Chlorophene preservatives: Environment tier II assessment

12 December 2019

CAS Registry Numbers: 120-32-1, 97-23-4, 10187-52-7, 22232-25-3, 70-30-4, 15435-29-7

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 4 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 3 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.

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Acronyms & Abbreviations

Grouping Rationale

This Tier II assessment considers the environmental risks associated with the industrial uses of a group of halogenated phenolic compounds which are known collectively as ‘chlorophenes’. These chemicals all have antimicrobial properties. They have a range of industrial uses including as ingredients of disinfectants and antibacterial soaps, and as preservatives in cosmetics. They also have non-industrial uses in pesticide and therapeutic products.

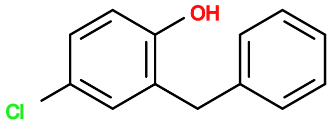
The Tier I assessments of these chemicals indicated that they are of potential concern to the environment. They are all very toxic to aquatic organisms and may, therefore, pose a risk to the aquatic environment if released into surface waters in the treated effluent discharged from sewage treatment plants (STP). A more in-depth assessment at Tier II level was recommended under the IMAP framework. This assessment will evaluate the potential for emissions of chlorophenes to the environment in more detail and consider whether risk reduction measures are required for their industrial uses in Australia.

Chemical Identity

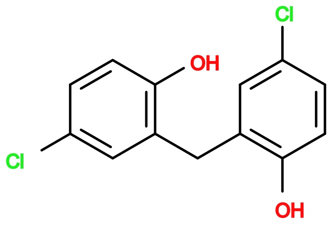
All of the chemicals in this group have a common diphenylmethane structure wherein one or both phenyl rings are hydroxylated and halogenated. Chlorophene (CP) has a single phenyl ring that is hydroxylated in the *ortho*- position to the methylene bridge, and a single chlorine atom substituent in the *para*-position to the hydroxyl group on the same ring. The other members of the group are *ortho*-hydroxylated on both phenyl rings. They are also halogenated on both phenyl rings and all have a chlorine atom substituent in the *para*-position to the hydroxyl group on each ring. These chemicals include dichlorophene (DCP), which has a single chlorine atom substituent on each phenyl ring, and its monosodium (NaDCP) and disodium (Na_2DCP) salts; hexachlorophene (HCP), which has three chlorine atoms on each phenyl ring; and bromochlorophene (BCP), which has a chlorine and a bromine atom on each ring.

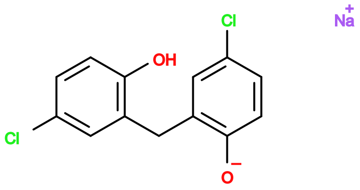
CP is manufactured by the chlorination of 2-benzylphenol (CAS RN 28994-41-4) (Fiege, et al., 2012). DCP and HCP are manufactured by condensation of the respective 4-chloro- (CAS RN 106-48-9) or 2,4,5-trichloro- phenol (CAS RN 95-95-4) with formaldehyde (Fiege, et al., 2012). The synthesis of DCP usually results in the formation of the trisphenol trimer, 2,6-bis(2-hydroxy-5-chlorobenzyl)-4-chlorophenol (CAS RN 6642-07-5), which is a by-product that can be present in technical mixtures in a range between 5 to 10 per cent (Cosmetic Ingredient Review, 2004). The process for making HCP forms small amounts of 2,3,7,8-tetrachloro-dibenzo-*p*-dioxin (CAS RN 1746-01-6) as a by-product, which is removed before HCP is formulated into products (Hites, 2011). BCP is manufactured by the bromination of DCP (Fiege, et al., 2012).

NaDCP and Na_2DCP become chemically equivalent to the parent acid (DCP) when released into the environment. Therefore, they are not separately considered in this assessment and the exposure assessment of DCP includes the contribution from uses of the two salts:

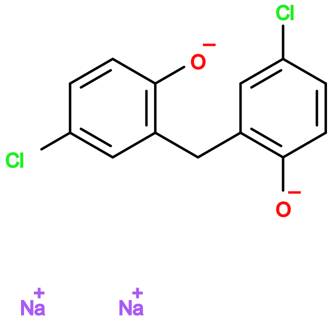
CAS RN	120-32-1
Chemical Name	Phenol, 4-chloro-2-(phenylmethyl)-
Synonyms	chlorophene (CP) preventol BP santophen 1 4-chloro-2-(phenylmethyl)phenol
Structural Formula	
Molecular Formula	$C_{13}H_{11}ClO$
Molecular Weight (g/mol)	218.68
SMILES	c1ccc(cc1)Cc2c(ccc(c2)Cl)O

CAS RN	97-23-4
Chemical Name	Phenol, 2,2'-methylenebis[4-chloro-

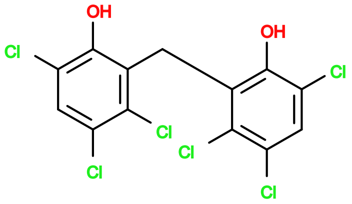
Synonyms	dichlorophene (DCP) dichlorophen nipacide DP 5,5'-dichloro-2,2'-dihydroxydiphenylmethane
Structural Formula	
Molecular Formula	$C_{13}H_{10}Cl_2O_2$
Molecular Weight (g/mol)	269.12
SMILES	c1cc(c(cc1Cl)Cc2c(ccc(c2)Cl)O)O

