Alkanes, C14-17, chloro-: Human health tier II assessment

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CAS Number: 85535-85-9

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	chlorinated paraffins, C14-17 medium-chained chlorinated paraffin (MCCP) CP-350 Witaclor 350 intermediate chain chlorinated paraffin
Structural Formula	**No Structural Diagram Available**
Molecular Formula	Unspecified
Molecular Weight (g/mol)	Unspecified
Appearance and Odour (where available)	Viscous liquid
SMILES	C(Cl)(CCCCCCCCCCC)CC

Import, Manufacture and Use

Australian

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

The chemical has reported commercial uses, including in flame retardants and fire-preventing agents and in plastic manufacture.

The chemical is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume of between 1,000 and 9,999 tonnes.

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 Cooperation and Development Screening information data set International Assessment Report (OECD SIAR); Galleria Chemica; the Substances and Preparations in the Nordic countries (SPIN) database; the OECD High Production Volume chemical program (OECD HPV); and the United States (US) Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR).

The chemical has reported domestic uses including in paints, lacquers and varnishes.

The chemical has reported commercial uses including in:

- adhesives (binding agents);
- fillers;
- flame retardants and extinguishing agents;
- insulating materials;
- surface treatments;
- secondary plasticiser for polyvinyl chloride (PVC);
- construction materials;
- cutting fluids;
- foaming agents;
- lubricants and additives; and
- softeners.

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the Switzerland Ordinance of the Federal Department of Home Affairs (FDHA) on articles and materials of 23 November 2005 Annex 6—List of permitted substances from 1 April 2013 for the manufacture of packaging inks, IV: List of additives, Part B: non-evaluated substances (Galleria Chemica).

The restrictions for the chemical, according to the Switzerland Ordinance of the FDHA Annex 6, IV: List of additives, Part B: non-evaluated substances are that:

- '...no transfer of these substances to food or food simulants can be detected...'; and
- '...must not be detectable in a migration test in the lowest possible concentration at which a substance may be detected...' (Galleria Chemica).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

- R64 (may cause harm to breastfed babies)
- R66 (repeated exposure may cause skin dryness or cracking)

Exposure Standards

Australian

No specific exposure standards are available.

International

The chemical has an exposure standard of 6 mg/m^3 (0.3 ppm) time weighted average (TWA) in Germany.

Health Hazard Information

Chlorinated paraffins (CPs) are generally divided into three categories based on their carbon chain lengths:

- $C_{10–13}$: Short-chained chlorinated paraffin (SCCP)
- $C_{14–17}$: Medium-chained chlorinated paraffin (MCCP)
- $C_{18–30}$: Long-chained chlorinated paraffin (LCCP)

Alkanes, $C_{14–17}$, chloro- (CAS No. 85535-85-9) contains complex components of 14–17 carbon chain lengths with a chlorine content of approximately 40–63 % by weight, and is thus categorised as an MCCP. Due to limited data availability, data from the related chemical in the SCCP group (CAS No. 85535-84-8), which is structurally analogous and has similar physico-chemical properties to the MCCP, are used where necessary to address human health hazards, including acute toxicity, genotoxicity and carcinogenicity.

Toxicokinetics

There are limited toxicokinetic data on the chemical. The available data suggest that there is significant oral absorption, poor dermal absorption and possible excretion in human breast milk.

In an animal study, the chemical was administered as a single oral gavage at a dose of 525 mg/kg bw to male rats (conducted according to the OECD Test Guideline (TG) 417). Four days following dosing, approximately 30 % of the chemical was absorbed. Distribution of the chemical was rapid to the liver and kidney (highest levels of 1.6 % and 0.07 % of the administered dose, respectively, by day one) but slower to the fat and skin/fur (highest levels of 2.5 % and 3.7 % of the administered dose, respectively, by days five and 12 following dosing). The elimination half-life was determined as approximately 2–5 days and two weeks for well-perfused (liver and kidney) and poorly-perfused (white adipose) tissues, respectively. Excretion was mainly via the faeces (71.4 %), with approximately 6 % excreted in the urine by day four after dosing.

