	C8H24O4Si4
Molecular Weight (g/mol)	296.6176
SMILES	C[Si]1(C)O[Si](C)(C)O[Si](C)(C)O[Si](C)(C)O1

Import, Manufacture and Use

Australian

The chemical was reported under previous mandatory and/or voluntary calls for information as having industrial use in Australia.

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 United States (US) Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary; the US National Library of Medicine's Household Products Database (HPD) and Hazardous Substances Data Bank (HSDB); the US Environmental Protection Agency's (EPA) Aggregated Computer Toxicology Resource (ACToR); the European Commission's Scientific Committee on Consumer Safety (SCCS) evaluations of the chemical (SCCP, 2005) and cyclomethicone (SCCS, 2010); the Health Canada/Environment Canada screening assessment of the chemical (Government of Canada, 2008); and the safety assessment of cyclic dimethyl polysiloxane compounds by the Cosmetic Ingredient Review (CIR) Expert Panel (Johnson et al., 2011).

The chemical has reported cosmetic uses including as:

- an antistatic agent;

- a humectant;
- an emollient;
- a hair conditioning agent;
- a skin conditioning agent;
- a viscosity controlling agent;
- a solvent; and
- a lubricant and foam control agent in cosmetics and toiletry products.

The chemical has reported domestic uses including as:

- an ingredient in home maintenance and automotive care products;
- an adhesive and binding agent; and
- a cleaning and washing agent.

The chemical has reported commercial uses including:

- as an insulating and impregnating material;
- as lubricant and additive;
- in paints, lacquers and varnishes;
- as a defoamer;
- in mould release agents;
- in surface treatments; and
- in construction materials.

The chemical has reported site-limited uses including:

- as an intermediate for manufacturing polydimethylsiloxane (PDMS);
- as an intermediate in making silicone fluids and elastomers;
- in industrial synthesis of long chain silicone polymers and copolymers;
- in preparation of methyl silicone oils; and
- as a process regulator.

The chemical has reported non-industrial uses including:

- as an ingredient in pesticide products;
- in anti-flatulence drugs; and
- as a component in medical devices, blood-handling equipment, blood defoaming agent, and surface treatment of wound dressings.

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is a flammable substance and, as such, is restricted by Annex XVII of the EU Commission Regulation (EC) No 552/2009 of 22 June 2009 amending Regulation (EC) No 1907/2006 of the European Parliament and of the Council on REACH. Flammable substances cannot be used in

substances and preparations placed on the market for sale to the general public in aerosol dispensers without the appropriate packaging and labelling (European Parliament and Council, 2009).

The United Kingdom had submitted to the European Chemicals Agency (ECHA) an Annex XV dossier proposing to restrict the use concentration of the chemical in wash-off personal care products at ≥0.1 %. The basis of the restriction is not on human health grounds but due to environmental concerns, with the chemical having met the Annex XIII criteria for being persistent, bioaccumulative, and toxic (PBT) and very persistent very bioaccumulative (vPvB). The ECHA Committee for Risk Assessment (RAC) and Committee for Socio-economic Analysis (SEAC) recently released their Opinion supporting the proposal.

The chemical is listed on the Government of Canada's Schedule 1—List of Toxic Substances Managed Under Canadian Environmental Protection Act (CEPA). The presence of the chemical in industrial effluents requires the preparation and implementation of pollution prevention plans (Government of Canada, 2013).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the human health risk phrase R62, Repr. Cat. 3 (reproductive toxicity), in the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

Health Hazard Information

The chemical, also referred to as octamethylcyclotetrasiloxane in this assessment, has a comparatively low molecular weight, high vapour pressure, and low viscosity. It belongs to the group of cyclic dimethyl polysiloxane compounds. These compounds contain the base unit $[–Si(CH_3)_2O–]_x$ in a cyclic formation. The chemical contains four base units (Government of Canada, 2008; Johnson et al., 2011). The purity of the chemical is usually > 95 % with the impurities decamethylcyclopentasiloxane (cyclopentasiloxane, decamethyl-; CAS No. 541-02-6) and hexamethylcyclotrisiloxane (cyclotrisiloxane, hexamethyl-; CAS No. 541-05-9) at maximum concentrations of 5 and 1 %, respectively (SCCP, 2005; SCCS, 2010).

Octamethylcyclotetrasiloxane 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 and decamethylcyclopentasiloxane (SCCP, 2005; Government of Canada, 2008; SCCS, 2010; Johnson et al., 2011).

Toxicokinetics

The toxicokinetics of octamethylcyclotetrasiloxane have been investigated in several human and animal studies, most of which were compliant with the principles of good laboratory practice (GLP). Based on the available in vivo and in vitro studies, the chemical: has low dermal absorption (<1 % in animals and humans) and inhalation absorption (5 % in animals and 12 % in humans); is readily distributed in lung and fat tissues; is metabolised via hydrolysis of the Si–O–Si bonds or demethylation of the silicon-methyl bonds to two major urinary metabolites in animals and humans (dimethylsilanediol and methylsilanetriol), irrespective of the administration route; and is excreted mainly in expired air, urine, and faeces.

In vivo studies - humans

Adult individuals aged 25-49 years were exposed to 10 ppm (122 µg/L) of the radiolabelled chemical (purity 99.03 %) either by a mouthpiece exposure system for two one-hour exposures (8 males and 4 females) or by a nasal device for two 16-hour exposures (6 males and 2 females). The average total intake levels were 11.5 mg (mouthpiece) and 14.8 mg (nasal), and the estimated uptake levels were 1.1 mg (mouthpiece) and 2.0 mg (nasal). The mean inhalation absorption reported was 12 %. Results of plasma levels indicated negligible amounts of the parent chemical in whole blood and analysis of plasma levels showed a non-linear blood clearance trend (SCCP, 2005; SCCS, 2010; Johnson et al., 2011).