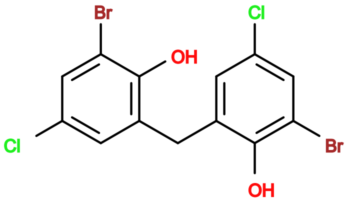
CAS RN	10187-52-7
Chemical Name	Phenol, 2,2'-methylenebis[4-chloro-, monosodium salt
Synonyms	monosodium dichlorophene (NaDCP)
Structural Formula	
Molecular Formula	$C_{13}H_9Cl_2NaO_2$

Molecular Weight (g/mol)	291.10
SMILES	c1cc(c(cc1Cl)Cc2c(ccc(c2)Cl))[O-].[Na+]

CAS RN	22232-25-3
Chemical Name	Phenol, 2,2'-methylenebis[4-chloro-, disodium salt
Synonyms	disodium dichlorophene (Na_2DCP)
Structural Formula	
Molecular Formula	$C_{13}H_8Cl_2Na_2O_2$
Molecular Weight (g/mol)	313.09
SMILES	c1cc(c(cc1Cl)Cc2c(ccc(c2)Cl)[O-])[O-].[Na+].[Na+]

CAS RN	70-30-4
Chemical Name	Phenol, 2,2'-methylenebis[3,4,6-trichloro-
Synonyms	hexachlorophene (HCP) hexachlorophane

	pHisoHex 2,2'-dihydroxy-3,3',5,5',6,6'-hexachlorodiphenylmethane
Structural Formula	
Molecular Formula	$C_{13}H_6Cl_6O_2$
Molecular Weight (g/mol)	406.89
SMILES	c1(Cl)c(Cl)c(Cc2c(Cl)c(Cl)cc(Cl)c2O)c(O)c(Cl)c1

CAS RN	15435-29-7
Chemical Name	Phenol, 2,2'-methylenebis[6-bromo-4-chloro-
Synonyms	bromochlorophene (BCP) brophen 3,3'-dibromo-5,5'-dichloro-2,2'-dihydroxydiphenylmethane
Structural Formula	
Molecular Formula	$C_{13}H_8Br_2Cl_2O_2$

Molecular Weight (g/mol)	426.92
SMILES	c1(Br)c(O)c(Cc2c(O)c(Br)cc(Cl)c2)cc(Cl)c1

Physical and Chemical Properties

The values for the melting point, vapour pressure, water solubility and octanol-water partition coefficient (K_{ow}) of CP were retrieved from the registration dossier for chlorophene which was submitted under the Registration, Evaluation, Authorisation and Restriction of Chemicals legislation in the European Union (REACH, 2019). The value for the water solubility of BCP was retrieved from the peer-reviewed scientific literature (Stibany, et al., 2017). The remaining physical and chemical property data for the non-ionic chemicals in this group are from the databases included in the OECD QSAR Toolbox (LMC, 2013), or they were calculated using standard quantitative structure (property) relationships (US EPA, 2008):

Chemical	CP	DCP	HCP	BCP
Physical Form	solid	solid	solid	solid
Melting Point	45.9°C (exp.)	177–178°C (exp.)	164–165°C (exp.)	189°C (calc.)
Vapour Pressure	0.01 mPa (exp.)	-	-	-
Water Solubility	117 mg/L at pH 7 and 20°C (exp.)	30 mg/L at 25°C (exp.)	140 mg/L at 25°C (exp.)	8.4 mg/L at 20°C (exp.)
Ionisable in the Environment?	no	yes	yes	yes
log K_{ow}	4.27 (exp.)	4.26 (exp.)	7.54 (exp.)	6.12 (calc.)

The chemicals in this group are weak organic acids. CP is a phenol with a single ionisable functional group, whereas DCP, HCP and BCP are all bisphenols and, hence, potential diprotic acids. The first dissociation reaction of these *ortho*-hydroxylated bisphenols results in the formation of a hydrogen bond between the phenoxide oxygen atom and the remaining acidic proton. This has the effect of increasing the acidity of the first and decreasing the acidity of the second phenol group (Mahler, 1954). The reported values for the first ionisation constant, pK_{a1}, and second ionisation constant (pK_{a2}) are as follows: CP, 9.59 (REACH, 2019); DCP, 7.6 (11.6) (Sanborn, 1974); and HCP, 4.95 (10.1) (LMC, 2013). The first dissociation of DCP and HCP occurs at near neutral pH which indicates that both of these chemicals will be at least partially ionised in environmental waters where the pH is generally in the range 4–9. The acid dissociation constants for BCP were measured in an ethanol-water mixture due to the low water solubility of this chemical. A measured pK_{a1} value of 6.4 (pK_{a2} = 12.3) was obtained (Fogg, et al., 1970), which indicates that BCP will also be ionised in the environment.

The chemicals in this group have low volatility and are either slightly soluble (BCP) or moderately soluble in water (CP, DCP and HCP). The chemicals have high K_{ow} values which indicates that they are moderately (CP and DCP) or highly (HCP and BCP) lipophilic.

Import, Manufacture and Use

Australia

No specific Australian industrial use, import, or manufacturing information has been identified for the chemicals in this group.

