Government of Canada Gouvernement du Canada

Screening Assessment

Internationally Classified Substance Grouping

Cresol (phenol, methyl-) Substances

Environment and Climate Change Canada

Health Canada

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Synopsis

Pursuant to sections 68 or 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Ministers of the Environment and Climate Change and of Health have conducted a screening assessment of the group of substances listed in the table below, referred to collectively as the cresols (phenol, methyl-) sub-group.

CAS RNs[a] and Domestic Substances List (DSL) names for substances in the cresols sub-group

CAS RN	DSL Name	Common Name
95-48-7*	Phenol, 2-methyl-	*o*-cresol
108-39-4*	Phenol, 3-methyl-	*m*-cresol
106-44-5*	Phenol, 4-methyl-	*p*-cresol
1319-77-3	Phenol, methyl-	Mixed cresols

[a] The Chemical Abstracts Service Registry Number (CAS RN) is the property of the American Chemical Society and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the government when the information and the reports are required by law or administrative policy, is not permitted without the prior, written permission of the American Chemical Society.

* This substance was not identified under subsection 73(1) of CEPA, but was included in this assessment because it was considered a priority based on other human health concerns.

These substances are part of the Internationally Classified Substance Grouping, which includes substances that were prioritised for screening assessment because they were classified by certain international agencies as potentially of concern for human health.

Manufacture of cresols in the 2011 calendar year was in the range of 100 000 to 1 000 000 kg, while imports were in the range of 10 000 to 100 000 kg according to surveys under section 71 of CEPA. Much of the manufacturing activity was associated with the incidental production of cresols during processing of other materials.

Cresols are widespread in nature, occurring naturally in plants and as natural components of crude oil, coal tar and brown cresylic-type mixtures. In addition, they can be produced endogenously by many organisms, such as mammals and micro-organisms. Cresols occur naturally in a variety of foods and beverages, but levels in foods are generally low. They are also natural products of incomplete combustion, and may be produced and released from natural fires associated with lightning, spontaneous combustion, and volcanic activity.

Cresols are organic substances with a variety of industrial and consumer applications. They are used as intermediates in the production of antioxidants, resins and plasticizers, pesticides, dyes, deodorizing and odour-enhancing

compounds, fragrances, pharmaceuticals and other chemicals (e.g., photographic developers, explosives). Cresols are also used as industrial cleaners and solvents, synthetic food flavours, preservatives in drugs, and fragrances in pest control products.

Based on certain assumptions and reported use patterns, cresols are expected to be released primarily to air, with releases also occurring to surface waters and soil. The chemical properties of high water solubility, moderate vapour pressure, and low to moderate sorption potential indicate that, when released into the environment, cresols can be expected to distribute into air, water or soil, depending upon the compartment of release. Cresols have been detected in all environmental media, including air, surface and ground waters, sediment, soil and biota. However, given the extensive natural presence of these substances in the environment, their occurrence in a medium cannot always be linked with anthropogenic activities.

High aerobic biodegradation rates and low bioaccumulation potential reduce the exposure potential of cresols to organisms. While cresols demonstrate low to moderate toxicity in laboratory testing, a number of aquatic and terrestrial species have demonstrated a capacity to effectively metabolize and excrete these substances, thereby reducing the potential for adverse effects. Cresols may have the potential to contribute to adverse ecosystem effects through rapid depletion of dissolved oxygen under conditions of large-scale release into waters with limited oxygen exchange. Quantitative analyses based on empirical and modelled toxicity and environmental concentration data were conducted for air, soil, surface waters and sediment; these predicted that the highest environmental concentrations of cresols originating from industrial sources will be much less than experimentally determined no-effect levels.

Monitoring data indicate that levels of cresols in the Canadian environment are generally low. However, cresols were present at very high concentrations in a limited number of sediment samples, and it is possible that organisms residing in the vicinity of these sampling locations may be adversely impacted by the presence of cresols. These sites are likely influenced by production of cresols from endogenous sources and/or associated with areas of known historical industrial contamination. Corresponding aqueous concentrations of cresols at a number of these sites in the Canadian environment were below detection limits despite the high sediment concentrations detected at these sites and the high water solubility of cresols, which places further weight on the likely contribution of endogenous production within the surface sediment.

