Medium and Long Chain Chlorinated Paraffins: Human health tier II assessment

30 June 2017

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Alkanes, C10-22, chloro-	104948-36-9
Alkanes, C10-21, chloro-	84082-38-2
Alkanes, C16-27, chloro-	84776-07-8
Alkanes, C18-28, chloro-	85535-86-0
Alkanes, C18-20, chloro-	106232-85-3
Alkanes, C22-40, chloro-	106232-86-4
Alkanes, C21-38, chloro	127133-59-9

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

Grouping Rationale

Chlorinated paraffins (CPs) are complex mixtures of polychlorinated n-alkanes with a varying carbon chain lengths that have been chlorinated to different degrees. The carbon chain length usually varies between 10 and 30 carbon atoms and the degree of chlorination can vary between 30 and 75 wt %. Based on their carbon chain lengths, the chlorinated paraffins have been categorised as:

1. Short chain chlorinated paraffins (SCCPs), carbon chain C10-13;

2. Medium chain chlorinated paraffins (MCCPs), carbon chain C14-17;

3. Long chain chlorinated paraffins (LCCPs), carbon chain C18-20 and

4. Very long chain chlorinated paraffins (vLCCPs), carbon chain C>20.

The chemicals, SCCPs are persistent, bioaccumulative, undergo long range transport to remote areas and are inherently toxic to some aquatic and invertebrate species and have been the focus of coordinated global action. Recently they have been marked for inclusion in Annex A of the Stockholm Convention on Persistent Organic pollutants (POPs).

The chemicals, MCCPs and LCCPs are used as alternatives to SCCPs for many applications.

The seven chemicals in the present group contain mixtures of congeners that, based on their carbon chain lengths, fall under either MCCP or LCCP category. Toxicology data for individual chemicals in this group are not available. The longer chain chlorinated paraffins (MCCPs and LCCPs), being larger molecules, have lower water solubility and vapour pressure than the SCCPs and are expected to be less toxic than the SCCPs. Since congeners in these groups differ only in carbon chain lengths and degree of chlorination, their toxicity is not expected to vary considerably. For this reason, and because of lack of toxicology data, it was decided to assess these chemicals as a single group and use data available for any of the MCCP or LCCP chemicals as surrogate data for the group.

Import, Manufacture and Use

Australian

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

The chemicals have reported commercial uses, including as flame retardants and fire-preventing agents, and site-limited used in the manufacture of other chemicals.

International

The following international uses have been identified through Galleria Chemica;

the Substances and Preparations in Nordic countries (SPIN) database; the Organisation for Economic Cooperation and Development Screening information data set International Assessment report (OECD SIAR); the OECD High Production Volume chemical program (OECD HPV); the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the United States (US) National Library of Medicine's Hazardous Substances Data Bank (HSDB); and Canada Priority Substance List Assessment Report (Government of Canada, 1993 & 2008).

The chemicals have reported domestic uses including in paints, lacquers and varnishes.

The chemicals have reported commercial uses, including:

- in adhesives (binding agents);
- in fillers;
- in insulating materials;
- in surface treatments;
- in cutting fluids;
- in foaming agents;
- as high pressure lubricant in cutting oils; and
- as a flame retardant/plasticiser in plastics, rubbers and textiles.

Restrictions

Australian

No known restrictions have been identified.

International

The chemicals are listed on the following (Galleria Chemica):

- Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient 'Hotlist'); and
- 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.

The restrictions for the chemicals, 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 stimulants can be detected…'; and
- '...must not be detectable in a migration test in the lowest possible concentration at which a substance may be detected…'.

Existing Worker Health and Safety Controls

Hazard Classification

None of the chemicals in this group are classified as hazardous. However, a related

MCCP, Alkanes, C14-17, chloro (CAS No.85535-85-9), is classified as hazardous, with the following hazard category and hazard statement for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

Reproductive toxicity – effects on or via lactation; H362 (May cause harm to breast-fed children).

Exposure Standards

Australian

No specific exposure standards are available.

International

The CPs have an exposure standard of 6 mg/m^3 (0.3 ppm) time weighted average (TWA) in Germany (Galleria Chemica).

Health Hazard Information

The chemicals, MCCPs and LCCPs have similar physico-chemical properties, are structural analogues and are known to have similar toxicological profiles. Limited toxicological data is available for LCCPs and MCCPS. For the purpose of this assessment, data for MCCPs are used to address human health hazards for all chemicals in this group. Owing to the wide range of chain length combinations, branches and chlorination available, it is not reasonable to expect there to be a full dataset of toxicology information that would cover each possibility of exposure and hazards for CPs. Hence, where data are not available on one particular MCCP chemical, it may be possible to read across to information available from another MCCP chemical (CAS No.85535-85-9).