CP, DCP and NaDCP have non-industrial uses as active constituents in registered agricultural and veterinary chemical products. CP is used in agricultural disinfectants (APVMA, 2018). DCP is used in parasiticide, herbicide, fungicide and antimicrobial products, and is an anthelmintic (worm treatment) for humans and animals (NICNAS, 2018). HCP has a therapeutic use as an active ingredient in medicinal cleansing lotions (NICNAS, 2016). HCP was also historically used in veterinary wound dressing sprays (DoEE, 1997). These non-industrial uses are outside the scope of this assessment.

International

Chlorophenes are used as antimicrobial ingredients and preservatives in cosmetic products (Fiege, et al., 2012). They are also used in general purpose cleaning and washing agents and disinfectants (Nordic Council of Ministers, 2019). DCP is also used as a preservative in the textile industry and as a cement additive (HSDB, 2006a). The scientific and patent literature indicate that BCP has uses as an antimicrobial ingredient in toothpaste and mouthwash (Stibany, et al., 2017).

HCP was used in antibacterial soaps and lotions, and in broad spectrum soil and foliar fungicides (HSDB, 2012).

CP and DCP were reported to be produced in or imported into the United States in volumes between 5–225 tonnes per year in 2002 (HSDB, 2006a, b). In the European Economic Area, CP is manufactured or imported in volumes between 0–10 tonnes per year (REACH, 2019).

Environmental Regulatory Status

Australia

The use of the chemicals in this group is not subject to any specific national environmental regulations.

CP has been identified as a chemical detected in sewage effluent in the guidelines for the use of recycled water developed under the National Water Quality Management Strategy (NWQMS, 2008). The guidelines provide a framework for the safe use of recycled water with the aim of protecting human health and the environment. The recommended maximum concentration of CP in recycled water to be reused as drinking water for human consumption is 350 nanograms per litre (ng/L).

Hexachlorophene is on the Schedule X list of organochlorine pesticides covered by the *Organochlorine Pesticides (OCP) Waste Management Plan* (DoEE, 2013).

United Nations

No chemicals in this group are currently identified as a Persistent Organic Pollutant (POP) (UNEP, 2001), an ozone depleting substance (UNEP, 1987), or a hazardous substance for the purpose of international trade (UNEP & FAO, 1998).

The tetrachlorodibenzo-*p*-dioxin by-product that is formed during the production of HCP is a POP that is captured by the listing of polychlorinated dibenzo-*p*-dioxins on Annex C (unintentional production) of the Stockholm Convention. Parties to the Convention are required to take measures to reduce or eliminate releases of polychlorinated dibenzo-*p*-dioxins from a range of sources including chemical production processes (UNEP, 2008).

OECD

CP is identified as a high-production volume (HPV) chemical by the OECD, which indicates that more than 1000 tonnes of the chemical is produced per year in at least one member country (OECD, 2009).

The chemical has not yet been sponsored for assessment under the Cooperative Chemicals Assessment Programme (CoCAP) (OECD, 2017).

Canada

CP, DCP, NaDCP and HCP are listed on the Canadian Domestic Substances List (DSL) as existing substances in commerce (Environment and Climate Change Canada, 2018). During the Categorization of the DSL, CP was categorised as not Persistent (not P), not Bioaccumulative (not B) and not Inherently Toxic to the Environment (not iT_E) (Environment and Climate Change Canada, 2019). DCP and HCP were categorised as Persistent (P), not Bioaccumulative (not B), and Inherently Toxic to the Environment (iT_E).

HCP is listed on the Canadian National Pollutant Release Inventory (NPRI) at reporting threshold 1A (NPRI, 2019). The chemical is reportable to the NPRI if it is manufactured, processed, or otherwise used at quantities greater than 10 tonnes.

HCP is listed on the Canadian Cosmetic Ingredient Hotlist of ingredients that are prohibited for use in cosmetic products (Health Canada, 2015).

BCP is not listed on the DSL.

China

CP, DCP, NaDCP, HCP and BCP are listed on the Inventory of Existing Chemical Substances in China (IECSC).

HCP is listed on the National Health Commission’s draft list of approved antibacterial active ingredients permitted for use in liquid products intended for direct human contact (NHC, 2019). The scope of the list does not cover cosmetics or antibacterial hand wash.

CP, DCP and BCP are not listed on the NHC approved active ingredients list.

European Union

CP is registered under the REACH legislation (ECHA, 2019). DCP, NaDCP, Na_2DCP, HCP and BCP are pre-registered under REACH (ECHA, 2017b).

CP is approved for use under the EU Biocidal Products Regulation (BPR) (ECHA, 2018). The regulation authorises the manufacture and use of biocidal and preservative chemicals on the European market, with the aim of high level consumer and environmental protection. The chemical is under review for use in product type PT02: disinfectant and algaecides not intended for direct application to humans and animals. It is not approved for use in product type PT03: veterinary hygiene, and has been identified in the BPR assessment as a candidate for substitution in this product type (ECHA, 2017a).

CP, DCP and BCP are listed on the European Commission's Cosmetic Ingredient database (CosIng) as antimicrobial ingredients and preservatives in cosmetics (CP, DCP and BCP), and as deodorants (DCP and BCP) (European Commission, 2019). CP, DCP and BCP are restricted to a maximum concentration in cosmetics of 0.2%, 0.5% and 0.1%, respectively. HCP is listed on the Annex II list of substances prohibited for use in cosmetic products.

Japan

DCP and HCP are prohibited for use in cosmetics in Japan due to reported photo-sensitising properties (MHLW, 2001).