The chemical is absorbed slowly through the human epidermis. An in vitro study conducted according to the OECD TG 428 applied the chemical at doses of 12.6 mg/cm^2 (unoccluded) and 125.8 mg/cm^2 (occluded) to human skin membranes for 24 hours using a flow-through apparatus. The majority of the applied dose (97 %) was removed by the washing procedure at the end of the exposure period, with 2.15 % recovered from the stratum corneum and 0.70 % from the epidermis. The conclusion from this study was that the maximum dermal absorption through human skin 24 hours after exposure was 0.7 % under the most conservative conditions (epidermal membrane, solubilising receptor fluid and prolonged exposure).

The limited human data available suggest that it is possible that the chemical could be excreted in human breast milk. A study reported that the mean level of total CPs in human breast milk based on pooled samples of two groups of women was 45 µg/kg lipid. Based on the highest deduced content of MCCP (22 %) in the total CP samples, the estimated concentration of the chemical was approximately 9 µg/kg in breast milk. In a further study, the chemical was found in 1/22 breast milk samples from the United Kingdom at a concentration of 61 µg/kg lipid, but was below the detection limit in the remaining 21 samples. A follow-up study found a median of 21 µg/kg lipid of the chemical in all 25 breast milk samples collected from the United Kingdom (EU RAR, 2008; REACH).

Acute Toxicity

Oral

The chemical has low acute toxicity based on results from animal tests following oral exposure. The median lethal dose (LD50) in rats is >4000 mg/kg bw. Sub-lethal effects such as piloerection, muscular incoordination, urinary/faecal incontinence, hepatocellular vacuolation and focal necrosis in the liver, and cloudy swelling of inner cortical cells in the kidneys were reported. However, the results of two single exposure studies using SCCPs were also reported in the same review. The report's limitations mean that the observed effects cannot clearly be attributed to the chemical or SCCPs (EU RAR, 2008; REACH).

Dermal

No data are available for the chemical. However, a structurally similar chemical in the SCCP group (CAS No. 85535-84-8) demonstrated low acute toxicity in animal tests following dermal exposure. The dermal LD50s are >13500 mg/kg bw and >2800 mg/kg bw in rabbits and rats, respectively (EU RAR, 1999; NICNAS, 2001; EU RAR, 2008; REACH). Therefore, it is predicted that the chemical has low acute toxicity following dermal exposure.

Inhalation

No data are available for the chemical. However, a structurally similar chemical in the SCCP group (CAS No. 85535-84-8) demonstrated low acute toxicity in animal tests following inhalation exposure. No signs of toxicity were observed in rats following a one-hour exposure of vapour or aerosol at a concentration of 3.3 mg/L (four-hour equivalent of exposure: 1.65 mg/L). In a separate study, the median lethal concentration (LC50) in rats was >48.17 mg/L following a one-hour exposure to vapour (four-hour equivalent of exposure: >24.09 mg/L) (EU RAR, 1999; NICNAS, 2001; EU RAR, 2008; REACH). Therefore, it is predicted that the chemical has low acute toxicity following inhalation exposure.

Corrosion / Irritation

Skin Irritation

The chemical is classified as hazardous with the risk phrase ‘Repeated exposure may cause skin dryness or cracking’ (R66) in the HSIS (Safe Work Australia). The available data support this classification.

In a rabbit study (conducted according to the OECD TG 404), occlusive application of 0.5 mL of undiluted chemical (40 % chlorination) caused slight skin irritation. Erythema and oedema (mean scores of 1.5 and 0.6, respectively) were observed 24–72 hours after application and scales were seen on the skin 6–10 days after application. Dry and hard skin and peeling of the outer-most skin layer were observed at 72 hours and 6–8 days after application, respectively (EU RAR, 2008; REACH).

In another rabbit study (conducted according to the OECD TG 404), occlusive application of 0.5 mL of undiluted chemical (52 % chlorination) caused slight skin irritation. Erythema and oedema (mean scores of 1.3 and 0.3, respectively) were observed at 24–72 hours after application and scales were seen on the skin 6–10 days after application (EU RAR, 2008; REACH).