Considered together, these factors reduce the overall level of concern for cresols in the Canadian environment. Considering all available lines of evidence presented in this Screening Assessment, there is low risk of harm to organisms or the broader integrity of the environment from these substances. It is concluded that *o*-, *m*- and *p*-cresol and mixed cresols do not meet the criteria under

paragraphs 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

It is expected that exposure to cresols from their naturally occurring presence in a variety of foods and beverages represents the primary sources of total intake for the Canadian population. For the human health assessment, the risk characterization for cresols focusses on the incremental exposure from anthropogenic sources, i.e., through inhalation of air in the vicinity of pulp and paper mills.

Carcinogenicity is a potential critical effect for cresols, although tumours occurred only at high oral doses in animal studies. Limited inhalation studies in experimental animals exposed to *o*- and/or *p*-cresol resulted in adverse effects on the respiratory tract, blood and liver. Margins of exposure between effect levels in animal studies and estimates of inhalation exposure to individuals in the vicinity of industrial sites were considered adequate to address uncertainties in the health effects and exposure databases.

Based on the adequacy of the margins between estimates of exposure and critical effect levels in experimental animals, it is concluded that *o*-, *m*- and *p*-cresol and mixed cresols do not meet the criteria under paragraph 64(*c*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is concluded that cresols do not meet any of the criteria set out in section 64 of CEPA.

Table of Contents

1. Introduction

Pursuant to sections 68 or 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and Climate Change and the Minister of Health conduct screening assessments of substances to determine whether these substances present or may present a risk to the environment or to human health.

The Substance Groupings Initiative is a key element of the Government of Canada's Chemicals Management Plan (CMP). The Internationally Classified Substance Grouping consists of six substances that were identified as priorities for action, as they met the categorization criteria under section 73 of CEPA and/or were considered as priority substances under the CMP based on human health concerns (Environment Canada and Health Canada 2013). Substances in this grouping have been identified by other jurisdictions as posing a concern for human health due to high hazard potential, as recognized by international agencies.

The Internationally Classified Substance Grouping includes four cresol (Phenol, methyl-) substances, and two other substances, i.e., Ethanol, 2-[(2-aminoethyl)amino]- (Chemical Abstracts Service Registry Number [CAS RN] 111-41-1) and Carbamic acid, ethyl ester (CAS RN 51-79-6). These substances are not necessarily similar in terms of chemical structure, physical-chemical properties, uses, or other assessment parameters, and therefore three separate Screening Assessments have been conducted within the Internationally Classified Substance Grouping, with one Screening Assessment for the sub-group of the four cresols, and individual assessments for Ethanol, 2-[(2-aminoethyl)amino]- and Carbamic acid, ethyl ester.

Screening assessments focus on information critical to determining whether substances within a grouping meet the criteria as set out in section 64 of CEPA, by examining scientific information to develop conclusions, incorporating a weight-of-evidence approach and precaution.[1]

[1] A determination of whether one or more of the criteria of section 64 are met is based upon an assessment of potential risks to the environment and/or human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and the use of consumer products. A conclusion under CEPA on the substances in the Chemicals Management Plan (CMP) is not relevant to, nor does it preclude, an assessment against the hazard criteria for the Workplace Hazardous Materials Information System (WHMIS) that are specified in the *Controlled Products Regulations* for products intended for workplace use. Similarly, a conclusion based on the criteria

This Screening Assessment includes consideration of information on chemical properties, hazards, uses and exposure, including additional information submitted by stakeholders. Relevant data were identified up to September 2014. Empirical data from key studies and some results from models were used to reach conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered.

The Screening Assessment does not represent an exhaustive or critical review of all available data. Rather, it presents the most critical studies and lines of evidence pertinent to the conclusion.