Sweden

CP, DCP, HCP and BCP are registered on the Swedish Chemicals Agency (KEMI) list of substances (KEMI, 2019).

The use of CP and BCP has been reviewed along with 16 other preservatives found in personal care products with a focus on their human health and environmental hazards. CP was reported to be used in the 100–1000 kg per annum volume range (KEMI, 2017). In this review, a lack of import and manufacturing data for BCP required the use of a 100 kg per annum introduction volume to assess the risks of this chemical, which is the threshold volume for reporting the use of chemicals to the chemical register (KEMI, 2017). There were no reported uses of BCP to KEMI in the years between 1995 and 2014.

United States of America

CP, DCP, NaDCP, Na_2DCP and HCP are listed on the United States Environmental Protection agency's (US EPA) Chemical Substance Inventory, established under the Toxic Substances Control Act (TSCA) 1976 (US EPA, 2018). All of these chemicals except Na_2DCP are registered as 'active' on the Chemical Substances Inventory, which indicates that they have recently been manufactured, imported or processed by industry in the USA.

The United States Food and Drug Administration (US FDA) has restricted the use of HCP to below 0.1% in cosmetics and prohibited use in cosmetics applied to mucous membranes (US FDA, 2017a). The US FDA has also banned the use of HCP and 18 other chemicals in over-the-counter antibacterial hand washes and soaps (US FDA, 2017b). The ban was based on the lack of evidence that antibacterial soaps provide better health protection than regular soap.

Environmental Exposure

All of the chemicals in this group are synthetic and their occurrence in the environment results exclusively from human activity. They can be emitted to the environment from both industrial and non-industrial uses.

Based on international use patterns, chemicals in this group are used as antimicrobial agents and preservatives in personal care products and cosmetics. The industrial uses of these chemicals in Australia are assumed to not differ significantly from those found internationally. Chlorophenes in personal care products and cosmetics are expected to be released down the drain to sewers in domestic wastewater as a normal part of their use in these products. Therefore, the primary exposure scenario considered for industrial uses of chemicals in this group involves emissions from sewage treatment plants.

Treatment of wastewater in sewage treatment plants will remove some fraction of the quantity of a chemical in the influent, depending on the efficiency of various degradation and partitioning processes. The removal efficiency for CP from wastewater has been shown to be between 73% (Yu, et al., 2006) and 88% (Kasprzyk-Hordern, et al., 2008), based on measured influent and effluent concentrations of this chemical at STPs in the United Kingdom (UK) and USA. Calculations for the removal of DCP in STPs indicate that 21% is removed by adsorption to sludge, with the remainder emitted to surface waters in effluent, assuming little biodegradation occurs (Struijs, 1996). HCP and BCP are hydrophobic chemicals and 85% removal in sludge is expected, with the remainder emitted to surface water in effluent, again assuming little biodegradation occurs. Sludge produced by STPs is typically removed and reused as a soil improver because of its high macro- and micro-nutrient content (ANZBP, 2017). Therefore, the chemicals in this group are also likely to be emitted to soil through the use of biosolids on agricultural land.

The exposure scenarios considered in this assessment involve emission of chlorophenes to environmental surface waters in effluent from STPs, and release to soil from the application of biosolids to land as a soil improver.

Environmental Fate

Dissolution, Speciation and Partitioning

DCP, HCP and BCP are expected to be present in environmental surface waters both as the parent acids and their respective mono-anions.

The calculated Henry's Law constants for the partitioning of the neutral form of the chemicals in this group range between 4.5×10^{-7} and 3.7×10^{-3} Pa-m^3/mol (US EPA, 2008). These low values indicate that the chemicals are only very slightly volatile from water and moist soil. The mono-anions of DCP, HCP and BCP can be assumed to have lower volatility than the parent acids; therefore, volatilisation will not be the dominant partitioning process for these chemicals.

The measured organic carbon normalised soil adsorption coefficient (K_{oc}) for CP (log K_{oc} = 3.4; (REACH, 2019)) and the calculated soil adsorption coefficients for DCP, HCP and BCP are high (log K_{oc} = 4.28–5.8) (US EPA, 2008). These high K_{oc} values indicate that these chemicals will have very low mobility (CP) or be immobile (DCP, HCP, and BCP) in soil.

Partitioning of chemicals between soil particles and pore water affects the bioavailability of chemicals in soil. The soil-water partition coefficient (K_p) for CP (K_p = 50.2 L/kg) was calculated according to a standard method (EPHC, 2009), using the measured K_{oc} value for this chemical and the default organic carbon fraction in soil (f_{oc} = 0.02). This value has been used to evaluate the toxicity of CP to soil organisms as outlined in the Environmental Effects section.

Calculations with a standard multimedia partitioning (fugacity) model assuming equal and continuous distributions to air, water and soil compartments (Level III approach) predict that CP will mainly partition to soil (79%), with the remainder partitioning to sediments (10%) and water (10%) (US EPA, 2008). In a scenario where release only occurs to water, 47% of the chemical remains in the water compartment and 53% partitions to sediment. Similar calculations for the other chemicals in this group indicate that they will primarily partition to the sediment compartment in this emission scenario (75–96%). However, it should be noted that these estimates are considered less reliable than for CP as standard fugacity models do not incorporate the influence of ionisation on partitioning behaviour.

Degradation

CP is inherently biodegradable. DCP, HCP and BCP are expected to degrade very slowly in the environment.