In a separate rabbit study, the chemical (40 % or 45 % chlorination) was applied occlusively to both abraded and non-abraded skin of the animals (six animals/group). No signs of skin irritation were observed with the 45 % chlorinated chemical and very mild skin irritation was observed in only one animal following application of the 40 % chlorinated chemical. Therefore, the chemical at 40 % chlorination is considered a slight skin irritant (EU RAR, 2008; REACH).

Three rat studies, all with limitations in reporting, indicate that the chemical is a mild skin irritant. In the first study, slight desquamation was observed in the animals following single or repeated exposure to the chemical. In a repeated exposure study, occlusive application of 0.1 mL of the chemical (exposed on alternate days) followed by a 24-hour exposure-free period caused mild skin irritation by the third application (EU RAR, 2008; REACH).

In a 12-day repeated exposure study, 0.1 mL of the chemical (40 % or 45 % chlorination) was applied under occlusive conditions on alternate days for 24 hours. Slight desquamation was observed in all rats by the final application. The 40 % chlorinated chemical resulted in slight erythema by the third application, leading to cracking, thickening and desquamation by the final application. The 45 % chlorinated chemical resulted in slight erythema and desquamation by the third application, leading to cracking, scabbing and hardening of the skin by the final application (EU RAR, 2008; REACH).

Eye Irritation

The chemical is reported to be a slight eye irritant in animal studies. The effects were not sufficient to warrant a hazard classification.

In two rabbit studies conducted according to the OECD TG 405, 0.1 mL of undiluted chemical (40 % or 52 % chlorination) was instilled into the conjunctival sac of one eye of each animal. Conjunctival redness (score 1) was observed in all three animals at one hour post application, and in 1/3 animals at 24 hours (both studies) and at 48 hours in the study with 40 % chlorinated chemical (EU RAR, 2008; REACH).

In a separate study, undiluted chemical (40 % or 45 % chlorination) was instilled into the conjunctival sac of three rabbits in each group. Slight initial pain (score 2/5) and transient conjunctival irritation (score 3) at 1–2 hours post instillation were recorded. However, no effects were seen at 24, 48 or 72 hours after exposure (EU RAR, 2008; REACH).

Reports from six other rabbit studies also cited no ocular irritation following single exposure of the chemical (EU RAR, 2008; REACH).

Sensitisation

Skin Sensitisation

The available information indicates that the chemical is not likely to be a skin sensitiser.

In a guinea pig maximisation test, 20 test animals and 10 control animals were initially treated with 20 % of the chemical in maize oil intradermally. At topical induction with the undiluted chemical, 'an intense, sometimes haemorrhagic, purulent inflammation', most likely associated with pre-treatment with Freund's complete adjuvant, was observed. Following the initial challenge using the undiluted chemical, 1/20 test and 1/10 control animals showed a reaction when checked 48 hours after the challenge (scores of 1 and 3, respectively). The second challenge did not result in positive skin reactions (EU RAR, 2008; REACH).

In two other guinea pig maximisation tests, no skin reactions were observed following intradermal induction at 5 % of the chemical and topical induction at 20 % of the chemical in olive oil. The challenge was conducted with a 20 % concentration of the chemical (EU RAR, 2008; REACH).

Repeated Dose Toxicity

Oral

A number of repeated dose oral toxicity studies in animals indicate that the main target organs for the chemical are the liver, thyroid and kidney. Overall, a 90-day rat study established a no observed adverse effect level (NOAEL) of 100 mg/kg bw/day based on kidney effects (EU RAR, 2008; SCHER, 2008). However, the doses at which effects were seen were not sufficient to warrant hazard classification.

In a repeated dose toxicity study, Fischer 344 (F344) rats (10 animals/sex/group) were fed the chemical in their diet at doses of 0, 30, 100, 300 or 3000 ppm (equivalent to 0, 2.38, 9.34, 23 or 222 mg/kg bw/day for males and 0, 2.51, 9.7, 24.6 or 242 mg/kg bw/day for females) for 90 days. No treatment-related deaths were observed. At the highest dose tested, increased liver weight (by 13–31 %), minimal centrilobular hepatocyte hypertrophy, increased hepatic microsomal T4-UDPGA glucuronyl transferase activity and thyroid hormone effects (decreased plasma free T3 and increased plasma TSH levels in males; increased plasma free T4 and TSH levels in females) were observed. Statistically significant decreases in plasma triglycerides (by 28–39 %) and cholesterol (by 14–23 %) were also observed in the 3000 ppm animals. Therefore, a NOAEL of 300 ppm of the chemical (23 and 24.6 mg/kg bw/day in males and females, respectively) was established in this study (EU RAR, 2008; REACH).

