Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Chlorocresol and chloroxylenol

Evaluation statement

14 January 2022

Table of contents

Contents

AICIS evaluation statement 4

Subject of the evaluation 4

Chemicals in this evaluation 4

Reason for the evaluation 4

Parameters of evaluation 4

Summary of evaluation 4

Summary of introduction, use and end use 4

Environment 5

Conclusions 6

Supporting information 7

Rationale 7

Chemical identity 7

Relevant physical and chemical properties 10

Introduction and use 10

Australia 10

International 10

Existing Australian regulatory controls 11

Public 11

Environment 11

International regulatory status 11

United Nations 11

European Union 12

United States of America 12

Environmental exposure 12

Environmental fate 13
Predicted environmental concentration (PEC) 15
Environmental effects 16
Effects on aquatic Life 16
Endocrine effects/activity 18
Predicted no-effect concentration (PNEC) 18
Categorisation of environmental hazard 19
Persistence 19
Bioaccumulation 19
Toxicity 19
GHS classification of environmental hazard 19
Environmental risk characterisation 19
References 21

AICIS evaluation statement

Subject of the evaluation

Chlorocresol and chloroxylenol

Chemicals in this evaluation

Name	CAS number
Phenol, 4-chloro-3-methyl-	59-50-7
Phenol, 4-chloro-3-methyl-, sodium salt	15733-22-9
Phenol, 4-chloro-3,5-dimethyl-	88-04-0

Reason for the evaluation

The Evaluation Selection Analysis indicated a potential risk to the environment.

Parameters of evaluation

This evaluation considers the environmental risks associated with the industrial uses of three phenolic biocides: 4-chloro-3-methylphenol (PCMC, CAS No. 59-50-7), 4-chloro-3-methylphenol sodium salt (PCMC-Na, CAS No. 15733-22-9) and 4-chloro-3,5-dimethylphenol (PCMX, CAS No. 88-04-0). These chemicals are listed on the Australian Inventory of Industrial Chemicals (the Inventory) and have been assessed for their risks to the environment according to the following parameters:

- Default domestic introduction volumes of 100 tonnes per annum
- Industrial uses listed in the 'Summary of Use' section
- Expected emission into sewage treatment plants (STPs) due to consumer and commercial use.

These chemicals have been assessed as a group as they are structurally similar and have similar use patterns.

Summary of evaluation

Summary of introduction, use and end use

There is currently no specific information about the introduction, use and end use of the chemicals in Australia. The chemicals in this group are used as antimicrobial preservatives and biocides in a variety of industry and household products worldwide. They are used in the following products according to reported international use data:

- Adhesive and sealant products

- Lubricant and grease products
- Personal care products
- Paint and coating products
- Plastic and polymer products
- Construction products
- Fabric, textile and leather products
- Ink, toner and colourant products
- Cleaning and furniture care products.

The chemicals in this group have non-industrial uses as disinfectants and preservatives in therapeutic and agricultural products. PCMX is the active ingredient in Dettol antiseptic concentrate.

There are no specific domestic introduction volume data available for these chemicals. PCMC is an Organisation for Economic Co-operation and Development (OECD) High Production Volume (HPV) chemical and appears to have a higher volume of use internationally than PCMX.

Environment

Summary of environmental hazards

According to domestic environmental hazard thresholds and based on the available data the chemicals are:

- Not Persistent (not P)
- Not bioaccumulative (not B)
- Toxic (T)

Environmental hazard classification

The chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) for environmental hazards as follows. This does not consider classification of physical hazards and health hazards.

Environmental Hazard	Hazard Category	Hazard Statement
Hazardous to the aquatic environment (acute / short-term)	Aquatic Acute 1	H400: Very toxic to aquatic life
Hazardous to the aquatic environment (long-term)	Aquatic Chronic 3	H412: Harmful to aquatic life with long-lasting effects

Summary of environmental risk

PCMC and PCMX are widely used as a preservative in a range of industry and household products. PCMX is used as a biocidal active ingredient in antimicrobial handwashes. Both chemicals are expected to be released to wastewater as a normal part of their use patterns.

The chemicals are highly toxic to aquatic organisms. They are not persistent in the environment after release and have a low potential for bioaccumulation.

Based on measured domestic and international concentrations in STP effluent the chemicals are expected to be present in Australian surface waters at concentrations below the level of concern.

Conclusions

The conclusions of this evaluation are based on the information described in this statement. Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* apply.

The Executive Director is satisfied that the identified environment risks can be managed within existing risk management frameworks. This is provided that all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Rationale

This evaluation considers the environmental risks associated with the industrial uses of PCMC, PCMC-Na and PCMX, three closely related p-chlorophenols. Chemicals in this group are used as preservatives in consumer products, including personal care products and cosmetics. They are also widely used as industrial biocides in polymer and leather manufacturing and as additives in concrete.

The known industrial uses for the chemicals in this group will lead to their release into sewers which may result in their emission to the aquatic environment in the treated effluents produced by sewage treatment plants (STPs). This is of concern because chemicals with preservative and biocidal properties are often very toxic to aquatic life.