CP is not readily biodegradable (REACH, 2019). An inherent biodegradability test conducted according to OECD Test Guideline (TG) 302B found 97% degradation under certain test conditions, indicating that the chemical will ultimately biodegrade in the environment (REACH, 2019). Modelling of the biodegradation of this chemical indicates that CP will have an ultimate biodegradation half-life of 1 year and 11 months (LMC, 2011).

Biodegradation screening tests following OECD TG 301C showed 0% degradation for both DCP (LMC, 2013) and HCP (NITE, 2019) after 28 days. Although these results appear to show that these two chemicals are recalcitrant, it should be noted that biocidal chemicals inhibit the efficacy of microbial degradation tests when applied in high concentrations (Kayashima, et al., 2013). In the case of the Japanese MITI test, a standard test substance concentration of 100 mg/L is used, which is well in excess of the concentration of HCP known to inhibit bacteria (5.2 mg/L) (Frederick, et al., 1974).

As there were no fully reliable biodegradation tests available for DCP, HCP and BCP, the microbial transformation of these chemicals was instead evaluated using quantitative structure-biodegradation modelling (LMC, 2011). The primary biodegradation step for these three chemicals is predicted to be aryl ring hydroxylation followed by ring cleavage. The estimated primary (and ultimate) degradation half-lives for DCP, HCP and BCP are 26.7 days (3 years), 3 months (4 years and 11 months), and 3 months (2 years and 2 months), respectively. Based on these calculated rates of biodegradation, all three of these chemicals can be expected to persist in the environment.

The biotransformation of chlorinated phenols in the environment can generate more lipophilic products as a result of the methylation of the phenolic oxygen atom (Bester, 2003; Haggblom, et al., 1988). *O*-methylation by microbes is an important part of the environmental chemistry of the POP, pentachlorophenol (CAS RN 87-86-5) (Haggblom, et al., 1988). This transformation significantly alters the partitioning behaviour and increases the bioaccumulation potential of the parent phenol (POPRC, 2013). No evidence for the *O*-methylation of chlorophenes in the environment was identified in this assessment.

A photodegradation half-life in water of 5 days was determined for CP in a 21 day photolysis test (Werner, et al., 1983). Aqueous photolysis of CP may, therefore, be a significant dissipation pathway for this chemical in clear surface waters. Analysis of photodegradation products from the photolysis of HCP indicate that the main products are the mono- or bis-dechlorinated analogues of the parent compound (Shaffer, et al., 1971). Photolysis data for DCP and BCP were not available.

The chemicals in this group have been detected in sediment cores extracted from two lakes in Switzerland, which indicates they may have long life times in the sediment compartment. CP, DCP, HCP and BCP were all detected in anaerobic sediments estimated to have been laid down in these lakes in the 1970s (Chiaia-Hernández, et al., 2017).

Bioaccumulation

The chemicals in this group have a low to moderate potential to bioaccumulate in aquatic organisms.

The log K_{ow} values for all chemicals in this group are above the domestic categorisation threshold for a bioaccumulation hazard (log $K_{ow} \geq 4.2$). However, measured and calculated bioconcentration factors (BCF) in fish are below the categorisation criterion for bioaccumulation (BCF ≥ 2000 L/kg). An OECD TG 305 test on CP gave a lipid normalised BCF of 55–56 L/kg in zebrafish (*Danio rerio*) (REACH, 2019) and the chemical has been observed to be metabolised and excreted in fish (HSDB, 2006b). Tests of the bioconcentration of DCP and HCP in common carp (*Cyprinus carpio*) gave BCFs in the range of 98–281 and 82–153 L/kg, respectively (NITE, 2019). No bioconcentration data for BCP were available, but calculated values of 400 L/kg in fish after accounting for the effects of biotransformation (US EPA, 2008) indicate that BCP will likely have similar bioaccumulation properties to HCP in fish.

HCP has been shown to bioconcentrate in other aquatic organisms. A BCF of 1500 L/kg has been measured in algae (*Oedogonium cardiacum*) and a BCF of 970 L/kg has been measured in freshwater snails (*Physa sp.*) (Sanborn, 1974).

Transport

The chemicals in this group are not expected to undergo long range transport.

The chemicals in this group have very low volatility and a strong tendency to partition to sediments and soils when released to the environment. This partitioning behaviour is expected to effectively limit their potential to undergo long range transport.

Predicted Environmental Concentration (PEC)

The PECs for CP, DCP, HCP and BCP in inland surface waters are 0.20 micrograms per litre (µg/L), 0.03 µg/L, 0.02 µg/L and 0.03 µg/L, respectively.

The exposure scenario considered in this assessment involves emissions of chlorophenes to surface waters in STP effluent and to soil in biosolids. International monitoring studies have identified CP, DCP and HCP in STP effluent. CP has been measured in effluent in two studies, one in the UK and one in the USA, at concentrations of 0.039 and 0.20 µg/L respectively (Kasprzyk-Hordern, et al., 2008; Yu, et al., 2006). Assuming the use of CP is similar in Australia, a conservative maximum concentration of 0.20 µg/L has been used for CP in STP effluent in Australia. In a different study performed in the USA, DCP and HCP were detected in STP effluent, but at levels that were below the quantification limit of the analytical technique (Heidlera and Haldena, 2009). In the absence of other information, the respective limits of detection for DCP and HCP in STP effluent from this study (0.03 µg/L and 0.02 µg/L) have been taken to provide a conservative upper estimate of the maximum concentrations of these chemicals in the effluents from STPs in Australia.