In a separate repeated dose toxicity study, F344 rats (15 animals/sex/group) were fed the chemical in their diet at doses of 0, 10, 100 or 625 mg/kg bw/day for 90 days. One control female and one 100 mg/kg bw/day female died during the study following blood collection, but the deaths were not related to treatment with the chemical. A statistically significant increase (25 %) in serum cholesterol was observed in the 625 mg/kg bw/day females. The observed liver and thyroid effects were not considered to be of toxicological significance to human health, given that humans are less sensitive to peroxisome proliferation and thyroid hormone perturbation than rats (see **Carcinogenicity**). Kidney lesions considered to be of toxicological significance only occurred in the 625 mg/kg bw/day animals, along with increases in urinary protein, bilirubin and urobilinogen. Absolute and relative kidney weights were also significantly increased in the 625 mg/kg bw/day animals. Therefore, a NOAEL of 100 mg/kg bw/day was established in this study, based on the kidney changes observed (EU RAR, 2008; REACH).

A 90-day repeated dose oral toxicity study in Wistar rats (24 animals/sex/group) was conducted at doses of 0, 500, 2500 or 5000 ppm (equivalent to 0, 33, 167 or 333 mg/kg bw/day for males and 0, 32, 160 or 320 mg/kg bw/day for females). No treatment-related deaths or clinical signs of toxicity were observed. Statistically significant increases in relative liver weights were observed in the 2500 and 5000 ppm males and the 500, 2500 and 5000 ppm females. Relative kidney weights were increased in the 5000 ppm animals. However, no histological abnormalities were observed using light microscopy (EU RAR 2008; REACH).

A 14-day repeated dose oral toxicity study in F344 rats (five animals/sex/group) was conducted at doses of 0, 150, 500, 1500, 5000 or 15000 ppm (equivalent to 0, 18, 58, 170, 550 or 1540 mg/kg bw/day for males and 0, 18, 58, 180, 580 or 1290 mg/kg bw/day for females). No treatment-related deaths or clinical signs of toxicity were observed. Statistically significant increases in absolute and relative liver weights were observed in the 5000 and 15000 ppm animals, while statistically significant decreases in absolute and relative ovary weights were observed in the 15000 ppm females. Diffuse mild hypertrophy was observed in the livers of the 5000 and 15000 ppm animals, but this was considered to be due to an increase in metabolic demand (adaptive changes) and/or peroxisome proliferation (EU RAR, 2008).

In a repeated dose toxicity study with dogs, statistically significant increases in serum alkaline phosphatase activity and relative liver weights were observed at 100 mg/kg bw/day in the male animals. 'Cloudy, pale and enlarged hepatocytes and an increase

in smooth endoplasmic reticulum (SER)' were observed in some animals at 30 and 100 mg/kg bw/day, but these changes were considered to be adaptive changes due to increased metabolic demand (EU RAR 2008; REACH).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the negative results from the available in vitro and in vivo genotoxicity studies, the chemical is not considered to be genotoxic.

In vitro studies

Negative results were observed in the following in vitro genotoxicity studies (EU RAR, 2008; REACH):

- three bacterial reversal mutation tests with five *Salmonella typhimurium* strains (TA98, TA100, TA1535, TA1537, TA1538) up to a maximum concentration of 5000 µg/plate, in the absence or presence of rat liver metabolic activation system; and
- a bacterial reversal mutation test with four *S. typhimurium* strains (TA98, TA100, TA1535, TA1538) at concentrations of 4, 20, 100, 500 and 2500 µg/plate, in the absence or presence of rat liver metabolic activation system.

In vivo studies

Negative results were observed in all in vivo genotoxicity studies.