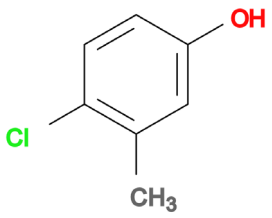
The evaluation selection analysis (ESA) of the chemicals in this group found that they are potentially of concern to the environment based on possible persistent and toxic characteristics. This assessment will evaluate the potential for emissions of the above mentioned chlorophenols to the aquatic environment in Australia and whether risk reduction measures are required for industrial uses of these chemicals.

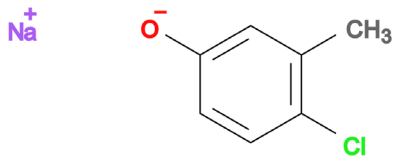
Chemical identity

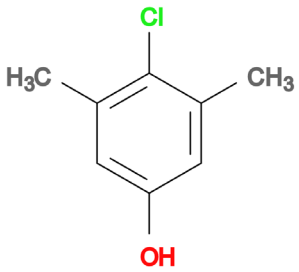
The chemicals in this group have a common *para*-chlorophenol structure. Each chemical contains either one methyl (PCMC and PCMC-Na) or two methyl (PCMX) groups in the *meta*- positions of the aryl ring. PCMC-Na is the sodium salt of PCMC.

The chemicals in this assessment belong to a larger class of chemicals known as chlorophenols. Chlorophenols are made industrially by the chlorination of the parent phenol with sulfuryl chloride or chlorine gas. For many chlorophenol chemicals, this method of manufacture may result in the formation of highly toxic impurities such as dioxins and chlorinated dioxins. This is not expected to occur for the preparation of the chemicals in this evaluation. The US EPA has reviewed the manufacture of PCMX and concluded that conditions are not appropriate for the creation of dioxin and chlorinated dioxins or dibenzofurans. No chlorinated dioxins were found at the limit of detection of 1 ppb in technical PCMX (US EPA, 1994).

PCMC-Na is the sodium salt of PCMC. Under aqueous environmental conditions PCMC-Na is expected to be protonated to create PCMC. The use of both chemicals industrially will contribute to the total volume of PCMC in the environment, therefore, PCMC-Na is not considered separately in this evaluation:

Chemical name	Phenol, 4-chloro-3-methyl-
CAS No.	59-50-7
Synonyms	PCMC p-chloro-m-cresol 2-chloro-5-hydroxytoluene 4-chloro-1-hydroxy-3-methylbenzene chlorocresol
Structural formula	
Molecular formula	C_7H_7ClO
Molecular weight (g/mol)	142.58
SMILES	CC1=C(C=CC(=C1)O)Cl
Chemical description	-

Chemical name	Phenol, 4-chloro-3-methyl-, sodium salt
CAS No.	15733-22-9
Synonyms	PCMC-Na p-chloro-m-cresol, sodium salt, sodium p-chloro-m-cresolate
Structural formula	
Molecular formula	C_7H_6ClNaO
Molecular weight (g/mol)	164.56
SMILES	CC1=C(C=CC(=C1)[O-])Cl.[Na+]
Chemical description	-

Chemical name	Phenol, 4-chloro-3,5-dimethyl-
CAS No.	88-04-0
Synonyms	PCMX 4-chloro-3,5-xylenol p-chloro-m-xylenol chloroxylenol
Structural formula	
Molecular formula	C_8H_9ClO
Molecular weight (g/mol)	156.61
SMILES	CC1=CC(=CC(=C1Cl)C)O
Chemical description	-

Relevant physical and chemical properties

Measured physical and chemical property data for PCMC and PCMX were retrieved from the registration dossier for the chemical submitted under the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation in the European Union (EU) (ECHA, 2021) and PubChem. Calculated values were estimated using EPI Suite (US EPA, 2017):

Chemical	PCMC	PCMX
Physical form	Solid	Solid
Melting point	67°C (exp.)	115°C (exp.)
Boiling point	235°C (exp.)	246°C (exp.)
Vapour pressure	6.7 Pa (exp.)	0.27 Pa (calc.)
Water solubility	3.8 g/L (25°C, exp.)	0.3 g/L (20°C, exp.)
Henry's law constant	0.248 $Pa{\cdot}m^3/mol$ (calc.)	0.139 $Pa{\cdot}m^3/mol$ (calc.)
Ionisable in the environment?	No	No
pKa	9.55	9.7
log K_{ow}	2.73 (25°C, exp.)	2.8 (20°C, exp.)

Introduction and use

Australia

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

The chemicals in this group are important disinfectant and preservatives in therapeutic products. PCMC has domestic therapeutic use as a preservative in therapeutic skin treatment products (Burry JN, 1975). PCMX is used as an active ingredient in Dettol topical antiseptic liquid and cream (TGA, 2021b). Household disinfectants containing PCMX are currently approved for use to inactivate the SARS-CoV-2 virus (COVID-19) by the TGA (TGA, 2021a). Therapeutic uses are outside of the scope of this assessment.

International

Available information indicates that the chemicals in this group are used worldwide as biocides, preservatives, stabilising agents and intermediates.

The chemicals in this group are used as preservatives in a range of industrial and household products. PCMC and PCMX are added to cosmetics and personal care products such as cleansing, moisturising and suntan preparations, and paste masks. All three chemicals may be used as preservatives in commercial products such as paints, surface treatments, concrete additives, leather and tanning agents, metalwork cutting fluids and oil recovery drilling fluids (PubChem, 2021).