Toxicokinetics

There are limited toxicokinetic data of the chemicals being present in humans. The available data from animal studies, suggest that there is significant oral absorption and limited inhalation and dermal absorption, due to their low vapour pressure and low water solubility. Absorption and metabolism of MCCPs and LCCPs are mainly related to the length of the carbon chain and degree of chlorination. The longer the carbon chain length and the higher the degree of chlorination, the less absorption and metabolism. The chemicals are mainly distributed to the liver, kidney, intestine, bone marrow, adipose tissue and ovaries. Chlorinated paraffins and/or their metabolites may cross the placental barrier and may be excreted in human breast milk. Excretion is mainly via the renal, biliary and the pulmonary routes (IPCS; EU RAR, 2008; US EPA, 2015). Excretion *via* faeces was the major route of elimination of radiolabelled material. Elimination of radioactivity from body tissues occurred with an elimination half-life of approximately 2-5 days (liver and kidney) or approximately 2 weeks (adipose tissue) (US EPA, 2015).

Acute Toxicity

Oral

The chemicals in this group have low acute toxicity based on the results from animal tests following oral exposure. The median lethal dose (LD50) in rats is >4000 mg/kg bw. No mortality was reported for doses tested in the range of 5000 to 60000 mg/kg. Clinical signs of toxicity such as piloerections, muscular un-coordination and urinary/faecal incontinence were reported (IPCS; REACH; EU RAR, 2008; IUCLID, 2009; NRCS, 2000; US EPA, 2015).

Dermal

No data are available on the dermal toxicity for the chemicals in this group. However, a structurally similar chemical in the SCCP group, alkanes, chloro C10-13 (CAS No. 85535-84-8) had low acute toxicity in animal tests following dermal exposure. The dermal LD50 values were >13500 mg/kg bw and >2800 mg/kg bw in rabbits and rats, respectively, suggesting this groups of chemicals are predicted to have low acute dermal toxicity (IPCS; REACH; EU RAR, 2008; IUCLID, 2009; NRCS, 2000; US EPA, 2015).

Inhalation

No data are available on inhalation toxicity for chemicals in this group. However, a structurally similar chemical in the SCCP group, alkanes, chloro C10-13 (CAS No. 85535-84-8) had low acute toxicity in animal tests following inhalation exposure. No mortality or other signs of toxicity were observed in rats following a one-hour exposure to vapour or aerosol at a concentration of 3.3 mg/L. In another inhalation study, the reported median lethal concentration (LC50) in rats was >48.17 mg/L (>48.17 g/m^3). Based on these data, it is concluded that the chemicals in this group have low acute inhalation toxicity (IPCS; REACH; EU RAR, 2008; IUCLID, 2009; NICNAS, 2015; NRCS, 2000; US EPA, 2015).

Corrosion / Irritation

Skin Irritation

Skin irritation studies for these chemicals are not available. A related MCCP, alkanes, C14-17, chloro- had a slight skin irritating effect in animal studies, particularly following repeated exposure. The effects were not sufficient to warrant hazard classification.

Studies were performed in accordance with OECD Test Guideline (TG) 404. In a rabbit skin irritation study, a C14-17 MCCP (CAS No.85535-85-9); (52 % chlorinated), occlusively applied to intact rabbit skin, produced slight erythema (mean score 1.3) and oedema (mean score 0.3) after 24-72 hours. Ten days after application, scales were seen on the skin. The chemical was considered a slight skin irritant (IPCS; REACH; EU RAR, 2008; EPA, 2015).

In four other studies, LCCPs (C19, 44 % chlorinated; C22-26, 42 % chlorinated; C20-30, 41-50 % and C20-30, 70 % chlorinated) were found to be non-irritating to the rabbit skin in three out of the four studies. Slight irritation was observed in 2/6 animals tested in the other study (IPCS; EU RAR, 2008; IUCLID, 2009; EPA, 2015).

Eye Irritation

Eye irritation studies for the chemicals in this group are not available. A related MCCP, alkanes, C14-17, chloro- (CAS No.85535-85-9), caused slight eye irritation in animal studies. The effects were not sufficient to warrant hazard classification. Based on these studies, the chemicals are expected to be at most slight eye irritants.

In two rabbit studies conducted according to the OECD TG 405, C14-17 MCCP (CAS No.85535-85-9) (40 and 52 % chlorinated) were instilled into the conjunctival sac of one eye of each animal. One hour after the application, conjunctival redness (score 1) was noted in 3/3 animals and at 1/3 at 24 and 48 hours (both studies). No iridial or corneal effects were observed in any of the studies (REACH; EU RAR, 2008; NICNAS, 2015).

The European Union Risk assesment Report (EURAR) on MCCP reported on six additional rabbit studies with no ocular irritation following single applications of C14-17 MCCPs (CAS No.85535-85-9) (EU RAR, 2008).