In an in vivo bone marrow chromosomal aberration assay (conducted according to the OECD TG 475) with male F344 rats (eight animals/group), the chemical (52 % chlorination) was administered for five days via oral gavage at concentrations of 0, 500, 1500 or 5000 mg/kg bw/day. There were no mortalities or treatment-related signs of general systemic toxicity associated with treatment. The frequency of chromosomal aberrations was not increased in the treated animals. Clear responses were obtained with the positive control substance (EU RAR, 2008; REACH).

In a mouse bone marrow micronucleus assay (conducted according to the OECD TG 474) with five animals/sex/group, the chemical (42 % chlorination) was administered in a single oral gavage dose of 5000 mg/kg bw and bone marrow was sampled at 18, 43 or 66 hours after administration. No increases in the incidence of micronuclei were observed in the polychromatic erythrocytes (PCEs) of treated animals. The positive control substance produced clear responses, verifying the sensitivity of the test system (EU RAR, 2008; REACH).

In a separate mouse bone marrow micronucleus assay with five animals/sex/group, the chemical (45 % chlorination) was administered in a single oral gavage dose of 0, 3125, or 5000 mg/kg bw and bone marrow was later sampled at 24, 48 and 72 hours. The animals treated with 3125 mg/kg bw chemical were only sampled 24 hours after administration. No increases in the incidence of micronuclei were observed in the PCEs of treated animals. The positive control substance produced clear responses (EU RAR, 2008; REACH).

A structurally similar chemical in the SCCP group (CAS No. 85535-84-8) did not induce mutations in bacteria both in the absence or presence of metabolic activation system. SCCPs tested negative in a mammalian cell gene mutation assay with Chinese hamster lung fibroblasts (V79), in vivo rat bone marrow cell chromosomal aberration assay and germ cell studies (EU RAR, 1999; NICNAS, 2001; EU RAR, 2008; REACH).

Carcinogenicity

No data are available for the chemical.

The available read-across data indicate that a structurally similar chemical in the SCCP group (CAS No. 85535-84-8) induces liver tumours in male and female rats and mice, thyroid tumours in female rats and mice, and kidney tubular cell adenomas and carcinomas in male rats. The liver tumours were considered to be associated with peroxisome proliferation in rats, while thyroid tumours were due to hyperplasia in response to reduced thyroid hormone levels (EU RAR, 1999; NICNAS, 2001; EU RAR, 2008; SCHER, 2008).

The induction mechanisms for liver and thyroid tumours (peroxisome proliferation and thyroid overstimulation, respectively) are considered to be of little or no relevance to humans (EU RAR, 1999; NICNAS, 2001; EU RAR, 2008; SCHER, 2008). Recent mechanistic evidence shows that a2μ-globulin binding to SCCPs could be a likely mechanism of action behind kidney tumours observed in male rats treated with SCCPs. While this mode of action is not considered relevant to humans, the mechanism behind kidney tumours has not been fully elucidated (EU RAR, 2008). Therefore, it is not possible to determine the relevance of SCCPs-induced kidney tumours observed in rats to humans.

However, the EU specialised experts in the fields of carcinogenicity, mutagenicity and reprotoxicity have agreed that it is not appropriate to read across data from SCCPs to MCCPs for carcinogenicity given the absence of animal tumour data for MCCPs and the toxicological differences observed between SCCPs and LCCPs (EU RAR, 2008; SCHER, 2008). Hence, there are insufficient data to determine a hazard classification for the chemical's carcinogenicity.

Reproductive and Developmental Toxicity

The chemical is classified as hazardous with the risk phrase ‘May cause harm to breastfed babies’ (R64) in the HSIS (Safe Work Australia). The available data support this classification.