PCMX is used as a biocide in antimicrobial wash products (Drugbank, 2021). It is a drop-in replacement for other antibacterial substances, such as triclosan and triclocarban, that were restricted in over-the-counter products in the United States of America by the Federal Drug Administration (FDA) in 2016 (FDA, 2016).

All substances in this group are used as intermediates for the manufacture of bulk and fine chemicals. PCMC can also be found as a stabiliser in print paste (ECHA, 2021).

PCMC and PCMX are added to polymer products and adhesives to protect from microbial growth (Ataman, 2021; Boucke, 2020; Harris, 2015; Lanxess, 2021). PCMC is also used as a stabiliser and processing aid in the manufacture of polymer coatings (Bhattacharya, 2020; Jouanneau, 2019).

PCMC is on the 2004 OECD High Production Volume (HPV) list. In the EU, the substance is used in the range of ≥10 to <100 tonnes per year (t/year), and PCMC-Na and PCMX at ≥1 to <10 t/year (ECHA, 2021). In the US, production of PCMC was 226.8–453.6 t and that of PCMC-Na and PCMX 4.5–226.8 t in 1998 (HSDB, 2021). The average annual use volume in the Nordic countries (2015-2019) was 16.7 t (PCMC) and 6 t (PCMC-Na).

Existing Australian regulatory controls

Public

PCMC is listed in the Poisons Standard in Schedule 5 as follows:

‘CHLOROCRESOL except in preparations containing 3 per cent or less of chlorocresol.’

Schedule 5 chemicals are labelled with ‘Caution’. These are ‘substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label’ (TGA, 2021c).

Environment

The use of PCMC, PCMC-Na and PCMX is not subject to any specific national environmental regulations.

International regulatory status

United Nations

PCMX is on the World Health Organisation (WHO) List of Essential Medicines (WHO, 2019).

European Union

PCMC is approved for use as a biocide in the EEA and/or Switzerland, for: human hygiene, disinfection, veterinary hygiene, product preservation, preservation of fibres, leather, rubber, or polymers, preservation for working / cutting fluids. It can be added to products such as liquid detergents, waxes, car care and cleaning products at a concentration of up to 0.5% (ECHA, 2017; 2021). PCMC-Na is approved for use as a biocidal active substance (ECHA, 2021). The BPR assessment of PCMC (Preservatives from products during storage) as a biocidal active categorised the chemical as not P, not B and not T. The chemical is not considered as a POP or an endocrine disruptor (ECHA, 2017). The approval for PCMC-Na as a biocidal active substance is no longer supported (ECHA, 2021a).

PCMC and PCMX are listed on the EU Cosmetic Products Regulation Annex V (allowed preservative in cosmetic products). PCMC is allowed in all cosmetic products except products applied on mucous membranes, with a maximum threshold of 0.2% (restrictions are in place against use in products applied on mucous membranes). PCMX is allowed in all cosmetic products at a maximum threshold of 0.5% (ECHA, 2021; European Commission, 2021).

United States of America

In 2016 the FDA issued a final rule that restricted the use of 19 active ingredients in over-the-counter consumer antiseptic washes, including triclosan and triclocarban, as they do not add any additional benefit to the final product. The FDA deferred the same ruling for chloroxylenol to allow for the submission of new safety and effectiveness data for this ingredient (FDA, 2016).

Environmental exposure

PCMC and PCMX may be found in household and commercial products available for use in Australia. The substances are used as preservatives internationally and products on the Australian market are assumed not to differ significantly from those available in other parts of the world.

Chemicals used in consumer products such as cosmetics, personal care products and antibacterial soaps are typically released to wastewater as a normal part of their use. Additionally, a substantial portion of chemicals used in commercial products such as metalwork cutting fluids and leather and tanning agents are expected to be released to wastewater (OECD, 2004; 2011). Treatment of this wastewater in sewage treatment plants will remove a fraction of the quantity of these chemicals from influents. Depending on the efficiency of various degradation and partitioning processes, a fraction of the quantity of chemicals in wastewater entering STPs can be emitted to the air compartment, to rivers or oceans in treated effluent, or to soil by application of biosolids to agricultural land. Emission of PCMC and PCMX to surface waters is the most relevant in this evaluation.

PCMC may be released to the environment from certain water treatment processes. A study of a Brazilian water treatment plant reported that PCMC was detected in treated drinking water despite not being identified in any incoming water samples. PCMC was detected in drinking water samples in the range of 0.15–0.52 μg/L in four of 12 samples. It was determined that the chlorinated species may form during the chlorination disinfection process due to reaction of organic matter with chlorine from inorganic chlorine oxidants (Ramos RL, 2021).

The chemicals in this group have commercial uses in polymers and adhesives. Diffuse releases of the substances into the environment may occur from migration to the surface of articles and subsequent release due to abrasion and wear from normal use.

Substantial releases of the chemicals in this group may occur to sewage and the environment from therapeutic uses. PCMX is used as a surface and hospital grade skin disinfectant which may be disposed in sinks after use. Non-industrial sources of PCMC, PCMC-Na and PCMX may contribute to a significant proportion of the total quantity detected in STP influent.