No domestic or international environmental monitoring data were identified for BCP in this assessment. In accordance with the IMAP Framework, the annual maximum volume of BCP introduced into Australia for industrial uses is assumed to be 100 tonnes (NICNAS, 2017). Based on estimated removal rates for this chemical in STPs, the calculated concentration of BCP in the riverine environment would be 12.7 µg/L. However, international information indicates that the scale of use of BCP appears to be somewhat smaller than other chemicals in this group, such as CP and DCP. The recent evaluation of this chemical in

Sweden used a default introduction volume of 100 kg per year, which is 0.1% of the IMAP default introduction volume. Based on the large difference in their apparent global usage volume, the PEC for BCP is unlikely to be larger than the PEC for DCP. For the purposes of this assessment, the PEC of 0.03 µg/L for DCP will be used for the environmental concentration of BCP.

Chlorophenes are both hydrophobic and not rapidly biodegradable and a significant fraction of the quantity of these chemicals in wastewater influent (up to 85%) may be removed by partitioning to sewage sludge. A measured concentration for DCP in biosolids from a US sewage treatment plant of 10 micrograms per kilogram (µg/kg) has been reported (Heidlera and Haldena, 2009). Using an application rate of 10 tonnes dry weight of biosolids per hectare, a mixing depth of 10 cm, and a soil bulk density of 1500 kg/m^3, the concentration of DCP in biosolids-amended soil is calculated to be 0.066 µg/kg immediately after application. For the purposes of this assessment, a similar soil concentration is assumed for CP.

Soil dwelling organisms are exposed to contaminants in soil through soil pore water. The concentration of CP present in the interstitial water in soil can be estimated using a standard approach outlined in the risk assessment manual for industrial chemicals (EPHC, 2009). Using this method, the PEC for CP in soil calculated above, and assuming average organic soil content and soil densities relevant to Australia, the concentration of CP in soil pore water is calculated to be 0.0019 µg/L (1.9 ng/L).

Environmental Effects

Chlorophenes are toxic to aquatic organisms across multiple trophic levels in both short and long-term exposure scenarios.

HCP has a specific mode of toxicity. At low concentrations it inhibits the action of the membrane-bound proteins responsible for oxidative phosphorylation leading to the arrest of respiration (Frederick, et al., 1974). This inhibition has been observed in both bacterial and mammalian systems (Frederick, et al., 1974). CP is reported to have a similar mode of action (ECHA, 2017a). At higher concentrations, HCP diffuses into cell membranes where it can disrupt the structure of the membrane and denature proteins leading to reduced cell viability or cell lysis (Frederick, et al., 1974).

DCP and BCP are expected to exhibit a similar mode of toxic action due to their structural similarity to HCP, although few studies have been conducted on these chemicals. The anthelmintic effects of DCP are reported to occur by inhibiting the respiration of *Ascaris* species (roundworm) in a similar manner to HCP (Bossche, et al., 2012).

Effects on Aquatic Life

Acute toxicity

The following measured freshwater median lethal concentration (LC50) and median effective concentration (EC50) values for model organisms across three trophic levels were retrieved from the scientific literature (BCP; (Stibany, et al., 2017)), the US EPA ECOTOX Knowledgebase database (DCP and HCP; (US EPA, 2019a)), or from the REACH registration dossier for chlorophene (CP; (REACH, 2019)). Tests were reported to be conducted on technical grades of the parent acids and test media were adjusted and maintained at pH 7–8 for the duration of the experiments:

Taxon	Endpoint	Method
Fish	CP: 96 h LC50 = 0.33 mg/L	Experimental *Lepomis macrochirus* (bluegill sunfish) US EPA OCSPP 850.1075

Taxon	Endpoint	Method
	DCP: 96 h LC50 = 0.31 mg/L HCP: 96 h LC50 = 0.021 mg/L	Experimental *Pimephales promelas* (fathead minnow) Flow-through
	BCP: 48 h EC50 = 0.21 mg/L	Experimental *Danio rerio* (zebrafish) OECD TG 236 fish-embryo Mortality
Invertebrates	CP: 48 h EC50 = 0.65 mg/L	Experimental *Daphnia magna* (water flea) US EPA OCSPP 850.1010
	DCP: 48 h LC50 = 0.05 mg/L	Experimental *Spicodiaptomus chilospinus* (zooplankton) Static mortality test
	HCP: 24 h EC50 = 0.122 mg/L	Experimental *Daphnia magna* (water flea) OECD TG 202 Intoxication
	BCP: 48 h EC50 = 0.17 mg/L	Experimental *Daphnia magna* (water flea) OECD TG 202 Immobilisation
Algae	CP: 96 h EC50 = 0.435 mg/L	Experimental *Anabaena flos-aquae* (cyanobacteria) OECD TG 201 Growth inhibition

Taxon	Endpoint	Method
	BCP: 72 h EC50 = 0.08 mg/L	Experimental *Desmodesmus subspicatus* (green algae) OECD TG 201 Growth inhibition

Chronic toxicity

The following measured no-observed effect concentration (NOEC) values were retrieved from the US EPA ECOTOX Knowledgebase database (DCP and HCP; (US EPA, 2019a)), or from the REACH registration dossier for chlorophene (CP; (REACH, 2019)):