In a separate study, a C22-26 LCCP (42 % chlorination) was instilled into the conjunctival sac of one eye of each of the three New Zealand White (NZW) rabbits. Slight transient conjunctivitis (score 3) was observed at 1-2 hours, which was completely reversible within the 7-day period. No effects on the cornea and iris were reported (EPA, 2015; IUCLID, 2009).

Sensitisation

Skin Sensitisation

Based on the following available information on related chemicals, the chemicals are not expected to be skin sensitisers.

In three guinea pig maximisation tests, no skin reactions were observed following intradermal induction and topical challenge with C14-17 MCCP (CAS No.85535-85-9) at 20–50 % concentrations. The chemical was not considered to be a skin sensitiser (IPCS; REACH; EU RAR, 2008; EPA, 2015).

In a separate guinea pig maximisation test, no skin reactions were observed following intradermal injection of a 5 % solution of an LCCP, C22-26 (42 % chlorination) in olive oil. The topical induction and challenge were conducted with 20 % concentration of the same chemical (IUCLID, 2009; EU RAR, 2008; EPA, 2015).

Repeated Dose Toxicity

Oral

Information on repeated dose toxicity of the chemicals in this group is not available. Based on the available data for related chemicals, the main target organs for these chemicals are expected to be the liver, thyroid and kidney. However, considering the no observed adverse effect levels (NOAELs) available from 90-day rat studies (100–900 mg/kg bw/d), and based on the treatment-related effects reported in various repeated dose toxicity studies, repeated oral exposure to the chemicals is not expected to cause serious damage to health.

In a repeated dose toxicity study, Fischer 344 rats (n=15/sex/group) were fed C14-17 MCCP (CAS No.85535-85-9) (52 % chlorination) in their diet at doses of 0, 10, 100 or 625 mg/kg bw/day for 90 days. A significant increase of 25 % serum cholesterol was observed in females at 625 mg/kg bw/day. Kidney lesions, including significant increase in absolute and relative kidney weights, increase in urinary protein, bilirubin and urobilinogen were observed in treated animals at 625 mg/kg bw/day and were considered to be toxicologically significant. Dose-related hepatocellular hypertrophy was observed in 13/15 males and 13/15 females at 625 mg/kg bw/day. Dose-related thyroid hyperplasia was observed in all treated males. The observed liver and

thyroid effects were not considered to be of toxicological significance to human health, given that humans are less sensitive to peroxisomal proliferation and thyroid hormone perturbation than rats (see **Carcinogenicity** section). A NOAEL of 100 mg/kg bw/day was established in this study, based on the kidney effects observed at 625 mg/kg bw/day (IPCS; EU RAR, 2008; EPA, 2015).

In another repeated dose toxicity study, F344 rats (n=10/sex/group) were fed C23 LCCP (43 % chlorination) in their diet for 90 days at doses of 0, 235, 469, 938, 1875 or 3750 mg/kg bw/day. Dose-related increase in incidence of granulomatous inflammation was observed in the livers in all treated female groups. No other effects on the body or organ weights were observed. No clinical signs of toxicity were observed. Microscopic examination of the liver of all treated rats showed increase in cytoplasmic vacuolisation and hepatocellular hypertrophy. Nephrosis was observed in kidney of male rats at 3750 mg/kg bw/day. The NOAEL of 900 mg/kg bw/day and LOAEL of 3750 mg/kg bw/day for males and females were reported (IPCS; IUCLID, 2009; EPA, 2015).

In a 14-day repeated dose oral toxicity study, F344/N rats (n=five/sex/group) were fed C14-17 MCCP (CAS No.85535-85-9) (52 % chlorination) in a diet at doses of 0, 150, 500, 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. Significant increases in absolute and relative liver weights and mild diffuse hepatocellular hypertrophy were observed at 5000 and 15000 ppm in all treated animals. Significant decreases in absolute and relative ovary weights were observed in females at 15000 ppm (1540 mg/kg bw/day). Male rats in the 170 mg/kg bw/day dose group showed a slight increase in cytochrome P-450 values, but this was not considered treatment-related. Diffuse mild hypertrophy was observed in the livers of the 5000 and 15000 ppm (580 and 1540 mg/kg bw/day) animals, which was considered to be due to an increase in metabolic demand (adaptive changes) and/or peroxisome proliferation. A NOEL of 170 mg/kg bw/day based on increased liver weights was established in this study (REACH; EU RAR, 2008; EPA, 2015).