The Screening Assessment was prepared by the Existing Substances programs at Health Canada and Environment and Climate Change Canada and incorporates input from other programs within these departments. The ecological and human health portions of this assessment have undergone external written peer review and/or consultation. Comments on the technical portions relevant to the environment were received from Dr. Pamela Welbourne, School of Environmental Studies, Queen's University; and Dr. Tim Fletcher, Ontario Ministry of Environment. Comments on the technical portions relevant to human health were received from Dr. Michael Dourson, Toxicology Excellence for Risk Assessment; Dr. John Risher, U.S. Agency for Toxic Substances and Disease Registry (ATSDR); Dr. Pamela Williams, Colorado School of Public Health, University of Colorado; and Dr. Barry Ryan, Rollins School of Public Health, Emory University. Additionally, the draft of this Screening Assessment was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the Screening Assessment remain the responsibility of Health Canada and Environment and Climate Change Canada.

The critical information and considerations upon which the Screening Assessment is based are provided below.

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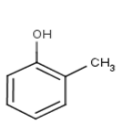
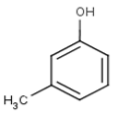
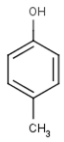
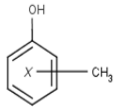
contained in section 64 of CEPA does not preclude actions being taken under other sections of CEPA or other Acts.

2. Identity of Substances

This Screening Assessment focuses on cresols (Phenol, methyl-). Cresols are isomeric phenols with a methyl substituent at the *ortho* (*o*-cresol), *meta* (*m*-cresol), or *para* (*p*-cresol) position relative to the hydroxyl group. This assessment involves four substances: three individual cresol isomers and a mixture of isomeric cresols. The identities of the individual substances are presented in Table 1. All four substances are being assessed as a group because they possess similar physical and chemical characteristics, and display comparable environmental and toxicological properties. For the purposes of this Screening Assessment, the term "cresols" refers to all substances in this group.

Table 1: Identity of the cresol substances

CAS RN	95-48-7	108-39-4	106-44-5	1319-77-3
DSL name (English)[a]	Phenol, 2-methyl-	Phenol, 3-methyl-	Phenol, 4-methyl-	Phenol, methyl-
Abbreviation/ common name	*o*-cresol	*m*-cresol	*p*-cresol	Cresol[b] mixed cresols
Other names	*ortho*-cresol; cresol;[b] 2-methylphenol	*meta*-cresol; cresol;[b] 3-methylphenol	*para*-cresol; cresol;[b] 4-methylphenol	Cresol;[b] methylphenol cresylic acid
Chemical group (DSL Stream)	Discrete organics	Discrete organics	Discrete organics	Discrete organics
Major chemical class or use	Phenols	Phenols	Phenols	Phenols
Major chemical sub-class	Cresols	Cresols	Cresols	Cresols
Chemical formula	C_7H_8O	C_7H_8O	C_7H_8O	C_7H_8O
Chemical structure				
SMILES	Oc(c(ccc1)C)c1	Oc(cccc1C)c1	Oc(ccc(c1)C)c1	Oc1ccccc1C
Molecular mass	108.14 g/mol	108.14 g/mol	108.14 g/mol	108.14 g/mol

Abbreviations: CAS RN, Chemical Abstracts Service Registry Number; DSL, Domestic Substances List; NCI, National Chemical Inventory; SMILES, Simplified Molecular Input Line Entry System.

[a] Identity for: TSCA (Toxic Substances Control Act Chemical Substance Inventory) systematic name, AICS (Australian Inventory of Chemical Substances), SWISS (Giftliste 1, List of Toxic Substances 1), PICCS (Philippine Inventory of Chemicals and Chemical Substances), ASIA-PAC (Asia-Pacific Substances Lists), NZIoC (New Zealand Inventory of Chemicals).

[b] Identity for: REACH (List of Pre-registered substances) and EINECS (European Inventory of Existing Commercial Chemical Substances).

Considerations for CAS RN 1319-77-3

The Domestic Substances List (DSL) name for CAS RN 1319-77-3 is “Phenol, methyl-.” The Chemical Abstracts Index Names published by the Scientific and Technical Information Network (STN) includes two names for CAS RN 1319-77-3, i.e. “Phenol, methyl-” and “Cresol”, and does not specify or define the composition of the substance (STN 2012). The U.S. Environmental Protection Agency (EPA) Registry Name and European Commission name for this CAS RN is “Cresol.”