Taxon	Endpoint	Method
Fish	CP: 30 d NOEC = 0.00058 mg/L	Experimental *Danio rerio* (zebrafish) OECD TG 210 Early life stage mortality
	DCP: 33 d NOEC = 0.0968 mg/L HCP: 33 d NOEC = 0.00408 mg/L	Experimental *Pimephales promelas* (fathead minnow) Flow through Early life stage mortality
Invertebrates	CP: 21 d NOEC = 0.0067 mg/L	Experimental *Daphnia magna* (water flea) EEC Part C, Method 20 Reproduction test
Algae	CP: 96 h NOEC = 0.06 mg/L	Experimental *Anabaena flos-aquae* (cyanobacteria) OECD TG 201 Growth inhibition

Endocrine Activity

CP, DCP and HCP have been identified as endocrine active chemicals; however, there is currently insufficient evidence available to indicate whether this activity will cause adverse effects on aquatic life at typical environmental exposure concentrations.

CP and DCP were identified as having (o)estrogenic and androgenic receptor activity in the ToxCast high-throughput endocrine activity screening tests (US EPA, 2019b, c). Further analysis of this test data by the US EPA indicates that CP and DCP have Area Under Curve (AUC) receptor activity scores of 0.392 and 0.367, respectively (Kleinstreuer, et al., 2017). AUC scores are between 0 and 1 where 0 indicates no activity and 1 indicates the androgenic receptor activity of the antagonist reference material, 17α-ethinyl estradiol (CAS RN 57-63-6). These AUC scores indicate that both CP and DCP are weak androgenic receptor antagonists; however, further testing is required to characterise any environmental hazard presented by this finding.

HCP is listed as a suspected endocrine disruptor on the Danish centre on endocrine disruptors (CeHoS) list of endocrine disrupting chemicals (CeHoS, 2017). HCP has been shown to have moderate anti-(o)estrogenic activity using two different receptor binding assays (Jung, et al., 2004). The CeHoS report recommended further characterisation of the activity exhibited by this chemical (CeHoS, 2017).

Effects on Sediment-dwelling Life

No studies on the effects of these chemicals on sediment-dwelling life were available.

Effects on Terrestrial Life

CP and DCP have inhibitory effects on soil microbes.

A respiration inhibition assay on the denitrifying soil microbe *Paracoccus denitrificans* gave lowest adverse effect concentrations (LOAEC) of 9.9 mg/L and 0.99 mg/L for CP and DCP respectively (Holzem, et al., 2014). This assay was run in an aqueous medium to simulate the chemical exposure through pore water to the organism. A standard OECD bacterial respiration inhibition test (OECD TG 216) done in soil gave a NOEC of 19 mg/kg dw for CP (REACH, 2019). Soil bacteria play an important role in nutrient cycling which is necessary for healthy soils.

An OECD TG 207 test on the effects of CP on the earthworm *Eisenia fetida* gave a 14 d LC50 of 428 mg/kg dw, with a NOEC of 173 mg/kg dw (REACH, 2019). An OECD TG 208 test on the plant, *Brassica napus* (canola), gave a 14 d EC50 of 120 mg/kg dw for CP (REACH, 2019).

No terrestrial toxicity data were available for HCP and BCP.

Predicted No-Effect Concentration (PNEC)

The aquatic PNECs for CP, DCP, HCP and BCP are 58, 500, 40.8 and 80 ng/L, respectively.

The fish 30 d NOEC value of 0.00058 mg/L for CP was used to derive a PNEC for this chemical. An assessment factor of 10 was used as sufficient acute and chronic toxicity data are available to characterise the toxicity of this chemical to aquatic organisms. The invertebrate 48 h LC50 of 0.05 mg/L and the fish 33 d NOEC of 0.00408 mg/L were used to calculate the respective PNECs for DCP and HCP. An assessment factor of 100 was used in both cases as incomplete acute and chronic toxicity data are available for these two chemicals. The PNEC for BCP was derived from the algae 72 h EC50 of 0.08 mg/L using an assessment factor of 1000. The use of a conservative assessment factor is justified in this case because there is evidence of a high ratio between the acute and chronic toxicity values for chlorophenes and there is also evidence of specific modes of toxicity at low concentrations for the chemicals in this group.

Categorisation of Environmental Hazard

The categorisation of the environmental hazards of the chemicals in this group according to domestic environmental hazard thresholds is presented below (EPHC, 2009; NICNAS, 2017):

Persistence

Persistent (P). Based on the available measured and calculated environmental transformation data indicating slow biodegradation, these chemicals are categorised as Persistent.

Bioaccumulation

Not Bioaccumulative (Not B). Based on the available measured bioconcentration data indicating BCFs < 2000 L/kg, CP, DCP and HCP are categorised as Not Bioaccumulative. Based on calculated BCF values in fish corrected to account for the effects of biotransformation, BCP is categorised as Not Bioaccumulative.

Toxicity

Toxic (T). Based on available acute ecotoxicity values below 1 mg/L and evidence of high chronic toxicity for CP and HCP, all chemicals in this group are categorised as Toxic.