In another human study, six adult males aged 24-52 years were exposed by a nasal device to the radiolabelled chemical (purity 98.91 %) at a single concentration of 10 ppm (122 µg/L) for one hour, which included two 10-minute exercise breaks. Continuous respiratory measurements of radioactivity concentrations reported a mean intake of 154 mg and uptake of 19 mg. Elimination of the absorbed dose of 28 % was measured. Rapid non-linear clearance (possibly tetra-phasic) from plasma and blood was postulated. The parent chemical was not detected in the urine while 25-30 % of the absorbed radioactivity was eliminated as metabolites. The following metabolites were determined 16 hours after exposure: trimethyldisiloxane-1,1,3,3-tetrol; tetramethyldisiloxane-1,3-diol; and hexamethyltrisiloxane-1,5-diol. The following metabolites were identified at greater than 16 hours after exposure: methylsilanetriol; dimethyldisiloxane-1,3,3,3,-tetrol; and dimethylsilanediol (SCCP, 2005; SCCS, 2010; Johnson et al., 2011). With the

exception of trimethyldisiloxane-1,3,3-triol, all the metabolites detected in this study were similar to those found in rat toxicokinetic studies described below.

In a non-GLP compliant dermal absorption study, 1.4 and 1 g of [^{13}C]-labelled chemical was applied to the axilla (armpit) of three males and three females, respectively. Samples of blood and exhaled air were collected before application and at the following time points after application: 1, 2, 4, 6, and 24 hours. Compared to baseline levels, there was a significant increase of radioactivity concentrations in blood, plasma, and exhaled air at all observation times. The peak concentrations of radiolabelled chemical in blood and exhaled air were seen 1 hour post administration (SCCP, 2005; SCCS, 2010; REACH).

In vivo studies - animals

The toxicokinetics of octamethylcyclotetrasiloxane was examined in different vehicles in an oral administration study. Female Fischer 344 (F344) rats were administered by gavage a single radiolabelled dose of 300 mg/kg bw of the chemical undiluted, in corn oil, in Emulphor, or in Simethicone fluid. This study was subdivided into preliminary and definitive phases. Corn oil and Simethicone were selected as the vehicles for the definitive phase based on the results of the preliminary phase (details not presented in the publicly available information). The chemical was also administered undiluted in the definitive phase. The absorption of the radiolabelled chemical was expressed as the total recovered radioactivity in the urine, carcass, expired volatiles, and expired CO_2. The absorption of the chemical was 52, 12, and 28 % when administered in corn oil, Simethicone, and neat, respectively, based on an area under the curve (AUC) analysis of blood levels of radioactivity. The concentration of radioactivity in the blood was highest 24 hours following administration (SCCP, 2005; SCCS, 2010; Johnson et al., 2011; REACH). The parent chemical was not detected based on the comparison of blood radioactivity AUC for the parent chemical and the metabolites. Excretion was mainly in the faeces. The metabolic profiles in the urine and the blood were similar for the animals administered the chemical undiluted and in a corn oil vehicle. Urinary metabolites were qualitatively similar in the undiluted, corn oil, and Simethicone vehicle groups. The following five metabolites were identified (REACH):

- $MeSi(OH)_3$ (methylsilanetriol);
- $Me_2Si(OH)$-O-$Si(OH)_3$ (dimethyldisiloxane-1,3,3,3-tetrol);
- $Me_2Si(OH)_2$ (monomer diol);
- $MeSi(OH)_2$-O-$Si(OH)Me_2$ (trimethyldisiloxane-1,1,3-triol); and
- $Me_2Si(OH)$-$OSi(OH)Me_2$ (dimer diol).

In a dermal absorption study, a mix of radiolabelled and non-radiolabelled chemical was applied to female F344 rats at doses of 0, 2, 4.8, or 10 mg/cm^2 for a duration of 1, 6, or 24 hours. The application was semi-occlusive using an aluminium skin depot containing a charcoal basket for collection of expired volatiles. At the end of the application and at 168 hours post-application, blood samples were collected by cardiac puncture, charcoal baskets were extracted, and the skin was washed and solubilised in 35 % tetraethylammonium hydroxide following excision. The radioactivity levels were measured by liquid scintillation counting. The dermal absorption of the chemical was low, with the majority (90 %) of the administered radioactivity volatilised from the skin surface within 1-6 hours post-application in all dose groups for all durations. There was a marked reduction in absorption rate over time, with absorption per unit time at the 24-hour duration significantly lower than at the 1-hour duration irrespective of the dose group (SCCP, 2005; SCCS, 2010; REACH).

In a whole-body inhalation exposure study, male and female F344 rats were exposed to radiolabelled chemical (purity 99.8 %) for six hours at a concentration of 700 ppm. Results indicated that total recovered radioactivity (observation time point not specified) was 5.63 % of the exposure concentration. The maximum tissue concentration of radioactivity was found in fat tissues 12 hours after exposure. The elimination half-lives in blood, plasma, and tissues were 13, 59, and 34-158 hours, respectively. The excretion routes were mainly through respiration (approximately 30 %), in the urine (approximately 47 %), and in the faeces (approximately 12 %). The radiolabelled parent chemical was not found in the urine at up to 48 hours of sampling. The recovered radioactivity in the urine and faeces was reportedly from polar metabolites. No metabolite information was provided in the study (SCCP, 2005; SCCS, 2010).