In the literature, several other names and definitions are associated with CAS RN 1319-77-3, and in general are associated with an isomeric mixture. The Merck Index (O’Neil 2001) describes CAS RN 1319-77-3 as a mixture of the three isomeric cresols, in which the *meta*- isomer predominates. According to the industry report “Cresols, Xylenols and Cresylic Acids” in the Chemical Economics Handbook (SRI 2012), mixed cresols “have no universal specification” (SRI 2012). CAS RN 1319-77-3 is commonly referred to as commercial cresols (IPCS 1995), cresylic acid (singular form) (IPCS 1995; OECD 2001), or tricresol (Fiege 2000; OECD 2001), which are specified as containing the three cresol isomers combined with small amounts of phenol and xylenols (Deichman and Keplinger 1981). In other references, CAS RN 1319-77-3 can also be associated with “cresylic acids” (pluralized form). However, as highlighted by IPCS (1995), the substance “cresylic acids” (in contrast to cresylic acid) is a mixture containing a very small amount of cresols (0 to 1% *m*- and *p*-cresol) and is composed primarily of xylenols (approximately 40 to 50%) and higher alkylated phenols (50 to 60%), with the possibility of some phenol (Sax and Lewis 1987). Both cresylic acid and cresylic acids are mixtures derived from coal tars (as opposed to synthetic production). For the purpose of this Screening Assessment, the common name used for CAS RN 1319-77-3 is “mixed cresols”, and is defined here as “a substance composed primarily of one or more of the cresol isomers.” However, there is variability in grade, scope, composition, source (synthetic or natural) and nomenclature of CAS RN 1319-77-3 between references considered and cited in this assessment.

Purity and Grade

Commercial cresols are manufactured in a wide range of grades and purities to suit the user's requirements (IPCS 1995; Fiege 2000). Technical-grade cresols are typically classified according to their *m*-cresol content, the most reactive isomer (Fiege 2000; ATSDR 2008), which is between 20% and 70%. North American technical-grade cresol contains approximately 20% *o*-cresol, 40% *m*-cresol, 30% *p*-cresol, and 10% phenol and xylenols (Deichmann and Keplinger 1981). An arbitrary standard for mixed cresols ("cresylic acid") is that over 50% boils above 204°C (Lewis 2001; SRI 2012). Other cresols-related mixtures include cresylics (compounds related to cresols) (CMR 2004) or tar acids, which are obtained from tar (Fiege 2000).

The individual isomer supplies are available at purity levels as low as 85% and as high as greater than 99% (IPCS 1995). Maximal amounts of impurities encountered in commercially available cresols are usually no more than 0.2% water, 0.15% pyridine bases, 0.1% neutral oils, and 0.01% sulphur. Synthetically produced cresols are practically free of pyridine bases and sulphur (Fiege 2000). The British Standards specify grade levels for *o*-cresol, *m*-cresol, *p*-cresol, cresylic acid of specified isomer content, and for so-called refined cresylic acid, based on their crystallizing point temperatures (Fiege 2000).

Additional Supporting Substances

Two CAS RNs are associated with the combination of *m*- and *p*-cresol (i.e., *m*-/*p*-cresol), occasionally referred to in the technical literature as dicresol (Fiege 2000). CAS RN 15831-10-4 specifies the proportions of each isomer and is identified as Phenol, 3-methyl-, compd. with 4-methylphenol (2:1) (STN 2013). CAS RN 84989-04-8 specifies the mixture source and is defined as "Tar acids, cresol fraction" with a specific definition: "the fraction of tar acid rich in 3- and 4-methylphenol, recovered by distillation of low-temperature coal tar crude tar acids." (STN 2013). Information on CAS RNs 15831-10-4 and 84989-04-8 was considered where deemed appropriate to identify sources of individual cresol isomers, and for greater comparison (where applicable) to relevant human health toxicological information.