Environmental fate

Partitioning

PCMC and PCMX predominately partition to water when released to the environment

Under environmentally relevant conditions, PCMC and PCMX are neutral organic chemicals that are moderately to readily soluble in water and moderately volatile. A calculated Henry's Law constant (0.14–0.25 $Pa \cdot m^3/mol$) indicates the compounds will be moderately volatile from water and moist soil. PCMC and PCMX are moderately lipophilic with measured log K_{OW} of 2.7 and 2.8 respectively.

The chemicals are moderately to highly mobile in soil based on measured data. Soil adsorption coefficients (K_{OC}) have been obtained through guideline studies. For PCMC a range of 161–508 L/kg was measured, depending on the type of soil used (ECHA, 2021). The K_{OC} for PCMX was determined to be 676 L/kg (Ohlenbusch, 2000).

PCMC and PCMX are expected to be released to the water compartment in STP effluent as a result of their use pattern. Fugacity calculations (Level III approach) assuming sole release to the aquatic environment predict that the substances will primarily remain in the water (95.7–97.3%) with some partitioning to the sediment (2.6–4.3%) compartments (US EPA, 2017).

Degradation

PCMC and PCMX are expected to degrade in the environment.

Calculations from standard Quantitative Structure-Activity Relationship (QSAR) models predict that PCMC and PCMX will degrade rapidly in air through reaction with hydroxyl radicals, with half-lives of 1.9 h (PCMX) to 5 h (PCMC) (US EPA, 2017). The substances have no hydrolysable functional groups and have been found to be hydrolytically stable at pH 4,7 and 9 (PCMX: $t_{1/2}$ > 1 year).

Due to the highly biocidal nature of PCMC and PCMX, the compounds interfere with standard biodegradability tests that are run at concentrations above the 10% effective concentration (EC_{10}) for microbial respiration. The measured EC_{10} for PCMC is 5.7 mg/L (ECHA, 2021).

A ready biodegradation experiment conducted according to OECD test guideline (TG) 301D found that PCMC is degradable under screening test timeframes, fulfilling the 10-day window criterion (4.5 mg/L, 85% O_2 consumption, 28 d)(ECHA, 2021). A non-guideline study of aerobic degradation using diluted waste activated sludge found that more than 80% PCMC had degraded after 14 d (Yu, 2006). A ready biodegradation experiment conducted

according to EU Method C.4-B (modified OECD screening test) found that PCMC-Na is readily biodegradable under screening test timeframes (9.03 mg/L, 83% DOC removal, 28 d) (ECHA, 2021).

PCMX was subjected to a modified ready biodegradability study that used microorganisms pre-adapted to PCMX at 5 mg/L (modified TG 301 D). The test substance concentration was selected to be below that which had been found to be inhibitory to microorganisms but was too low to reliably determine biodegradability by carbon removal. Based on analysis of the preadaptation process, the study determined that PCMX was inherently biodegradable (ECHA, 2021). A non-guideline study of aerobic degradation using diluted waste activated sludge found less than 60% biotransformation of PCMX after 21 days; when the incubation time was extended to 50 days, degradation reached over 80% (Yu, 2006). Another publication found that fungal species *Cunninghamella elegans* and *Trametes versicolor* were able to remove 70% and 79% of PCMX within 120 h of incubation (Nowak, 2021). When exposed to an immobilised isolate of the bacterium *Klebsiella pneumoniae*, under optimised conditions, primary degradation of PCMX was *ca.* 90% after 9 hours (Ghanem, 2017).

Based on the weight of evidence, PCMX is likely to be degradable in the environment. The structural similarity of PCMC to PCMX would suggest that the latter is unlikely to be persistent in the environment based on the ready biodegradability of the former. The degradability of PCMC is suitable to be read across to PCMX for the following reasons:

- *Structural similarity*: The chemicals have identical functional groups, PCMX differing only by the addition of a methyl group on the aryl ring.
- *Physicochemical property similarity*: the chemicals have a similar lipophilicity (log K_{OW} = 2.73 vs 2.8) implying similar bioavailability of the chemicals.
- *Predicted common degradation pathways*: The microbial degradation pathways of both chemicals have been studied for different microorganisms and appear to follow the same two degradation pathways. The chemicals can undergo either methyl oxidation to the corresponding benzoic acid and/or aryl-ring oxidation and subsequent degradation by the catechol degradation pathway (Ha, 2020; Nowak, 2021).
- *Degradation*: similar biodegradation patterns with a short lag time, followed by a rapid primary metabolism within 48–60 h (Choi, 2019; Frietsch, 1991).

A primary degradation half-life of 34–56 hours was estimated for PCMX based on kinetics observed in a simulated activated sludge bioreactor (Choi, 2019).

Bioaccumulation

The chemicals in this group are expected to exhibit a low potential to accumulate in aquatic life. Experimentally determined bioconcentration factors (BCFs) for PCMC and measured log K_{ow} values for all chemicals are below the domestic categorisation threshold for bioaccumulation (EPHC, 2009).

A bioconcentration study conducted in a continuous flow system (20 μg/L PCMC) with six weeks exposure using European carp (*Cyprinus carpio*) reported a BCF of 6.7–13. (ECHA, 2021). In a study with native Australian animals, BCF values were determined for a mussel (*Mytilus edulis*) and the fish yellowtail (*Trachurus novaezelandiae*) caught in Sydney harbour (Jennings, 1996). After exposure to PCMC (100 μg/L in seawater) for one week, a dimensionless BCF value of 37.75 ± 2.27 was reported for the mussels and 120.8 ± 5.2 for the fish. PCMC was readily eliminated from fish and mussels once placed back into pure water (Jennings, 1996).