In another 14-day study, F344/N rats (n=five/sex/group) were fed a LCCP, C22-26 (43 % chlorination), in corn oil by gavage at doses of 0, 30, 100, 300, 1000 or 3000 mg/kg bw/day. No treatment-related deaths or clinical signs of toxicity were observed. Significant increases in cytochrome P-450 levels were reported, mostly in females in all groups (59 % increase at 30 mg/kg bw/day; 36 % increase at 100 mg/kg bw/day; 38 % increase at 300 mg/kg bw/day; 47 % increase at 1000 mg/kg bw/day and 65 % increase at 3000 mg/kg bw/day). However, this effect was not dose-related and not considered to be treatment-related. No increase in liver weights were observed. The NOAEL for both males and females of 3000 mg/kg bw/day was proposed in this study (IPCS; IUCLID, 2009; EPA, 2015).

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 on related chemicals, the chemicals are not considered to be genotoxic.

In vitro studies

Negative results were observed in the following in vitro genotoxicity studies: (REACH; EU RAR, 2008; IUCLID, 2009; EPA, 2015; SIAM, 2009).

- three bacterial reversal mutation tests using C14-17 MCCP (CAS No.85535-85-9) (42 % chlorination) in five *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 up to maximum concentrations of 5000 µg/plate, in the absence or presence of rat liver metabolic activation system;

- four Ames tests using C18-26 LCCPs in *S. typhimurium* strains TA98, TA100, TA1535 and TA1538 up to maximum concentrations of ≥10,000 µg/plate, in the absence or presence of rat liver metabolic activation system; and

- bacterial reverse mutations tests using C14-17 MCCP (CAS No.85535-85-9) in *S. typhimurium* strains TA98, TA100, TA1535 and TA1538 up to maximum concentrations of 2500 µg/plate, in the absence or presence of rat liver metabolic activation system.

Weak positive results were observed with LCCPs in mammalian cells in the following: (IUCLID, 2009; SIAM, 2009)

- a chromosomal aberration test using C23 LCCP in Chinese Hamster Ovary cells at concentrations up to 5000 µg/plate, with metabolic activation; and

- a sister chromatid exchange assay using C23 LCCP at concentrations up to 5000 µg/plate, with and without activation).

In vivo studies

Negative results were observed in the following in vivo genotoxicity studies: (IPCS; NICNAS, 2015; REACH; EU RAR, 2008; IUCLID, 2009; EPA, 2015; SIAM, 2009).

- in vivo bone marrow chromosomal aberration assay using C14-17 MCCP (CAS No.85535-85-9) in male F344/N rats at concentrations of 0, 500, 1500 or 5000 mg/kg bw/day. No mortalities or treatment-related signs of toxicity were observed;

- two mouse bone marrow micronucleus assays using C14-17 MCCP (CAS No.85535-85-9) in mice at single gavage doses of up to 5000 mg/kg bw/day;

- a rat bone marrow assay using C23 LCCP at concentrations up to 5000 mg/kg bw/day; and

- a mouse lymphoma assay using C23 LCCP.

Carcinogenicity

No data are available for the MCCPs. The International Agency for Research on Cancer (IARC) has concluded that there is limited evidence for carcinogenicity of the LCCPs in experimental animals. The available data indicate that the chemicals are not likely to be carcinogenic.

In a 103-week carcinogenicity study, F344/N rats (groups of 50/sex/dose) were treated with C23 LCCP (43 % chlorination) in corn oil by gavage at doses of 0, 1875 or 3750 mg/kg bw/day (males) and 0, 100, 300 or 900 mg/kg bw/day (females), five days a week. Significantly increased incidence of adrenal medulla phaeochromocytoma were reported in treated females (1/50 control; 4/50 at 100 mg/kg bw/day; 6/50 at 300 mg/kg bw/day and 7/50 at 900 mg/kg bw/day). No other treatment-related effects were seen on the survival of rats or on the body weights in male rats. Females in the 300 and 900 mg/kg bw/day dose groups had 5 % lower body weights as compared to the controls. Diffused lymphohistiocytic inflammation of the liver and of the pancreatic and mesenteric lymph nodes in both sexes was the primary non-neoplastic lesion observed. Congestion of the spleen was a secondary effect. All treated female groups had increased incidence of adrenal medullary phaeochromocytoma but no evidence of hyperplasia. No other pathological lesions were observed. The NOAEL of >3750 mg/kg bw/day for male rats and 100 mg/kg bw/day for female rats was reported (IPSC; IARC, 1990; IUCLID, 2009).

In a mouse study, groups of B6C3F1 mice (50/sex/dose) were orally treated with C23 LCCP (43 % chlorination) in corn oil at doses of 0, 2500 or 5000 mg/kg bw/day for five days a week. Mean body weights of both male and female mice at 2500 mg/kg bw/day were lower than controls at 13 weeks and mean body weights of females in the 5000 mg/kg bw/day group were higher than controls. Overall, survival rate was reduced in treated females due to an utero-ovarian infection. No other treatment-related clinical signs of toxicity and non-neoplastic lesions were reported. Male mice had increased incidence of malignant lymphoma (6/50 in controls; 12/50 at 2500 mg/kg bw/day and 16/50 at 5000 mg/kg bw/day) and female mice showed increased incidence of hepatocellular carcinoma (4/50 in control; 3/49 at 2500 mg/kg bw/day and 10/50 at 5000 mg/kg bw/day) (IPSC; IARC, 1990; IUCLID, 2009).