In a nose-only inhalation exposure study, F344 rats (50/sex/dose) were exposed to radiolabelled chemical (purity 99.58-99.8 %) for six hours at actual concentrations of 0, 7.52, 70.4, or 716 ppm. The absorbed doses were 4.99-5.47 % in males and 5.10-5.52 % in females. Dose-dependent increases in radioactivity levels in the blood and plasma were observed in both sexes. The radiolabelled chemical was mainly distributed to the tissues, especially to fat. The maximum radioactivity levels in blood, plasma, and tissues were reported up to three hours following dosing, except in fat tissues, where the radioactivity levels increased up to 48 hours following dosing. Elimination was mainly through respiration and in the urine, with the lowest proportion in the faeces. The mean terminal half-lives ranged from 68 hours in the plasma to 154 hours in the skin (SCCP, 2005; SCCS, 2010; Johnson et al., 2011; REACH). Similar results were reported in another nose-only inhalation exposure study. Groups of F344 rats (5/sex/dose) were exposed to concentrations of 0, 7, or 700 ppm non-radiolabelled chemical for 6 hours/day for 14 days, followed by a single exposure to the same doses of radiolabelled chemical for 6 hours on day 15. The purity of the non-radiolabelled and radiolabelled chemical was up to 99.8 %. The absorbed doses ranged from 4.38 to 6.14 %, with the absorption independent of sex and exposure dose. Fat tissues contained the highest amount of radioactivity. Approximately 89.2-92.8 % of the administered dose was excreted as follows: 37.4-40.0 % in urine; 12.6-19.1 % in faeces; 25.9-35.4 % as expired volatiles; 2.06-4.54 % as expired CO_2; and 1.31-1.86 % in cage wash (SCCP, 2005; SCCS, 2010; REACH).

A nose-only inhalation study examined the toxicokinetics in F344 and Sprague Dawley (SD) rats exposed to a single 700 ppm dose of the chemical (purity not specified) for six hours. Radioactivity retentions in F344 and SD rats were 8.3 and 5.9 %, respectively. The elimination rate was similar in both strains. The main routes identified were in urine (30 %), faeces (20 %), and expired volatiles (25 %). A lower amount of the parent chemical was found in F344 than in SD rats. The two major metabolites, which accounted for 70-100 % of the radioactivity in the urine, were dimethylsilanediol [$Me_2Si(OH)_2$] and methylsilanetriol [$MeSi(OH)_3$] (Johnson et al., 2011; REACH).

Intravenous (i.v.) administration of the radiolabelled chemical (purity >97 %; vehicle ethanol, Emulphor EL620, and saline in a 1:1:7 by volume ratio) was conducted in male and female SD rats at a single dose of 7 or 70 mg/kg bw, or 14 consecutive daily doses of 7 mg/kg bw. Dose-dependent radioactivity was well distributed throughout the body as shown in a whole-body autoradiography, with the majority found in the fat, liver, and kidneys of both sexes. The peak concentrations of radioactivity were recorded half an hour after administration in the liver, kidneys, and lungs of both sexes. Fat tissues had the highest levels of radioactivity, higher in females than in males, at 120 hours after administration. Liquid scintillation counting at this time point showed that the retained radioactivity was 19 % in female tissues and 11.3 % in male tissues. Repeated dosing of the chemical showed accumulation in all tissues. Tissue concentrations were 4-5 times higher at the 70 mg/kg bw dose than at the 7 mg/kg bw dose. Metabolism was reportedly more extensive in males than in females, with the administered radioactivity eliminated in expired air (22.4 and 35.2 % in males and females, respectively), urine (48.1 and 28.5 % in males and females, respectively), faeces (10.4 and 7.9 % in males and females, respectively), and expired CO_2 (6.5 and 3.2 % in males and females, respectively) (SCCP, 2005; SCCS, 2010; Johnson et al., 2011).

The urinary metabolites of the chemical were determined in another intravenous study. Groups of F344 rats were administered a mix of radiolabelled and non-radiolabelled chemical at a single i.v. dose of 70 mg/kg bw with and without a four-day metabolic induction using phenobarbital in four females, and eight males and females, respectively. The metabolites were identified using high performance liquid chromatography (HPLC). No parent chemical was detected in the samples. Dimethylsilanediol [$Me_2Si(OH)_2$] and methylsilanetriol [$MeSi(OH)_3$], comprising 75-85 % of the total radioactivity, were identified as the two major metabolites. Demethylation of the silicon-methyl bonds of octamethylcyclotetrasiloxane was verified as a clear metabolic pathway due to the presence of the methylsilanetriol metabolite. Five minor metabolites were detected and include (SCCP, 2005; SCCS, 2010; Johnson et al., 2011):

- tetramethyldisiloxane-1,3-diol [$MeSi(OH)$-O-$Si(OH)Me_2$];
- hexamethyltrisiloxane-1,5-diol [$Me_2Si(OH)$-$OSiMe_2$-OSi-$(OH)Me_2$];
- trimethyldisiloxane-1,3,3-triol [$MeSi(OH)_2$-O-$Si(OH)Me_2$];
- dimethyldisiloxane-1,1,3,3-tetrol [$MeSi(OH)_2$-O-$Si(OH)_2Me$]; and
- dimethyldisiloxane-1,1,1,3,3-pentol [$Si(OH)_3$-O-$Si(OH)_2Me$].

In vitro studies

In a study conducted in accordance with the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 428 (in vitro skin absorption; 1994 draft), the chemical in personal care product formulations (concentrations ranged from 5 to 95.8 %) was applied (semi-occlusive) to Yucatan miniature pig (n=3) skin membranes. Independent of the type of formulation and concentration, most of the radioactivity (> 90 % of the applied dose) volatilised from the skin surface. The total absorption in the skin and receptor fluid was approximately 0.05 % of the applied dose (SCCP, 2005; SCCS, 2010; Johnson et al., 2011). Similar results were obtained in another study conducted according to OECD TG 428, with more than 90 % of the administered radioactivity evaporated from dermatomed human abdominal skin (n=6) applied a single dose of the radiolabelled chemical (undiluted or in a formulated antiperspirant). Dermal absorption values (approximately 0.5 %) were reported for the neat and antiperspirant formulation applications (SCCP, 2005; SCCS, 2010; Johnson et al., 2011; REACH). In a human skin/nude mouse model applied with the radiolabelled chemical, the mean distribution of the recovered radioactivity in the dermis, epidermis, and adipose tissue of the skin were 29, 61, and 10 %, respectively. Approximately 1 % of the applied dose was absorbed with most of the administered radioactivity (94 %) volatilised (SCCP, 2005; SCCS, 2010; Johnson et al., 2011; REACH).