No measured BCF values were found for PCMX. Calculations show a BCF in the range of 25–70 L/kg (US EPA, 2017).

Predicted environmental concentration (PEC)

The predicted environmental concentration of PCMC is 4.4 μg/L based on Australian monitoring data. The PEC for PCMX is 3 μg/L, based on international monitoring data.

PCMC and PCMX are expected to enter the environment from STP effluent. Initial estimations using a standard STP exposure model indicate 88% removal from wastewater by partitioning processes and biodegradation in the STP (Struijs, 1996). Assuming 100 tonnes per annum introduction of the chemicals into Australia and 100% release of these chemicals to sewage, a predicted environmental concentration of 7.3 μg/L is estimated.

Domestic and international monitoring data suggest that these modelled concentration values may be overestimates.

An 1993-1994 Australian study measured PCMC concentrations in Sydney sea water, around sites of industrial, sewage and stormwater discharge points. The chemical was detected at quantifiable levels in only one of several samples collected over a 24 h period from STP deep-water ocean outfalls (final effluent before discharge into the sea). The mean concentration in that sample was 4.4 ± 2.9 μg/L (Jennings, 1996).

PCMC and PCMX have been detected in sewage influent and effluent internationally.

At a wastewater treatment plant in Baltimore (US), PCMC and PCMX levels were recorded at 0.4–0.6 μg/L in sewage influent and 0–0.08 μg/L in effluent composite samples, with a removal efficiency of 80-99% (Yu, 2006). At a STP in South Africa, PCMX was observed in influent water at concentrations of 27–105 μg/L but was not detected in effluent or at the wastewater treatment plant (WWTP) outfall site (Mann, 2019).

A monitoring program in the UK detected <0.030–0.358 μg/L PCMX in river samples up- and downstream of WWTPs. The same study showed a high detection frequency of PCMX in WWTP samples, where concentrations of 4–65 μg/L were found in influent and 0.08–3 μg/L in effluent samples after primary level sewage treatment (Kasprzyk-Hordern, 2009). The highest effluent value of 3 μg/L is used as a conservative environmental concentration of PCMX in Australian surface waters.

A study in Belgium used a system of passive sampling to determine environmentally realistic chemical mixtures in seawater. As part of this study, sampling over a timeframe of 85 d detected an average concentration of 0.68 μg/L PCMX in one of four locations (Ostend coastal waters) (Moeris, 2021)

Environmental effects

Effects on aquatic Life

The chemicals in this group are expected to cause toxic effects at low concentrations in aquatic organisms across multiple trophic levels.

PCMC and PCMX have a specific mode of toxicity common to phenols. They have the potential to bind to proteins on cell walls through the hydroxyl group. This may lead to membrane disrupting processes, leaking of the cell contents and uncoupling of oxidative phosphorylation. After diffusion into the cell the chemicals can undergo protein binding and can shut down important enzymic functions. At high phenolic concentrations, proteins and nucleic acids are coagulated and cease to function, leading to cell death (Denyer, 1986; Drugbank, 2021; McDonnell, 1999; Otter, 2006).

Incomplete chronic toxicity data are available to fully assess the toxic effects of PCMX to aquatic life. The chronic endpoints for PCMC are suitable to be read across to PCMX for the following reasons:

- *Structural similarity*: the chemicals have identical functional groups, PCMX differing only by the addition of a methyl group on the aryl ring.
- *Hydrophobicity*: the chemicals have a similar lipophilicity (log K_{OW} = 2.73 vs 2.8) implying similar magnitude of potential baseline narcotic effects.
- *Mode of action (MoA)*: the chemicals share a mode of toxic action common to phenols. Profiling with the OECD QSAR Toolbox identified that they have unspecific reactivity class 3 according to the Verhaar scheme.
- *Detoxification processes*: phenols such as PCMC and PCMX are detoxified and excreted by higher organisms including fish by conjugation with glucuronate (James, 2010; Kasokat, 1987). The chemicals are expected to have similar metabolism and excretion behaviour *in vivo* predominately though enzymatic esterification of the hydroxy group.
- *Similar magnitude of available endpoints*: the available acute and chronic endpoints for both chemicals are of a similar order of magnitude, and this trend is expected to continue for the remaining endpoints for PCMX based on MoA and structural similarity.