Summary

Phenol, 4-chloro-2-(phenylmethyl)- (CP); phenol, 2,2'-methylenebis[4-chloro- (DCP); phenol, 2,2'-methylenebis[4-chloro-, monosodium salt (NaDCP); phenol, 2,2'-methylenebis[4-chloro-, disodium salt (Na_2DCP); phenol, 2,2'-methylenebis[3,4,6-trichloro- (HCP); and phenol, 2,2'-methylenebis[6-bromo-4-chloro- (BCP) are categorised as:

- P
- Not B
- T

Risk Characterisation

Chlorophenes are very toxic to aquatic life with evidence of specific modes of toxicity at low concentrations including potential endocrine activity. These chemicals are expected to undergo slow biodegradation in the environment and they have the potential to accumulate in the sediment compartment. Although the chemicals do not appear to have high volume uses as industrial chemicals, international exposure information shows that they are emitted to surface waters in STP effluent and to soils through the application of biosolids. The exposure information includes contribution from all sources, including non-industrial.

Based on the PEC and PNEC values determined above, the following Risk Quotients (RQ = PEC ÷ PNEC) have been calculated for release of the chemicals into the riverine environment:

Chemical	PEC (µg/L)	PNEC (µg/L)	RQ

Chemical	PEC (µg/L)	PNEC (µg/L)	RQ
CP	0.20	0.058	3.4
DCP	0.03	0.5	0.06
HCP	0.02	0.04	0.5
BCP	0.03	0.08	0.37

An RQ of less than 1 indicates that DCP and HCP are not expected to pose an unreasonable risk to the environment based on the estimated emissions, as environmental concentrations are below the levels likely to cause harmful effects.

The PEC for CP in surface waters exceeds the no unacceptable adverse effect level which indicates that the chemical may pose an unreasonable risk to the aquatic environment. This calculation is based on the more conservative of two international monitoring measurements, and there is, therefore, uncertainty about the magnitude of the risks in Australia. Nevertheless, CP is on international lists of environmental contaminants of emerging concern and has been a focus of studies on the environmental emissions of ingredients in personal care products. Based on the calculated RQ and the high chronic toxicity of CP to aquatic organisms, monitoring of this chemical in the Australian environment is recommended.

It is noted that there are no chronic toxicity data nor environmental concentration data available for BCP and there are significant concerns related to the long term aquatic toxicity of chlorophenes. The long-term impacts of low level emissions of BCP to the aquatic environment are, therefore, uncertain. Further evaluation of this chemical may be required if information becomes available to indicate that BCP is being introduced in significant volumes for industrial uses, or if the chemical is detected in the aquatic environment at concentrations exceeding 0.1 µg/L.

Industrial uses of chlorophenes are not likely to pose an unreasonable risk to soil organisms based on the available information. The concentration of CP in soil pore water resulting from the application of biosolids is < 2 ng/L, which is more than five orders of magnitude below the concentrations of CP and DCP which inhibit respiration of soil bacteria.

Key Findings

Chlorophenes are antimicrobial preservatives used globally in personal care products and cosmetics. They have non-industrial uses in Australia as pesticides and therapeutics which may contribute to environmental emissions of these chemicals. International exposure information indicates that chemicals in this group are emitted to surface waters in effluent from sewage treatment plants. They are also released to soil in biosolids. Similar exposure pathways are assumed for Australia.

All members of this group are highly toxic to aquatic organisms, and three members of this group have been identified as endocrine active chemicals with either anti-androgenic or anti-(o)estrogenic activity *in vitro*. They are also persistent in the environment and may accumulate in the sediment compartment.

The risk characterisation for CP showed that emissions of this chemical to surface waters may pose an unreasonable risk to the aquatic environment. It is recommended that agencies and organisations responsible for water quality management in Australia consider including CP in the list of aquatic contaminants that are routinely monitored in sewage effluent and surface waters. Industrial uses of CP and other chlorophenes in this group are not considered to pose an unacceptable risk to the soil environment.

The chemicals in this group are not PBT substances according to domestic environmental hazard criteria.

Recommendations

It is recommended that chlorophene is added to the list of contaminants that are monitored in sewage treatment effluents and surface waters in Australia.

Environmental Hazard Classification

In addition to the categorisation of environmental hazards according to domestic environmental thresholds presented above, the classification of the environmental hazards of phenol, 4-chloro-2-(phenylmethyl)- (CP); phenol, 2,2'-methylenebis[4-chloro-, phenol (DCP); phenol, 2,2'-methylenebis[4-chloro-, monosodium salt (NaDCP); phenol, 2,2'-methylenebis[4-chloro-, disodium salt (Na_2DCP); phenol, 2,2'-methylenebis[3,4,6-trichloro- (HCP); and phenol, 2,2'-methylenebis[6-bromo-4-chloro- (BCP) according to the third edition of the United Nations' Globally Harmonised System of Classification and Labelling of Chemicals (GHS) is presented below (UNECE, 2009):

Hazard	GHS Classification (Code)	Hazard Statement
Acute Aquatic	Category 1 (H400)	Very toxic to aquatic life
Chronic Aquatic	Category 1 (H410)	Very toxic to aquatic life with long lasting effects

The classification of the aquatic hazards of these chemicals has been performed based on the toxicity data presented in this assessment. The classification of NaDCP and Na_2DCP was carried out using the toxicity data for the parent acid, DCP, after correcting for the molecular weight of the salts. The long-term aquatic hazard classification of DCP, NaDCP and Na_2DCP was determined using the most stringent outcome method as outlined in the GHS guidance for classification of chemicals with insufficient chronic toxicity data. The long-term aquatic hazard classification for BCP was determined considering the lack of rapid degradability and high octanol-water partition coefficient for this substance.

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