Acute Toxicity

Oral

Octamethylcyclotetrasiloxane has low acute toxicity following oral exposure based on results from earlier animal studies (predating GLP). Although the details of these studies are lacking in the publicly available literature, the reported median lethal dose (LD50) values were > 2000 mg/kg bw in rats (SCCP, 2005; SCCS, 2010; Johnson et al., 2011; REACH).

Dermal

Octamethylcyclotetrasiloxane has low acute toxicity following dermal exposure based on results from earlier animal studies (predating GLP). Although the details of these studies are lacking in the publicly available literature, the LD50 values were reported as > 2000 mg/kg bw in rats and rabbits (SCCP, 2005; SCCS, 2010; Johnson et al., 2011; REACH). The studies in rats were reportedly conducted similarly to the OECD TG 402 (REACH).

Inhalation

Octamethylcyclotetrasiloxane has low acute toxicity based on results from animal studies following inhalation exposure. The median lethal concentration (LC50) in rats is 36 mg/L. Observed sub-lethal effects included rapid breathing, hunched posture, stiff gait, and ruffled fur.

In a study conducted in accordance with OECD TG 403, with deviation (no control group), F344 rats (5/sex/dose) were exposed to the aerosolised chemical (purity of 96 %; mass median aerodynamic diameter of up to 4 µm) at concentrations of 20.12, 30.03, or 54.37 mg/L by nose-only inhalation

for four hours. The animals were observed four times at the following post-exposure intervals: 1-6 days; 6-9 days; 9-12 days; and 12-15 days. Mortalities observed in the treatment groups were: 0 in the 20.12 mg/L dose; 1/5 males and 2/5 females in the 30.03 mg/L dose; and 4/5 males and 5/5 females in the 54.37 mg/L dose. Clinical signs seen include hunched posture, stiff gait, and ruffled fur. Towards the end of the exposure period, tachypnoea (uncharacteristic rapid breathing) was observed in the surviving animals of the 30.03 and 54.37 mg/L dose groups. These effects resolved in all animals after six days. At necropsy, effects observed in the animals that died include: red discolouration of the lungs of the animals in the 30.03 and 54.37 mg/L dose groups; presence of dark red or reddish foci of the thymus of one male and one female in the 30.03 mg/L dose group, and one male in the 54.37 mg/L dose group; and reddish staining of the mandibular lymph nodes of one male in the 54.37 mg/L dose group. The gross pathology changes in the lungs were considered related to treatment, while the changes in the thymus and lymph nodes were considered incidental (SCCP, 2005; SCCS, 2010; Johnson et al., 2011; REACH).

Several earlier (pre-GLP) acute inhalation toxicity investigations in rats are available (SCCP, 2005; SCCS, 2010). The limited reporting of the studies indicated no mortality at unspecified doses.

Observation in humans

In a previously described study in humans aged 25-49 years (see **Toxicokinetics**), self-reported clinical effects, with similar observations in both nasal and mouthpiece exposure systems, include cough, sputum production, shortness of breath, chest pain, throat irritation, nasal congestion, headache, fatigue, nausea, sneezing, chest tightness, and eye irritation. These effects were not considered to be related to treatment (SCCP, 2005; SCCS, 2010) and were rated as minimal (score=1) based on the scoring scale from 1 (minimal/not noticeable unless asked) to 5 (incapacitating) (SCCP, 2005; Government of Canada, 2008; SCCS, 2010; Johnson et al., 2011).

Corrosion / Irritation

Respiratory Irritation

The chemical caused local respiratory irritation at high concentrations in acute inhalation toxicity studies (see **Acute toxicity: observation in humans**) and in nose-only inhalation studies in rats (see **Repeat dose toxicity: inhalation**). The effects in the nose and lungs were considered to be adaptive responses and not related to the treatment of the chemical (SCCP, 2005; Government of Canada, 2008; SCCS, 2010).

Skin Irritation

Based on the limited reporting of available studies in rabbits, octamethylcyclotetrasiloxane produced no skin irritation.

In a skin irritation study conducted similarly to OECD TG 404 (non-GLP), 0.5 mL of neat chemical was applied to intact and abraded skin of New Zealand White (NZW) rabbits (n=6; sex not specified). No skin reactions were seen in the intact skin. Desquamation was observed in abraded skin but fully resolved within 72 hours. No other details were provided (REACH).

In another study, neat chemical was applied to intact and abraded skin of the ear and abdomen of NZW rabbits (n=4; sex not specified). Minimal skin reactions were seen following 10 applications on intact skin, while slight irritation was seen following three applications on abraded skin. No other details were provided (Johnson et al., 2011).

Eye Irritation

Based on the results from eye irritation studies in rabbits, octamethylcyclotetrasiloxane was found to be not irritating.

In a study conducted in accordance with OECD TG 405, neat chemical (purity not specified) was instilled into the conjunctival sac of female NZW rabbits (n=3). The other eye was used as control. The treatment-related effects on the cornea, iris, and conjunctivae were evaluated at the following timepoints after instillation: 1, 24, 48, and 72 hours; and 7 days. The mean eye irritation score at the 24-, 48-, and 72-hour observation periods was 0.3 for conjunctival effects. No effects were seen on the cornea and iris (REACH).