Acute toxicity

The following measured median lethal concentration (LC_{50}) and median effective concentration (EC_{50}) values for model organisms across three trophic levels were retrieved from the registration dossiers for PCMC and PCMX under EU REACH legislation, from the databases in QSAR toolbox and from the US EPA ECOTOX Knowledgebase website (ECHA, 2021; LMC, 2020; US EPA, 2020):

Taxon	Endpoint	Method
Fish	PCMC: 96 h LC_{50} = 0.92 mg/L PCMX: 96 h LC_{50} = 0.36 mg/L	*Oncorhynchus mykiss* (rainbow trout) Semi-static conditions, mortality EPA OPP 72-1
	PCMX: 96 h LC_{50} = 1.4 mg/L	*Oncorhynchus mykiss* (rainbow trout) Semi-static conditions, mortality OECD TG203
Invertebrate	PCMC: 48 h EC_{50} = 2.3 mg/L	*Daphnia magna* (water flea) Static conditions, immobilisation EPA OPP 72-2
	PCMX: 48 h EC_{50} = 2.7 mg/L	*Daphnia magna* (water flea) Static conditions, immobilisation OCSPP 850.1010
Algae	PCMC: 72 h EC_{50} = 10 mg/L	*Scenedesmus subspicatus* (green algae) Static conditions, growth DIN 38 412
	PCMX: 72 h EC_{50} = 3.8 mg/L	*Desmodesmus subspicatus* (green algae) Static conditions, growth OECD TG 201

Chronic toxicity

The following measured no-observed-effect concentrations (NOEC) for model organisms across three trophic levels were retrieved from the registration dossiers for PCMC and PCMX under EU REACH legislation (ECHA, 2021):

Taxon	Endpoint	Method
Fish	PCMC: 28 d NOEC = 0.15 mg/L	*Oncorhynchus mykiss* (rainbow trout) Semi-static conditions, growth OECD TG 215
	PCMX: 28 d NOEC = 0.15 mg/L	Read across from PCMC *Oncorhynchus mykiss* (rainbow trout) Semi-static conditions, growth OECD TG 215
Invertebrates	PCMC: 21 d NOEC = 0.32 mg/L	*Daphnia magna* (water flea) Semi-static conditions, reproduction OECD TG 211
	PCMX: 21 d NOEC = 0.32 mg/L	Read across from PCMC *Daphnia magna* (water flea) Semi-static conditions, reproduction OECD TG 211
Algae	PCMC: 72 h NOEC = 1.9 mg/L	*Chlorella pyrenoidosa* (green algae) Static conditions, growth OECD TG 201
	PCMX: 72 h NOEC = 2.5 mg/L	*Desmodesmus subspicatus* (green algae) Static conditions, growth OECD TG 201

Endocrine effects/activity

PCMC and PCMX demonstrate weak endocrine activity and are not expected to cause adverse endocrine effects on aquatic life at typical environmental exposure concentrations.

PCMC exhibited a weak binding capacity to (o)estrogen receptors (Blair RM, 2000), and ToxCast high-throughput screening for endocrine activity identified PCMC and PCMX as having weak (o)estrogenic activity (Browne, 2015; US EPA, 2021).

Predicted no-effect concentration (PNEC)

The PNEC for PCMC and PCMX is 15 µg/L.

A freshwater PNEC for the chemicals in this group was derived from the measured fish chronic ecotoxicity endpoint for PCMC (28 d NOEC = 0.15 mg/L). An assessment factor of 10 was applied to the pivotal endpoint as there are reliable chronic ecotoxicity data for the chemicals available for three trophic levels (EPHC, 2009).

Categorisation of environmental hazard

The categorisation of the environmental hazards of the evaluated chemicals according to domestic environmental hazard thresholds is presented below (EPHC, 2009).

Persistence

Not Persistent (Not P). Based on results from standard biodegradability tests that show ready biodegradability of PCMC, all chemicals in this group are categorised as Not Persistent.

Bioaccumulation

Not Bioaccumulative (Not B). Based on low measured and predicted bioconcentration factors (BCF) in fish the chemicals are categorised as Not Bioaccumulative.

Toxicity

Toxic (T). Based on available acute ecotoxicity values below 1 mg/L the chemicals are categorised as Toxic.

GHS classification of environmental hazard

The aquatic hazard of PCMC, PCMC-Na and PCMX is classified as Acute Category 1 (H400) and Chronic Category 3 (H412) under the Globally Harmonised System of Classification and Labelling of Chemicals (GHS, Rev. 7) (UNECE, 2017) The classification of the acute and chronic (long-term) aquatic hazards posed by the chemicals was performed based on the measured ecotoxicity data presented in this assessment and noting that the three substances are assessed as readily degradable under specific conditions, and have BCF values <500 L/kg.

Environmental risk characterisation

Based on the PEC and PNEC values determined above, the following Risk Quotient (RQ = PEC ÷ PNEC) have been calculated for release of PCMC and PCMX into rivers:

River	PEC	PNEC	RQ
PCMC	4.4 µg/L	15 µg/L	0.29
PCMX	3 µg/L	15 µg/L	0.2

For rivers, an RQ less than 1 indicates that the chemicals are not expected to pose a high risk to the environment based on estimated emissions, as environmental concentrations are below levels likely to cause harmful effects.

Uncertainty

This evaluation was conducted based on a set of information that may be incomplete or limited in scope. Some relatively common data limitations can be addressed through use of conservative assumptions (OECD, 2019) or quantitative adjustments such as assessment factors (OECD, 1995). Others must be addressed qualitatively, or on a case-by-case basis (OECD, 2019).