Given the similarities in physicochemical properties in MCCPs and SCCPs and their effects on some toxicological endpoints, particularly the effects seen on the liver, thyroid and kidneys after repeated exposure, it is reasonable to presume that the carcinogenic potential of MCCPs will be similar, at least in qualitative terms, to that of SCCPs. The SCCPs have been investigated in animal studies and found to induce liver, thyroid and kidney tubular cell adenomas and carcinomas. On

mechanistic considerations, the liver and thyroid tumours were considered to be of little or no relevance to human health.

Recent mechanistic evidence shows that a2μ-binding is probably the primary mechanism for kidney tumour formation induced by SCCPs in male rats. The available evidence strongly suggests that the underlying mechanism would not be relevant to humans. Therefore, overall, SCCPs, and by analogy MCCPs, should be considered not to pose a carcinogenic hazard to humans.

However, the EC Group of Specialised Experts in the fields of Carcinogenicity, Mutagenicity and Reprotoxicity concluded that there were data gaps leading to uncertainty about the relevance of these tumours for humans. The relationship between a2μ mechanism and kidney tumours was not adequately established in this case and therefore the criteria for no classification for SCCPs were not met, and hence, they recommended that the current classification of SCCPs with Carc Cat 3 be retained.

The Specialised Experts also agreed that a read-across from SCCPs to MCCPs was not justified for carcinogenicity, and consequently MCCPs could not be classified for this endpoint (EU RAR, 2008).

There is no available information on the carcinogenic potential of C18-20 or C20-30 LCCPs. The results from rat and mice studies and other chlorinated paraffins in general, show that these do not have significant genotoxic potential. Therefore, MCCPs and LCCPs have low carcinogenic potential for humans (IPSC; IARC, 1990; EU RAR, 2008; IUCLID, 2009; SIAR, 2009; EPA, 2015; NICNAS, 2015).

Reproductive and Developmental Toxicity

Alkanes, C14-17, chloro-, a MCCP (CAS No. 85535-85-9) is classified as hazardous under the category, 'Reproductive toxicity - Effects on or via lactation'; [H362 - May cause harm to breast-fed children] in the HCIS (Safe Work Australia). The available data support this classification, and MCCPs are considered to be reproductive toxicants. Similar effects were not seen in the one available study on LCCPs.

In a developmental toxicity study conducted according to the OECD TG 414, female Charles Rivers (CD) rats (25/dose) were treated with C14-17 MCCP (CAS No.85535-85-9) (52 % chlorination) by gavage, at doses of 0, 500, 2000 or 5000 mg/kg bw/day on gestation days 6-19. All animals were examined on day 20. No treatment-related adverse effects on mortality, body weight gain or uterine weights of dams were observed. Wet, matted and yellow-stained hair in the anogenital area and/or soft stools were observed in the 2000 and 5000 mg/kg bw/day dose groups. No treatment-related adverse effects were observed in the foetuses and no adverse developmental effects are observed. A NOAEL of 5000 mg/kg bw/day for developmental toxicity was established (IPCS; REACH; OECD, 2000; EU RAR, 2008; EPA, 2015; NICNAS, 2015).

In a one-generation study conducted according to the OECD TG 421, groups of 12-17 Sprague Dawley (SD) rats were administered C14-17 MCCP (CAS No.85535-85-9) in diet at 0, 300, 600 or 1200 ppm (equivalent to 0, 21, 44 and 84 mg/kg bw/day (males) and 0, 23, 47 and 99 mg/kg bw/day (females)) for four weeks before pairing, and throughout pairing, gestations and lactation until the animals were euthanised, post natal day 21 of the treatment. No adverse treatment-related clinical effects were observed. The F0 females in the 1200 ppm (~ 99 mg/kg bw/day) had marginally higher absolute and relative liver weights. The number of implantations, litter size, sex ratio, litter survival rate, fertility and gestation lengths were unaffected by the treatment. It was concluded that C14-17 MCCP (52 % chlorination) had no adverse effects on the pre- and post-natal survival and growth of the F1 offspring up to weaning. A NOAEL of 1200 ppm (~ 100 mg/kg bw/day prior to birth and 212 mg/kg bw/day during lactation) for F1 offspring and a NOEAL of 600 ppm (~ 47 mg/kg bw/day) for maternal toxicity were established (IPCS; REACH; SIAR, 2004; EU RAR, 2008; EPA, 2015; NICNAS, 2015).