In another study conducted similarly to OECD TG 405 (non-GLP), the mean eye irritation scores at the 24-, 48-, and 72-hour observation periods following instillation of the neat chemical (purity not specified) to the eyes of male NZW rabbits (n=6) were 0.22, 0.17, and 0 for effects on the conjunctivae, iris, and cornea, respectively. No other details were provided. The chemical was not irritating based on the test conditions (REACH).

In earlier studies (pre-GLP) submitted to the SCCS, minimal irritation was observed following instillation of the chemical (purity and dose not specified) in the eyes of rabbits (strain not specified). Eye irritation effects observed were reportedly resolved after 24 hours (SCCP, 2005; SCCS, 2010).

Observation in humans

The chemical may have an anti-irritant effect based on the available information.

Four different sunscreen products containing dimethicone (CAS No. 9006-65-9) and cyclomethicone were applied to the skin of patients with rosacea (facial erythema). One minute following application of the products, the patients scored the irritancy from a scale of 0 (no symptoms) to 4 (intolerable discomfort). The study reported that when dimethicone and cyclomethicone were removed from the sunscreen products, the resulting formulations were found to be more irritating, indicating that these chemicals may have anti-irritancy potential (Johnson et al., 2011).

Sensitisation

Skin Sensitisation

Octamethylcyclotetrasiloxane was not found to induce dermal sensitisation when tested in guinea pig maximisation tests (GPMT).

In a GPMT conducted in accordance with EEC Directive 79/831, female albino guinea pigs (n=20) were induced with 1 % of the chemical (purity 99 %) in paraffin oil intracutaneously, followed by a 48-hour topical application of neat chemical on the shaved neck and back area. The animals were challenged after 14 days with neat chemical and 10 % of the chemical in paraffin oil applied by closed patch. No skin reactions were observed at the 24- and 48-hour observation periods (SCCS, 2005; SCCP, 2010).

In another GPMT conducted in accordance with OECD TG 406, female albino guinea pigs (n=20) were treated intradermally at 1 % of the chemical (purity not specified) in paraffin oil, followed by a 24-hour occlusive application of neat chemical on the shaved left flank skin. The animals were challenged after 28 days with the neat chemical and 10 % of the chemical in paraffin oil applied occlusively. No skin reactions were observed at the 24-, 48-, and 72-hour observation periods (REACH).

Repeated Dose Toxicity

Oral

Repeated oral exposure to octamethylcyclotetrasiloxane is not considered to cause serious damage to health.

In two separate 14-day studies, the chemical (purity >98 %) in 0.5 % (w/v) methylcellulose vehicle was administered by gavage daily for two weeks to SD rats (8/sex/dose) at doses of 0, 25, 100, 400, or 1600 mg/kg bw/day or female NZW rabbits (n=6) at doses of 0, 500, or 1000 mg/kg bw/day. No overt signs of toxicity were observed in either species. Treatment-related effects in rats include decreased bodyweight at 1600 mg/kg bw/day (sex not specified) and increased liver weights in both sexes at 400 and 1600 mg/kg bw/day (SCCP, 2005; SCCS, 2010). Morphometric and electron microscopic examination of the liver showed that the increased liver weights were due to hepatocellular hyperplasia (Johnson et al., 2011). All treated rabbits exhibited significant decreases in food consumption and bodyweight. Changes in the spleen and thymus were also observed in the rabbits but were reportedly not dose-dependent (SCCP, 2005; SCCS, 2010; Johnson et al., 2011).

In a 28-day feeding study, the chemical (as liquid drops encapsulated in a capsule composed of 80-90 % gelatine, 5 % modified cornstarch, and 15 % sucrose) was administered to SD rats (5/sex) in the diet. The dose level of the chemical was 2.1 % of the diet with an approximate daily intake estimated from 200 to 300 mg/kg bw/day. The chemical was fed to two groups, young and adult rats, with corresponding controls for each of the treatment groups. Reported clinical signs of toxicity include stress, rough fur and emaciation. Decreased food consumption and reduced bodyweight gain were observed. At necropsy, depleted body fat reserves and watery caecal contents were seen in the treated animals (SCCP, 2005; SCCS, 2010; Johnson et al., 2011).

Rats (unspecified strain) and rabbits (unspecified strain) administered the chemical at 500 mg/kg bw/day in the diet for 8 months (rats) and 12 months (rabbits) showed no effects of treatment (Government of Canada, 2008). No other details were provided.

Dermal

Repeated dermal exposure to octamethylcyclotetrasiloxane is not considered to cause serious damage to health.

In a study conducted similarly to OECD TG 410, the neat chemical (as Baysilone; 99.8 % purity) was applied to the shaved intact flank skin of NZW rabbits (5/sex/dose) at doses of 0, 0.1, 0.3, or 1.0 mL/kg bw/day (approximately equivalent to 0, 96, 190, or 960 mg/kg bw/day) five days a week for three weeks. The open application of the chemical was followed by a two-week recovery period. No treatment-related effects on clinical signs, survival, bodyweight gain, food consumption, haematology, clinical chemistry, urinalysis, and histopathology were observed (SCCP, 2005; SCCS, 2010; REACH).

Inhalation

Repeated inhalation exposure to octamethylcyclotetrasiloxane is not considered to cause serious damage to health. Consistent effects in the liver (weight increase and enzyme induction) were observed in rats, but were reversible and not accompanied by symptoms of overt hepatotoxicity.