The most consequential areas of uncertainty for this evaluation are:

- The proposed Australian environment concentrations of PCMX in this evaluation are reliant on consistency between Australian and International per-capita use and release patterns. Consequently, this assessment does not account for internal regulatory, economic, social or other pressures that may influence emission scenarios now or in the future. The concentration value of 3 µg/L for PCMX have been selected as the best conservative estimate based on available information at this time.
- Significant environmental releases of these chemicals may occur from non-industrial sources. The chemicals have a high-volume use in therapeutic applications. There is insufficient information available to determine what percentage of the release is from industrial sources, therefore, it is likely that the PEC used in this evaluation is overestimated for industrial releases.
- Handwashing products containing PCMX may be used in response to recent public health initiatives implemented in Australia. This may increase the release of the chemical to STP as consumers wash their hands with these products more frequently. This increased use may not be reflected in the calculated PEC and the resultant risk quotient.

References

Ataman C (2021). *PCMX (Para Chloro Meta Xylenol)*. Accessed September 2021 at https://www.atamanchemicals.com/pcmx-para-chloro-meta-xylenol_u23841/.

Bhattacharya S, Kim D, Gopal S, Tice A, Lang K, Dordick J, Plawsky J, Linhardt R (2020). Antimicrobial effects of positively charged, conductive electrospun polymer fibers. *Materials science & engineering. C, Materials for biological applications,* **116**, pp 111247.

Blair RM FH, Branham WS, Hass BS, Dial SL, Moland CL, Tong W, Shi L, Perkins R, Sheehan DM (2000). The Estrogen Receptor Relative Binding Affinities of 188 Natural and Xenochemicals: Structural Diversity of Ligands. *TOXICOLOGICAL SCIENCES,* **54**, pp 138-153.

Boucke E (2020). Decorative Panel and Decorative Floor Covering Consisting of Said Panels, (WIPO) WIPO. Available at https://patents.google.com/patent/WO2020114643A1.

Browne P, Judson RS, Casey WM, Kleinstreuer NC, Thomas RS (2015). Screening Chemicals for Estrogen Receptor Bioactivity Using a Computational Model. *Environmental Science & Technology,* **49**(14), pp 8804-8814.

Burry JN KJ, Reid JG, Turner T (1975). Chlorocresol sensitivity. *Contact Dermatitis,* **1**(1), pp 41-42.

Choi D, Oh S (2019). Removal of Chloroxylenol Disinfectant by an Activated Sludge Microbial Community. *Microbes and Environments,* **34**(2), pp 129-135.

Denyer S, Hugo WB, Harding VD (1986). The biochemical basis of synergy between the antibacterial agents, chlorocresol and 2-phenylethanol. *International Journal of Pharmaceutics,* **29**(1), pp 29-36.

Drugbank (2021). *Chloroxylenol: Uses, Interactions, Mechanism of Action*. https://go.drugbank.com/drugs/DB11121.

ECHA (2017). BPR Assessment Report: Chlorocresol (CMK).

ECHA (2021). *Registered substances*. European Chemicals Agency (ECHA), Helsinki, Finland. Accessed Month 202x at https://echa.europa.eu/information-on-chemicals/registered-substances.

EPHC (2009). *Environmental Risk Assessment Guidance Manual for Industrial Chemicals*. Environment Protection and Heritage Council (EPHC), Canberra, Australia. Accessed July 2021 at http://www.nepc.gov.au/resource/chemical-risk-assessment-guidance-manuals.

European Commission (2021). *Cosmetic ingredient database*. European Commission, Brussels, Belgium. Accessed September 2021 at http://ec.europa.eu/growth/sectors/cosmetics/cosing/.

FDA (2016). *Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use*. Food and Drug Administration,

Frietsch G (1991). Effects and Degradation of 4-Chloro-3-cresol in a System of Natural Self-purification. *Wat. Res.,* **25**(6), pp 717-727.

Ghanem K, El-Ahwany AMD, Farag AM, Ghanem DAM (2017). Optimization the Degradation of Chloroxylenol by Free and Immobilized Klebsiella Pneumoniae D2. *International Journal of Current Advanced Research,* **6**(10), pp 7082-7091.

Ha D, Nguyen OT (2020). Degradation of p-chlorocresol by facultative Thauera sp. strain DO. *3 Biotech,* **10**(2), pp 46.

Harris K (2015). Polymer Antimicrobial Composition, (WIPO) WIPO. Available at https://patents.google.com/patent/WO2015189569A1/zh.

HSDB (2021). *Hazardous Substances Data Bank*. PubChem.

James M (2010). Steroid catabolism in marine and freshwater fish. *The Journal of steroid biochemistry and molecular biology,* **127**(3-5), pp 167-175.

Jennings J, de Nys R, Charlton TS, Duncan MW, Steinberg PD (1996). Phenolic Compounds in the Nearshore Waters of Sydney, Australia. *Mar. Freshwater Res.,* **47**, pp 951-959.

Jouanneau J, Spahr TA, Laffitte J-A (2019). WO 2019067342 A1: Poly(Aryl Etherketone) Based Varnish For Wire Coating And Method Coating A Wire From A Solution, (WIPO) WIPO. Available at https://patents.google.com/patent/WO2019067342A1/en.

Kasokat T, Nagel R, Urich K (1987). The metabolism of phenol and substituted phenols in zebra fish. *Xenobiotica,* **17**(10), pp 1215-1221.

Kasprzyk-Hordern B, Dinsdale RM, Guwy AJ (2009). The removal of pharmaceuticals, personal care products, endocrine disruptors and illicit drugs during wastewater treatment and its impact on the quality of receiving waters. *Water Research,* **43**(2), pp 363-380.