In a developmental study using C22-26 LCCP (43 % chlorination), groups of pregnant CD rats were administered the chemical by gavage at 0, 500, 2000 or 5000 mg/kg bw/day from days 6-19 gestation days. No adverse effects in appearance, mean body weight gain, mortality rate and no signs of developmental effects were observed. There was a non-significant increase in mean implantation loss and a slight decrease in the mean number of viable foetuses in the dams receiving 5000 mg/kg bw/day. Three females aborted during the study, one at 2000 mg/kg bw/day and two at the 5000 mg/kg bw/day). A NOAEL of 2000 mg/kg bw/day for maternal toxicity and teratogenicity was reported (IPCS; IUCLID, 2009; SIAR, 2009; EPA, 2015).

In two separate teratogenicity studies conducted according to OECD TG 414, C14-17 MCCP (CAS No.85535-85-9) was tested in pregnant female rabbits and mated female CD rats at doses up to 100 mg/kg bw/day and 5000 mg/kg bw/day, respectively. No treatment-related mortalities or clinical signs of toxicity and no developmental effects were observed. Two NOAELs of 100 mg/kg bw/day and 5000 mg/kg bw/day were established in rabbits and rats, respectively (IPCS; REACH; SIAR, 2004; EU RAR, 2008; EPA, 2015; NICNAS, 2015).

A developmental toxicity range-finding study (details of study not available) showed that administration of approximately 100 and 400 mg/kg bw/day MCCPs via the diet had no effect on fertility or other reproductive parameters; however, internal hemorrhaging and deaths in pups were observed beginning from 74 mg/kg-bw/day up to approximately 400 mg/kg-bw/day. Internal hemorrhaging was not seen in the adult animals at doses as high as 400 mg/kg bw/day. However, when dams were exposed to approximately 500 mg/kg-bw/day MCCPs during cohabitation, gestation and lactation, signs of hemorrhaging were observed in dams that died at the time of parturition. Taken together, the results of these studies indicate a possible LOAEL for internal hemorrhaging and deaths in pups at an oral dose of 74/mg/kg-bw/day (IRDC, 1985).

Studies were conducted to further investigate the possible mechanism of high mortality in pups associated with internal haemorrhages observed in one reproductive toxicity study. Wistar rats (five males and 10 females/group) were administered C14-17 MCCP (CAS No.85535-85-9) in diet at 0, 100, 1000 or 6250 ppm (~ 0, 6, 62 or 384 mg/kg bw/day (males) and 0, 8, 74 or 463 mg/kg bw/day (females)) for 28 days before and during mating, and in females up to post-natal day 21. No deaths, abnormalities or treatment-related fertility effects were observed in the parental (F0) rats. No first filial generation (F1) pups survived to weaning on the 6250 ppm litters, due to internal haemorrhages, indicating that the pups had either died as a result of receiving the test substance through breast milk, or that the milk that was produced by dams was deficient in factors essential for pup survival, or both. Haematoma was reported in all 6250 ppm litters. Haematological assays in the pups showed decrease in factor X, resulting in a disruption of a vitamin K-dependent clotting system. Pups survival was reduced by 11 % in the 1000 ppm litters. A NOAEL of 100 ppm (~ 8 mg/kg bw/day) in the offspring during lactation was established for this study (REACH; SIAR, 2004; EU RAR, 2008; EPA, 2015; NICNAS, 2015).

It was suggested that the newborn pups are potentially sensitive subpopulation during lactation and at the time of parturition. The foetus relies on clotting factors via mother's milk, and severe deficiency in vitamin K levels and related clotting factors in the pups results in haemorrhaging.

Studies were conducted to investigate two possible mechanisms for haemorrhage in the pups (EPA, 2015). One proposed mechanism was that MCCPs decreased plasma concentrations of vitamin K in the milk that pups receive by inducing breakdown of vitamin K in lactating rats. The second proposed that MCCPs transferred to the pups through breast milk causing disruption of the pup clotting system.

A study was conducted to test the first mechanism in adult SD rats (three groups of six females) using C14-17 MCCP (CAS No.85535-85-9) (52 % chlorination) via gavage at doses of 0, 500 or 1000 mg/kg bw/day for 21 days, either fed normal diet or a vitamin-K-deficient diet. Animals on normal diet showed significant decreases in plasma concentrations of a clotting factor, but no effect on prothrombin clotting times. Animals fed a vitamin-K deficient diet also showed reduction of clotting factors but with lowered plasma vitamin-K levels in high-dose group. It was concluded that MCCPs had no adverse effect on the blood clotting system in adult females treated at a dose of 1000 mg/kg bw/day for three weeks and the haemorrhaging effects in pups were unlikely to be mediated by reduced vitamin K levels in breast milk (EPA, 2015; NICNAS, 2015).