In a study conducted in accordance with OECD TG 412, F344 rats (10/sex/dose) were exposed to the chemical (purity >95 %) by nose-only inhalation for 6 hours/day, 5 days/week for four weeks. The actual concentrations used were 0, 2.78, 5.13, 8.62, and 14.21 mg/L (days 1-5) and 13.25 mg/L (days

6-29). The chemical was in vapour phase at the three lower doses and 20 % liquid aerosol at the highest two doses since its saturated vapour concentration was determined to be 130 mg/L. Dose-dependent clinical signs, which include hunched posture, stiff or abnormal gait, head tilt, and ruffled fur, were observed at ≥5.13 mg/L. Treatment-related increase in absolute and relative liver weights in all treated animals, and decrease in absolute and relative thymus weights (males at 14.21 mg/L dose group; females at 13.25 and 14.21 mg/L dose groups) were observed. Histopathological changes observed in all exposed groups include minimal to slight lung alveolar inflammation, ultrastructural changes in hepatocytes, vacuolation of the zona fasciculata of the adrenal cortex, and decreased relative mitochondria volume. Increased vaginal mucification and decrease in the mean corpora lutea score were seen in all exposed females. The no observed adverse effect concentration (NOAEC) established in this study was 2.78 mg/L (SCCP, 2005; SCCS, 2010; Johnson et al., 2011; REACH).

In a multi-species study, whole body 28-day inhalation exposures to 0 or 700 ppm (0 or 8.4 mg/L) of the chemical (purity ≥97 %) were conducted in CD-1 mice (10/sex/dose), NZW rabbits (5/sex/dose), Hartley guinea pigs (10/sex/dose), and Syrian golden hamsters (10/sex/dose). No mortalities or clinical signs were reported in any species. Treatment-related increases in relative liver weights were observed in male and female mice, and female hamsters. No effects of treatment were noted in rabbits or guinea pigs (SCCP, 2005; SCCS, 2010; Johnson et al., 2011; REACH).

In another multi-species study, whole body 35-day inhalation exposures to 0, 10, or 700 ppm (0, 0.12, or 8.4 mg/L) of the chemical (purity ≥99.7 %) were conducted in SD rats (10/sex/dose), CD-1 mice (10/sex/dose), NZW rabbits (5/sex/dose), guinea pigs (strain not specified) and Syrian golden hamsters (10/sex/dose). The study examined liver responses, specifically urinary metabolites and liver enzyme induction, across the different species following exposure to the chemical. No overt signs of toxicity or mortalities were seen in any species. Liver weights were significantly increased in rats, mice, and hamsters exposed at 700 ppm. The demethylated metabolite of the chemical was found in the urine of all species, with the greatest concentrations in hamsters, mice, and rats. In female rats exposed at 700 ppm, hepatic cell proliferation was reported, but this returned to normal levels after exposure. The liver enzymes glutathione-S-transferase, epoxide hydrolase, and ethoxycoumarin deethylase were induced in male and female rats, but the enzyme induction was attributed to an adaptive response specific to rats (SCCP, 2005; SCCS, 2010; Johnson et al., 2011; REACH).

In a study conducted in accordance with OECD TG 413, F344 rats (20/sex/dose) were exposed to the chemical (purity >99.42 %) by nose-only inhalation exposure for 6 hours/day, 5 days/week for 13 weeks at concentrations of 0, 35, 122, 488, or 898 ppm (0, 0.42, 1.48, 5.91, or 10.87 mg/L). Reversible effects observed at the 488 and 898 ppm groups include changes in blood biochemistry, increased absolute and relative liver weights, increased absolute and relative adrenal weights, and decreased absolute and relative thymus weights. All the exposed animals showed irritation effects such as minimal to slight alveolar macrophage foci and chronic interstitial inflammation of the lung. The reported effects in females at 898 ppm group were reversible decrease in ovary weight and vaginal mucification, and increased incidence of ovarian atrophy (SCCP, 2005; Government of Canada, 2008; SCCS, 2010; Johnson et al., 2011; REACH). Similar effects were observed in another 13-week study (equivalent to OECD TG 413) in F344 rats exposed to the chemical at 0, 34, 120, 480, or 883 ppm (0, 0.3, 1.2, or 12 mg/L). A NOAEC of 480 ppm was established in this study based on ovarian hypoactivity and vaginal mucification observed at the highest dose (Johnson et al., 2011; REACH).

Another 13-week study was conducted similarly to OECD TG 413. Groups of SD rats (10/sex/dose) were exposed (whole-body) to the chemical (unspecified purity) for six hours/day, five days/week for 13 weeks at 0, 5, 10, or 300 ppm (0, 0.06, 0.12 or 3.6 mg/L). No treatment-related effects on clinical signs, food consumption, body weights, haematology, serum biochemistry, urinalysis, ophthalmology, or macroscopic or microscopic tissue evaluations were reported. At the end of the exposure period, liver weights in females were significantly increased at the 300 ppm dose group, but returned to similar levels as the control group animals after the four-week recovery period. Histopathology revealed no signs of hepatomegaly. The NOAEC established in this study was 10 ppm (0.12 mg/L) (SCCP, 2005; SCCS, 2010; Johnson et al., 2011; REACH). Similar results were reported in another 13-week study in SD rats (10/sex/dose) exposed (whole-body) to the chemical (purity 97 %) at doses of 0, 50, 300, or 700 ppm (0, 0.06, 3.6, or 8.4 mg/L) for six hours/day, seven days/week. No treatment-related effects in clinical signs, body weights, haematology, serum biochemistry, urinalysis, or ophthalmology were reported. Increased absolute and relative liver weights were observed in all exposed male groups and in females at the 300 and 700 ppm dose groups. The liver weight changes reportedly reversed after recovery in males only (SCCP, 2005; SCCS, 2010; Johnson et al., 2011; REACH).