In a one-generation reproductive toxicity study (conducted according to the OECD TG 421), Wistar rats (five males and 10 females/group) were administered the chemical in their diet at 0, 100, 1000 or 6250 ppm (approximately 0, 6, 62 or 384 mg/kg bw/day for males and 0, 8, 74 or 463 mg/kg bw/day for females) for 28 days before and during mating, and (in females only) up to post-natal day 21. Five male and 10 female pups were selected at random from each group, and fed the same diet as their parents from weaning up to 70 days of age. No deaths, abnormalities or treatment-related fertility effects were observed in the parental (F0) rats. A statistically significant decrease (12 %) in food consumption was observed in the 6250 ppm female F0 rats during week five. No first filial generation (F1) pups survived to weaning in the 6250 ppm litters (possibly due to internal haemorrhages). Pup survival was reduced by 11 % in the 1000 ppm litters. Decreased activity and swollen black/dark eyes were observed in a few F1 pups in several of the 1000 and 6250 ppm litters. Dose-related occurrence and severity of subcutaneous haematoma, pallor, blood around the orifices, pale liver, kidneys, lungs and spleen and blood in the cranial cavity and brain were increased, but were not statistically significant in the 1000 and 6250 ppm F1 pups. Haematoma was noted in all 6250 ppm litters. A NOAEL of 100 ppm (approximately 8 mg/kg bw/day) in the offspring during lactation was established for this study (OECD, 2000; EU RAR, 2008; REACH).

In another one-generation reproductive toxicity study (conducted according to the OECD TG 421), groups of 12–17 Sprague Dawley (SD) rats were administered the chemical in their diet at 0, 300, 600 or 1200 ppm for four weeks before pairing, and throughout pairing, gestation and lactation until the animals were euthanised. No adverse treatment-related effects were observed in the animals except marginally higher absolute and relative liver weights in the 1200 ppm F0 females, which is consistent with the effects seen in repeated dose toxicity studies. A NOAEL of 1200 ppm (approximately 100 mg/kg bw/day prior to birth and 212 mg/kg bw/day during lactation) for pre- and post-natal survival and growth of the F1 offspring up to weaning was established for this study, as well as a NOAEL of 600 ppm (approximately 47 mg/kg bw/day) for maternal toxicity based on observed liver effects (OECD, 2000; EU RAR, 2008; REACH).

In a teratogenicity study (conducted according to the OECD TG 414), pregnant female rabbits (16 animals/group) were orally administered the chemical at doses of 0, 10, 30 or 100 mg/kg bw/day on gestational days (GD) 6–27. No treatment-related mortalities or clinical signs of toxicity were observed in the dams. The low level of abortions and the increased number of viable foetuses were not considered to be of toxicological significance. A NOAEL of 100 mg/kg bw/day was established for this study (OECD, 2000; EU RAR, 2008; REACH).

In a separate teratogenicity study (conducted according to the OECD TG 414), mated female Charles River CD rats (25 animals/group) were orally administered the chemical at doses of 0, 500, 2000 or 5000 mg/kg bw/day on GD 6–19. Clinical signs of maternal toxicity (including wet and/or matted fur in the anogenital region and increased incidences of soft stools) were

observed at doses of 2000 and 5000 mg/kg bw/day. No treatment-related developmental effects were observed at 5000 mg/kg bw/day. Thus a NOAEL of 5000 mg/kg bw/day was established for this study (OECD, 2000; EU RAR, 2008; REACH).

Several studies were conducted to further investigate the possible mechanism of high mortality in pups associated with internal haemorrhages observed in the one-generation reproductive toxicity study summarised at the beginning of this section. In a one-generation reproductive toxicity study, 0 or 6250 ppm of the chemical (approximately 0 or 3125 mg/kg bw/day) was fed to groups of male and female Wistar rats during pre-mating and to the females up to day 10 of pregnancy, throughout pregnancy or throughout pregnancy and lactation. After confirmation of mating, the females were separated into the following groups under the following conditions:

1. control diet and rearing own pups;
2. chemical diet and rearing pups from group 3 control females;
3. control diet and rearing pups from group 2 treated females;
4. chemical diet and rearing own pups; and
5. chemical diet up to day 10 of pregnancy and then rearing own pups while fed the control diet.

No treatment-related adverse effects were observed during pre-mating period and pregnancy. The pups from groups 2 and 4 had significant increases in pup mortality (77 % and 67 %, respectively compared with 4 % for group 1) and haemorrhages were observed in 17 % and 8 % of these deaths in groups 2 and 4, respectively. Throughout lactation, these pups also showed statistically significant reduction in the concentration of clotting factor X in their blood samples. Based on these observations, it was proposed that the chemical was either transferred through the breast milk, resulting in disruption of the vitamin K-dependent clotting system in the pups, or there was a reduction of vitamin K in the breast milk due to maternal treatment-related effects, with consequent impairment of the clotting system in the pups (EU RAR, 2008; REACH).