To test the second proposed mechanism, a one-generation reproductive toxicity study was conducted in groups of SD rats fed C14-17 MCCP (CAS No.85535-85-9) at doses of 0 or 6250 ppm (~ 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 treated animals. Treatment-related mortality was recorded in five dams at the time of parturition (16 % mortality). Haemorrhaging was reported in 3/5 dams and one male in clinical necropsy. The study was prematurely terminated after day 4 of lactation, as only a few pups survived, with majority of these pups showing internal haemorrhages. The conclusions from this study were that the foetus receives sufficient vitamin K via the placenta, but becomes severely deficient in vitamin K and related clotting factors after birth, when it relies on mother's milk for these factors. The chemical was also present at considerably high levels in the milk, which could lead to further reduction of vitamin K levels received and consequently resulting in haemorrhaging (REACH; SIAR, 2004; EU RAR, 2008; NICNAS, 2015).

Risk Characterisation

Critical Health Effects

Information on the health effects of chemicals in this group is not available. Based on the toxicology data of a related MCCP (CAS No.85535-85-9), the critical health effect for risk characterisation for MCCP is the systemic long-term effect of causing harm to breast-fed children.

Public Risk Characterisation

Although use in domestic products in Australia is not known, the chemicals are reported to be used in domestic products overseas (see **Import, manufacture and use** section). Incidental exposure may occur during use of surface treatment products containing these chemicals. The main route of exposure is through dermal route. However, considering the extremely poor dermal absorption, these chemicals are unlikely to be a concern for public health. Therefore, the risk for public health is not considered to be unreasonable and further risk management is not considered necessary for public safety.

Occupational Risk Characterisation

Exposure may occur during product formulation, 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 chemicals at lower concentrations could also occur while using formulated products containing the chemicals. 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 effect, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise exposure are implemented. The chemicals 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 HCIS (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

Assessment of these chemicals are considered to be sufficient, provided that labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

The medium chained chlorinated paraffins (MCCPs) are recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This assessment does not consider classification of physical and environmental hazards.

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Reproductive and Developmental Toxicity	Not Applicable	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 oral exposure to the chemicals 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 chemicals are used. Examples of control measures that 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 chemicals, 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 chemicals.

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 chemicals 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 these chemicals has not been undertaken as part of this assessment.

References

USEPA (2015) TSCA new chemicals review program Standard review risk assessment on Medium-chain chlorinated paraffins (pmnp-12-0453) And Long-chain chlorinated paraffins (pmnp-12-0433). Premanufacture Notification Number: P-12-0453-0433. Office of Chemical Safety and Pollution Prevention. Accessed 14 June 2017, at **https://www.epa.gov/sites/production/files/2015-12/documents/dover_-_standard_review_risk_assessment_p-12-0282-0284_docket_0.pdf**.

Approved Criteria for Classifying Hazardous Substances [NOHSC: 1008(2004)] Third edition. Accessed May 2017, **http://www.nohsc.gov.au/pdf/Standards/approved_criteriaNOHSC1008_2004.pdf**.

EURAR (2008) Risk Assessment of Alkanes, C14-17, Chloro (Medium-Chained Chlorinated Paraffins) Cas No. 85535-85-9 Einecs No. 287-477-0 2008. **https://echa.europa.eu/documents/10162/13630/trd_rar_uk_mccp_en.pdf/b879f97d-9cea-49e1-9a84-4b3c6a4eb447**.

European Commission Cosmetic Ingredients and Substances (CosIng) Database. Accessed May 2017 at **http://ec.europa.eu/consumers/cosmetics/cosing/**

Galleria Chemica. Accessed May 2017 at **http://jr.chemwatch.net/galleria/**

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed at **http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html**

Government of Canada 1993. Priority Substances List Assessment Report on Chlorinated Parraffins. Accessed May 2017 at **http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/psl1-lsp1/paraffins-paraffines/paraffins-paraffines-eng.pdf**

Hart D; Wickramaratne GSDE; Banham P, Chart I and Gaskell B (1985). Chlorinated Parraffin (52 % Chlorination of Intermediate Chain Length N-Paraffins): Investigation into the Possible Mechanism of Haemorrhage in Offsprin Rats. CTL/P/1293. ICI Central Toxicology Laboratory, Alderley Park, Cheshire, UK.