Two additional substances, phenol (CAS RN 108-95-2) and 2,4-dimethylphenol (CAS RN 105-67-9), were used as a source of analogue data in the evaluation of potential for adverse effects in terrestrial species, specifically earthworms. This was done to more closely examine possible toxicity in earthworms, in light of monitoring data that report the measured presence of cresols in these organisms. The use of these two analogues is discussed more fully in the Ecological Effects section of this assessment (see Table 9-3).

3. Physical and Chemical Properties

A summary of physical and chemical properties for the cresols is provided in Table 2 (details for the individual substances are available in the supporting document, Environment Canada 2015a).

Although physical and chemical properties vary between substances, cresols are generally highly miscible (i.e., soluble) in water, have moderate vapour pressure, and have low to moderate octanol-water partition coefficient (K_{ow}) and organic carbon-water partition coefficient (K_{oc}) values. Cresols are weak acids; however, pKa values of 10.07 to 10.32 (Table 2) indicate that the neutral (non-ionized) form of the substance will predominate within the environmentally relevant pH range of 6 to 9.

Table 2: Summary of physical and chemical properties for the cresols[a]

Property	Type	Value	Temperature (°C)	Reference
Physical form	Experimental	Liquid or solid	Room	OECD 2001, 2005; ATSDR 2008
Melting point (ºC)	Experimental	11.8–35.5	NA	OECD 2001, 2005
Melting point (ºC)	Modelled	15.7	NA	MPBPVPWIN 2010
Boiling point (ºC)	Experimental	191–202	NA	OECD 2001, 2005
Boiling point (ºC)	Modelled	191	NA	MPBPVPWIN 2010
Density (kg/m^3)	Experimental	1034–1047	20	OECD 2001, 2005; ATSDR 2008
Vapour pressure (Pa)	Experimental	14.7–39.9	25	Daubert and Danner 1985, 1989; OECD 2001, 2005

Property	Type	Value	Temperature (°C)	Reference
Vapour pressure (Pa)	Modelled	16.6–33.4	25	MPBPVPWIN 2010
Henry's Law constant ($Pa \cdot m^3/mol$)	Experimental	0.09–0.12	25	Gaffney et al. 1987; Altschuh et al. 1999
Henry's Law constant ($Pa \cdot m^3/mol$)	Modelled	0.06–0.40	25	HENRYWIN 2011
Log K_{ow} (dimensionless)	Experimental	1.94–2.17	NS	OECD 2001, 2005
Log K_{ow} (dimensionless)	Modelled	2.06	25	KOWWIN 2010
Log K_{oc} (dimensionless)	Experimental	1.34–1.69	NS	Boyd 1982
Log K_{oc} (dimensionless)	Modelled	2.17–2.49	25	KOCWIN 2010
Log K_{oa} (dimensionless)	Modelled	6.26–6.42	25	KOAWIN 2010
Water solubility (mg/L)	Experimental	21 500–26 000 (miscible)	25	OECD 2001, 2005
Water solubility (mg/L)	Modelled	8890–9246	25	WSKOWWIN 2010
pK_a (dimensionless)	Experimental	10.09–10.28	NS	Kortum et al. 1961

Property	Type	Value	Temperature (°C)	Reference
pK_a (dimensionless)	Modelled	10.07–10.32	25	ACD/pK_aDB 2005

Abbreviations: log K_{ow}, octanol-water partition coefficient; log K_{oc}, organic carbon-water partition coefficient; log K_{oa}, octanol-air partition coefficient; pK_a, acid dissociation constant; NA, not applicable; NS, not specified.
[a] Substances used in this summary include the following CAS RNs: 95-48-7, 108-39-4, 106-44-5 and 1319-77-3.