In a combined repeat dose toxicity/carcinogenicity study conducted in accordance with EPA OPPTS 870.4300 method and equivalent to OECD TG 453, F344 rats were exposed (whole-body, six hours/day, five days/week) to the chemical (purity >99 %) at 0, 10, 30, 150, or 700 ppm (0, 0.12, 0.36, 1.82, or 8.49 mg/L) in four groups as follows (SCCP, 2005; Government of Canada, 2008; SCCS, 2010; REACH):

- 6 animals/sex/dose exposed for six months then sacrificed;
- 10 animals/sex/dose exposed for 12 months then sacrificed;
- 20 animals/sex/dose exposed for 12 months with a 12-month recovery period; and
- 60 animals/sex/dose exposed for 24 months then sacrificed.

No treatment-related clinical signs or effects on ophthalmology and urinalysis were reported. Dose-dependent decreases in serum enzyme activity (aspartate aminotransferase, alanine aminotransferase, creatine kinase, and lactate dehydrogenase) were seen in both sexes. Following 6-month exposure, the concentration of the chemical in the plasma, liver, and fat tissues increased with increasing doses (higher in females than in males, except at 700 ppm; statistical significance not reported). A general trend of increasing absolute liver weight with increasing doses was seen, with statistical significance observed at the following doses and exposure periods compared to controls: 700 ppm (female) and 30 ppm (male) following 6 months of exposure; 150 and 700 ppm (both sexes) following 12 months exposure. The liver weight increase was correlated with centrilobular hepatocyte hypertrophy. Absolute and relative kidney weights in both sexes were increased at 700 ppm following 12 and 24 months exposure, with increased severity of chronic nephropathy reported in the animals from the latter group. Absolute and relative uterus weights, supported by microscopic observations of endometrial epithelial hyperplasia, were increased at 700 ppm following 24 months' exposure. Treatment-related effects in the respiratory tract observed at 700 ppm include increased incidences of goblet cell hyperplasia in the nasal mucosa (in both sexes at 12 and 24 months' exposure) and hyperplasia of squamous epithelium in nasal vestibule (in both sexes at 24 months' exposure), and suppurative (pus-forming) rhinitis (in males at 12 months' exposure) (SCCP, 2005; Government of Canada, 2008; SCCS, 2010; REACH).

Observation in humans

No effects on immunotoxicity or pro-inflammatory adjuvant parameters were reported in a double-blind, placebo-controlled crossover study in human volunteers orally administered the chemical at 12 mg/day for 14 days. No other details were provided (Government of Canada, 2008).

Genotoxicity

Based on the weight of evidence from the available well-conducted in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic.

In vitro studies

Most in vitro studies indicated negative results (SCCP, 2005; Government of Canada, 2008; SCCS, 2010; Johnson et al., 2011; REACH) including:

- several bacterial reverse mutation assays (similar to OECD TG 471) in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, with and without metabolic activation at concentrations up to 12.5 mg/plate;
- mammalian cell gene mutation test (similar to OECD TG 476) in mouse lymphoma cells, with and without metabolic activation at concentrations up to 50 µg/mL;
- mammalian chromosome aberration test (similar to OECD TG 473) in Chinese hamster ovary (CHO) cells, at concentrations up to 0.01 mg/mL (without metabolic activation) and 0.03 mg/mL (with metabolic activation);
- mammalian chromosome aberration test (similar to OECD TG 473) in mouse lymphoma cells, at concentrations up to 0.05 µL/mL (without metabolic activation) and 0.1 µL/mL (with metabolic activation);
- sister chromatid exchange (SCE) assay in CHO cells, with and without metabolic activation at concentrations up to 3 µg/mL (without metabolic activation) and 30 µg/mL (with metabolic activation); and
- DNA repair assay in *Escherichia coli* strain W3110, with and without metabolic activation at concentrations up to 5 µL/plate.

The chemical was positive in a chromosomal aberration test in mouse lymphoma cells. Chromosomal aberrations were induced following metabolic activation and at the high dose only. No dose-response relationship was reported in this test (Government of Canada, 2008; Johnson et al., 2011).

In vivo studies

In a mammalian bone marrow chromosomal aberration test conducted similarly to OECD TG 475, octamethylcyclotetrasiloxane was negative for induction of chromosomal aberrations in SD rats exposed to 700 ppm of the chemical by whole-body inhalation exposure for six hours/day for five days (SCCP, 2005; Government of Canada, 2008; SCCS, 2010; REACH).

In a dominant lethal assay conducted similarly to OECD TG 478, octamethylcyclotetrasiloxane was negative for induction of chromosomal damage in germ cells in SD rats administered the chemical by gavage for five days/week for eight weeks at doses of 0, 100, 500, or 1000 mg/kg bw/day (SCCP, 2005; Government of Canada, 2008; SCCS, 2010; REACH).

Carcinogenicity

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

In a previously described combined repeat dose toxicity/carcinogenicity study in F344 rats exposed (whole-body) to the chemical for 24 months (see **Repeat dose toxicity: inhalation** section), the survival rate of the animals exposed to 700 ppm of the chemical was decreased compared to controls as follows: 38 and 58 % in treated males and females, respectively; compared to 58 and 72 % in the control group males and females, respectively. The increased mortality was attributed to increased incidence of mononuclear cell leukaemia (MCL) observed in both sexes at this dose. MCL is reportedly specific to rats, particularly the F344 strain; hence, the relevance of this tumour to humans is unlikely. Histopathological examination of sections of the uterus of the surviving females at the 700 ppm dose group showed a statistically significant increased incidence of endometrial adenoma. The study authors correlated this neoplastic lesion with hormonal dysregulation due to the potential activation of the signalling pathways through the dopamine receptor by the chemical, and may be of limited toxicological relevance to humans (SCCP, 2005; Government of Canada, 2008; SCCS, 2010; Johnson et al., 2011; REACH). However, the SCCS (2010) and the Government of Canada (2008) indicated that a comprehensive mode of action analysis of the dopamine agonist-like activity of the chemical is required to support this correlation.