Lanxess (2021). *Preventol PCMC Preservative*. Accessed September 2021 at https://lanxess.com/en/Products-and-Solutions/Products/p/PREVENTOL--PCMC-PRESERVATIVE.

LMC (2020). *The OECD QSAR Toolbox*, v 4.4.1. Laboratory of Mathematical Chemistry (LMC), University "Prof. Dr. Assen Zlatarov", Burgas, Bulgaria. Available at https://qsartoolbox.org/.

Mann B, Bezuidenhout JJ, Bezuidenhout CC (2019). Biocide resistant and antibiotic cross-resistant potential pathogens from sewage and river water from a wastewater treatment facility in the North-West, Potchefstroom, South Africa. *Water Science & Technology,* **80.3**, pp 551-562.

McDonnell G, Russell AD (1999). Antiseptics and Disinfectants: Activity, Action, and Resistance. *Clinical Microbiology Reviews,* **12**(1), pp 147-179.

Moeris S, Vanryckeghem F, Demeestere K, De Schamphelaere KAC (2021). A margin of safety approach for the assessment of environmentally realistic chemical mixtures in the marine environment based on combined passive sampling and ecotoxicity testing. *Science of the Total Environment,* **765**.

Nowak M, Zawadzka K, Szemraj J, Goralczyk-Binkowska A, Lisowska K (2021). Biodegradation of Chloroxylenol by Cunninghamella elegans IM 1785/21GP and Trametes

versicolor IM 373: Insight into Ecotoxicity and Metabolic Pathways. *International Journal of Molecular Sciences,* **22**.

OECD (1995). *Guidance document for aquatic effects assessment*. Organisation for Economic Co-operation and Development, Paris.

OECD (2004). OECD Series on Emission Scenario Documents, *Emission Scenario Document on Leather Processing*. https://www.oecd-ilibrary.org/environment/leather-processing_9789264221178-en.

OECD (2011). OECD Environment, Health and Safety Publications Series on Emission Scenario Documents, *Emission Scenario Document on the Use of Metalworking Fluids*. https://www.oecd-ilibrary.org/environment/metalworking-fluids_9789264220980-en;jsessionid=VVE-_dATX0B9QdPA5T8tvtlf.ip-10-240-5-177.

OECD (2019). *Guiding Principles and Key Elements for Establishing a Weight of Evidence for Chemical Assessment, Series on Testing and Assessment No. 311, Environment, Health and Safety Division, Environment Directorate.* http://www.oecd.org/chemicalsafety/risk-assessment/guiding-principles-and-key-elements-for-establishing-a-weight-of-evidence-for-chemical-assessment.pdf.

Ohlenbusch G, Kumke MU, Frimmel FH (2000). Sorption of phenols to dissolved organic matter investigated by solid phase microextraction. *The Science of the Total Environment,* **253**, pp 63-74.

Otter R (2006). *A study of the mechanism of action of triclosan and PCMX*. University of Brighton, Accessed at https://ethos.bl.uk/OrderDetails.do?uin=uk.bl.ethos.434883.

PubChem (2021). *PubChem Chemical Structure Search*. National Library of Medicine. https://pubchem.ncbi.nlm.nih.gov/.

Ramos RL MV, Lebron YAR, Santos AV, Santos LVS, Amaral MCS (2021). Phenolic compounds seasonal occurrence and risk assessment in surface and treated waters in Minas Gerais - Brazil. *Environmental Pollution,* **268**.

Struijs J (1996). *SimpleTreat 3.0: a model to predict the distribution and elimination of chemicals by sewage treatment plants*. National Institute of Public Health and the Environment, Bilthoven, The Netherlands.

TGA (2021a). *Disinfectants for use against COVID-19 in the ARTG for legal supply in Australia*. Therapeutic Goods Administration (TGA), Canberra, Australia. https://www.tga.gov.au/disinfectants-use-against-covid-19-artg-legal-supply-australia.

TGA (2021b). *ARTG search*. https://tga-search.clients.funnelback.com/s/search.html?query=&collection=tga-artg.

TGA (2021c). *Poisons Standard June 2021*. Canberra, Australia. Accessed Month 202x at https://www.legislation.gov.au/Details/F2020L01255.

UNECE (2017). *Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Seventh Revised Edition*. United Nations Economic Commission for Europe (UNECE), Geneva, Switzerland. Accessed Month 202x at http://www.unece.org/trans/danger/publi/ghs/ghs_rev07/07files_e0.html.

US EPA (1994). Reregistration Eligibility Decision (RED), Chloroxylenol.

US EPA (2017). *Estimation Programs Interface (EPI) Suite™ for Microsoft Windows*®, v 4.11. United States Environmental Protection Agency (US EPA), Washington DC, USA. Available at https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface.

US EPA (2020). *ECOTOX Knowledgebase*. United States Environmental Protection Agency (US EPA), Duluth, USA. Accessed Month 202x at https://cfpub.epa.gov/ecotox/.

US EPA (2021). *CompTox Chemicals Dashboard*. https://comptox.epa.gov/dashboard.

Yu J, Bouwer EJ, Coelhan M (2006). Occurrence and biodegradability studies of selected pharmaceuticals and personal care products in sewage effluent. *Agricultural Water Management,* **86**, pp 72-80.