Hazardous Substances Data Bank (HSDB). Accessed May 2017 at **http://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm**

International Agency for Research on Cancer (IARC) 1990. IARC monographs on the evaluation of carcinogenic risks to humans, Volume 48. Some Flame retardants and textile chemicals, and exposure in the textile manufacturing industry. Accessed May 2017 at **http://monographs.iarc.fr/ENG/Monographs/vol48/mono48.pdf**

International Uniform Chemical Information Database (IUCLID) Dataset 2009. Paraffin waxes and Hydrocarbon waxes, chloro (CAS No. 63449-39-8). Accessed May 2017 at **http://webnet.oecd.org/HPV/UI/SIDS_Details.aspx?id**

IRDC (1985). Chlorinated paraffin: Reproduction range-finding study in rats. IRDC Report No. 438/049. International Research and Development Corporation, Mattawan, Michigan, USA 49071, cited in EURAR, 2008.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) 2006. Australian High Volume Industrial Chemicals List (AHVICL) Accessed May 2016 at **http://www.nicnas.gov.au/Industry/Australian_High_Volume_Industrial_Chemicals/NICNAS_AHVICL_2006_PDF.pdf**

National Industrial Chemicals Notification and Assessment Scheme (NICNAS, 2015). Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II Assessment for alkanes, C14-17, chloro (MCCP; Cas no 85535-85-9. Accessed June 2017 at **https://www.nicnas.gov.au/chemical-information/factsheets/chemical-name/**

National Research Council (US) Subcommittee on Flame-retardant Chemicals (NRCS, 2000). Toxicological risks of Selected Flame-retardant Chemicals. Washington (DC): National Academies Press (US); 2000. 19, Chlorinated Parraffins. Availabe from: **http://www.ncbi.nih.gov/books/NBK225654/**

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier. Alkanes, C14-17, chloro- (CAS No. 85535-85-9). Accessed February 2015 at **http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances**

Safe Work Australia (SWA). Hazardous Chemical Information System (HCIS). Accessed May 2017 at **http://hcis.safeworkaustralia.gov.au/**.

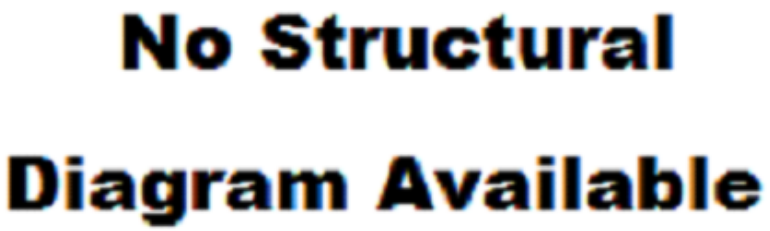
Substances in Preparations in Nordic Countries (SPIN). Accessed May 2017 at **http://spin2000.net/**

Last Update 30 June 2017

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Alkanes, C10-22, chloro-** chloroparaffins

CAS Number	104948-36-9
Structural Formula	
Molecular Formula	Unspecified
Molecular Weight	Unspecified

Chemical Name in the Inventory and Synonyms	**Alkanes, C10-21, chloro-**
CAS Number	84082-38-2
Structural Formula	
Molecular Formula	Unspecified
Molecular Weight	Unspecified

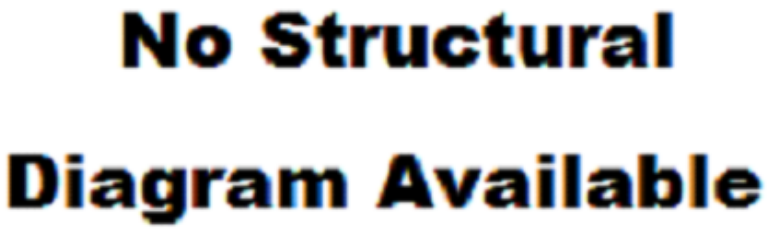
Chemical Name in the Inventory and Synonyms	**Alkanes, C16-27, chloro-**
CAS Number	84776-07-8
Structural Formula	**No Structural Diagram Available**
Molecular Formula	Unspecified
Molecular Weight	Unspecified

Chemical Name in the Inventory and Synonyms	**Alkanes, C18-28, chloro-**
CAS Number	85535-86-0
Structural Formula	**No Structural Diagram Available**
Molecular Formula	Unspecified
Molecular Weight	Unspecified

Chemical Name in the Inventory and Synonyms	**Alkanes, C18-20, chloro-**
CAS Number	106232-85-3
Structural Formula	**No Structural Diagram Available**
Molecular Formula	Unspecified
Molecular Weight	Unspecified

Chemical Name in the Inventory and Synonyms	**Alkanes, C22-40, chloro-**
CAS Number	106232-86-4
Structural Formula	**No Structural Diagram Available**

Molecular Formula	Unspecified
Molecular Weight	Unspecified

Chemical Name in the Inventory and Synonyms	**Alkanes, C21-38, chloro**
CAS Number	127133-59-9
Structural Formula	
Molecular Formula	Unspecified
Molecular Weight	Unspecified

Share this page