To test if reduced vitamin K levels in breast milk affected the clotting system, a preliminary study was conducted with a group of female SD rats on a normal or a vitamin K_3-deficient diet. The animals were administered 0, 500 or 1000 mg/kg bw/day of the chemical for 21 days. Clotting factor X levels were unaffected in all treated animals and only the vitamin K_3-deficient diet animals treated with 1000 mg/kg bw/day of the chemical showed a reduction in plasma vitamin K levels. Administration of the chemical resulted in a significant decrease in plasma concentrations of clotting factor VII in animals fed a normal diet. However, this effect was not sufficient to cause a biologically significant increase in prothrombin clotting times in the animals. A decrease in plasma concentrations of clotting factor VII was observed in all the vitamin K_3-deficient diet animals, indicating that this effect was not likely to be related to the chemical treatment. Overall, it was concluded that the chemical (up to 1000 mg/kg bw/day) does not affect the blood clotting system in adult female rats. Thus, the haemorrhagic effects on the pups were not likely to be caused by reduced vitamin K levels in the breast milk (EU RAR, 2008; REACH).

To test if disruption in the clotting system of the pups was due to the chemical being transferred through breast milk, a one-generation reproductive toxicity study was conducted with groups of SD rats fed with 0 or 6250 ppm of the chemical (approximately 0 or 513 and 538 mg/kg bw/day for males and females, respectively) for four weeks before mating, then throughout cohabitation, gestation, and about two weeks of lactation. After day four of lactation, pup mortality increased dramatically among the treated animals. The study was prematurely terminated (day 12 of lactation), as only a few pups had survived. The majority of these pups showed signs of internal haemorrhages. By day four of lactation, the pup liver weight from the treated group was significantly increased compared with the control pups.

A mean level of 1057 mg/L of the chemical was detected in milk from the treated animals compared with none in milk from the control group on the first day of lactation. On day 12 of lactation, maternal plasma vitamin K levels measured in samples from animals in the treated dams were significantly decreased compared with control dams. The clotting abilities of factors VII and X in the treated adult females were also decreased compared with the control dams. However, this did not affect the prothrombin clotting times, suggesting that the functional reserve of vitamin K in the adult females was sufficient. The reduction in maternal plasma vitamin K levels subsequently led to decreased vitamin K levels in the treated dam milk. The pups from the treated dams also showed reduced clotting abilities of factors VII and X compared with control pups. Maternal death during parturition (associated with haemorrhaging) was observed in 5/32 dams treated with the chemical.

These data suggest that the functional reserve of vitamin K in the adults treated with the chemical might be sufficient to provide vitamin K to the foetus via the placenta. However, severe deficiencies in vitamin K and clotting factors occur when the pups rely on the mothers' milk after birth. The chemical was also present at considerable levels in the milk, which could lead to a further reduction of vitamin K levels received and consequently resulting in haemorrhaging (OECD, 2000; EU RAR, 2008; REACH).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation includes a systemic long-term effect, reproductive toxicity (i.e. may cause harm to breastfed babies). The chemical can also cause skin dryness and cracking through repeated exposure.

Public Risk Characterisation

Although use in domestic products in Australia is not known, the chemical is reported to be used in products with potential domestic use overseas including in paints, lacquers and varnishes (see **Import, manufacture and use**). Although the chemical is not sold directly to the public, exposure might occur through paint products containing the chemical and the main route of exposure is through skin contact. Considering the low dermal absorption rate (0.7 %), the chemical is unlikely to be a concern for public health. Therefore, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety.

Occupational Risk Characterisation

During product formulation, exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to 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 and local health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise 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 legislation as adopted by the relevant state or territory. No further assessment is 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]
Irritation / Corrosivity	Repeated exposure may cause skin dryness or cracking (R66)*	Repeated exposure may cause skin dryness and cracking (AUH066)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Reproductive and Developmental Toxicity	May cause harm to breastfed babies (Xn; R64)*	May cause harm to breast-fed children (H362)

[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 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 which could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- health monitoring for any worker who is at risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health;
- 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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