Reproductive and Developmental Toxicity

Octamethylcyclotetrasiloxane is classified as hazardous—toxic to reproduction, category 3—with the risk phrase ‘Possible risk of impaired fertility’ (Xn; R62) in the HSIS (Safe Work Australia). The available data support this classification. The chemical does not show specific developmental toxicity, with developmental effects observed secondary to maternal toxicity.

Developmental toxicity

There were no treatment-related effects observed for developmental toxicity parameters in dose range-finding and in embryofoetal toxicity studies in female SD rats and NZW rabbits exposed by whole-body inhalation to the chemical six hours/day for up to 29 days at concentrations up to 700 ppm. Maternal toxicity effects reported in these studies include decreased food consumption and bodyweight gain at ≥500 ppm in the treated animals (SCCP, 2005; Government of Canada, 2008; SCCS, 2010; Johnson et al., 2011; REACH).

In a study conducted similarly to OECD TG 414 (prenatal developmental toxicity), pregnant NZW rabbits (n=6/dose) were administered the chemical (purity not specified) daily by gavage at doses of 0, 50, 100, 500 or 1000 mg/kg bw/day for a total of 29 days' exposure. Marked decreases in food consumption and bodyweight gain were reported at doses ≥100 mg/kg bw/day. Developmental toxicity effects, which were secondary to maternal toxicity, include increased spontaneous abortions at doses ≥500 mg/kg bw/day, and increased post-implantation losses and decreased number of live foetuses at 1000 mg/kg bw/day (SCCP, 2005; Government of Canada, 2008; SCCS, 2010; Johnson et al., 2011; REACH).

In a neurodevelopmental toxicity study conducted according to EPA OPPTS 870.3800 (reproduction and fertility effects), which is similar to OECD TG 416 (two-generation reproduction toxicity), the first parental generation (F0) SD rats (30/sex/dose) were exposed to the chemical (purity not specified) at 0, 70, 300, 500, and 700 ppm concentrations by whole-body inhalation for six hours/day, for 70 consecutive days prior to mating, during mating, throughout gestation until GD 20, and on lactation day five until study termination. At post-natal day 22, the male and female F0 offspring (F1) were exposed to the same conditions as the F0 animals. The F1 offspring (F2) were not exposed to the chemical. Fertility parameters of the F0 and F1 generations, neonatal survival, growth and development, and neurobehavioural and neuropathological changes in the developing F2 offspring were examined in this study. The study results indicated that there were no neurodevelopmental effects in either sex (SCCP, 2005; Government of Canada, 2008; SCCS, 2010; Johnson et al., 2011; REACH).

Reproductive toxicity

Several reproductive toxicity studies are available which include one-generation, dose range-finding, and “phased-female” inhalation studies (whole-body and nose-only) in F344 and SD rats at concentrations up to 898 ppm. The extensive evaluation of these studies by the European Commission SCCS (previously the Scientific Committee on Consumer Products (SCCP)) (SCCP, 2005; SCCS, 2010), the Government of Canada (Government of Canada, 2008), and the CIR Expert Panel (Johnson et al., 2011) indicated that the chemical is toxic to reproduction. The findings from these studies showed that the chemical does not affect male rat fertility. The NOAEC for female fertility effects was established at 300 ppm based on the following observations on female rat fertility parameters consistently reported in these evaluations:

- reduced numbers of ovulated eggs from “phased-female” studies;
- decreased corpora lutea, number of uterine implantation sites, total number of pups born, and mean live litter size at high exposures in one-generation reproductive toxicity studies; and
- fertility effects seen in the absence of maternal toxicity.

In the two-generation reproductive and developmental toxicity study described above, no treatment-related effects were observed in male reproductive parameters. The following effects on female reproduction were observed: statistically significant decrease in mating and fertility indices in F1, and mean live litter size and mean number of pups in F0 and F1 at doses ≥500 ppm; extended parturition and dystocia in F0 at doses ≥500 ppm; and increased oestrus cycle length, reduced corpora lutea, and decreased number of pregnancies in F1 at 700 ppm (SCCP, 2005; Government of Canada, 2008; SCCS, 2010; Johnson et al., 2011; REACH).

There was no clear indication in any of these studies on whether the reproductive toxicity effects from exposure to the chemical were due to the parent chemical or its metabolites.

Other Health Effects

Endocrine Disruption

The chemical has weak oestrogenic and anti-oestrogenic activity from several in vitro uterotrophic bioassays in rats, with an indirect oestrogen receptor-mediated mode of action of very low potency (SCCP, 2005; Government of Canada, 2008; SCCS, 2010). Although some studies indicated that the reproductive effects of the chemical were associated with the inhibition of luteinising hormone (LH) surge in rats, the relevance of the results to humans is uncertain (SCCP, 2005; Government of Canada, 2008; SCCS, 2010; Johnson et al., 2011).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (reproductive toxicity).

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. The European Commission SCCS (2010) and the

Government of Canada (2008) derived the margin of safety (MOS) or margin of exposure (MOE) from the widely dispersive use of the chemical in cosmetics based on its critical health effect and concentrations in personal care products of up to 20 %. Results of the MOS/MOE estimates indicated that the chemical, when used in cosmetic products, does not pose a human health risk. Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure may 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 the chemical 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.

Given the critical systemic long-term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

Based on the available data, the hazard classification in the (HSIS) (Safe Work Australia) is considered appropriate.

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 at this stage.

There is a current EU restriction proposal on the chemical in wash-off personal care products based on environmental concerns (see **Restrictions: International** section). If, during the REACH authorisation process, data become available which may affect the human health outcomes, further assessment may be required.

Regulatory Control

Work Health and Safety

The chemical is recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)*	Suspected of damaging fertility - Cat. 2 (H361f)

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

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

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

Advice for industry

Control measures

Control measures to minimise the risk from oral, dermal, and inhalation exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical[s], if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;

- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to 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 are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

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

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

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

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