Depending on the temperature, cresols are either crystalline solid or liquid (IPCS 1995). Cresols have a phenolic odour and as pure substances are colourless, but become yellow to brown over time and are highly flammable (Fiege 2000; O'Neil et al. 2001). Their mixtures sometimes have a slightly stronger tinge, ranging from yellow to brown (Fiege 2000). Cresols are miscible in water, and therefore can absorb moisture from air (Fiege 2000). The solubility of cresols in phenol and in many organic solvents (e.g., aliphatic alcohols, ethers, chloroform and glycerol) is high (Fiege 2000). Cresols undergo electrophilic substitution reactions at the vacant *ortho* or *para* positions relative to the hydroxyl group. They also undergo condensation reactions with aldehydes, ketones or dienes (Fiege and Bayer 1987). Based on the volatility classification scheme described by Spicer et al. (2002), *o*-cresol is a volatile organic compound (VOC), while *m*-cresol and *p*-cresol are semi-volatile organic compounds (Spicer et al. 2002), although some references refer to cresols in general as VOCs.

4. Sources

Cresols are widespread in nature, and are natural components of crude oil and coal tar (OECD 2005; ATSDR 2008), and of brown mixtures such as creosote (ATSDR 2002), cresolene and cresylic acids (Sax and Lewis 1987). Cresols occur naturally in plants: they are present in the oils of various conifers, oaks, and sandalwood trees, and in the oils and essences of various plants and flowers (Furia and Bellanca 1975; Fiege and Bayer 1987; IPCS 1995). Cresols are constituents of wood tar, or wood creosote, which is derived primarily from beechwood (ATSDR 2002) and also from juniper tar oils and birch oils (OECD 2005). *p*-Cresol has been identified as a component of wood creosote at approximately 14% total peak area, while *o*-cresol has been identified at 3% total peak area (ATSDR 2002).

Mammals produce *p*-cresol endogenously from the metabolism of various aromatic compounds (IPCS 1995; ATSDR 2008). Humans excrete, on average, 50 mg (Bone et al. 1976; Renwick et al. 1988) to 87 mg (Geigy 1984) of *p*-cresol in urine per day, probably as conjugates (Vanholder et al. 2011). In addition,

cresols are produced as metabolic intermediates in the degradation of bound phenols by soil micro-organisms (IPCS 1995; ATSDR 2008).

Cresols occur naturally in a variety of foods, including fruits, meats, spices, eggs, essential oils and milk products (TNO 2013). Beverages such as coffee, teas, wine and spirits also naturally contain cresols (Fiege and Bayer 1987; Burdock 2010). Cresol levels in food are generally low (ATSDR 2008), with the exceptions of some foods, such as coffee and alcohol, as reported in the international literature (see Section 13.1.6).

As incomplete combustion products, cresols may be emitted into the air during the combustion of cigarettes (Nazaroff and Singer 2004). Under the Canadian *Tobacco Reporting Regulations*, tobacco companies are required to provide Health Canada with information on the yields of cresol emissions of certain tobacco products sold in Canada, as summarized in the Supporting Document, Appendix S1 (Health Canada 2015). Cresols have been measured in both the gas and particle phases of smoke released from vegetation (Schauer et al. 2001), and in residential wood smoke and stoves (Hawthorne et al. 1988, 1989).

Cresols can also be produced anthropogenically. Internationally, cresols are high-production-volume (HPV) chemicals with a variety of industrial uses. Cresols were listed as U.S. HPV chemicals, because a quantity of greater than 1 million pounds was produced in or imported into the United States in 1990. Cresols are also HPV chemicals in Europe, and were assessed under the Organisation for Economic Co-operation and Development (OECD) HPV Programme (OECD 2001; OECD 2005).

Production of commercial cresols can be obtained from natural or synthetic sources. Natural cresols are commercially isolated (ATSDR 2008; SRI 2012) from coal gasification, coking of coal tars, and spent petroleum refinery caustics in a ratio, internationally, of approximately 50:35:15 (Fiege 2000). Cresols have also been increasingly produced by synthesis (Fiege 2000; SRI 2012). In 2000, approximately 60% of cresol consumption in the United States, Europe and Japan comprised synthetic cresols and 40% comprised natural cresols (Fiege 2000). The synthetic processes currently in use are alkali fusion of toluenesulfonates, alkaline chlorotoluene hydrolysis, splitting of cymene hydroperoxide, and methylation of phenol in the vapour phase (Fiege 2000).

Approximately 55% of the global output of cresol is processed in the form of mixed isomers, and the remainder is processed as pure *o*-cresol and pure *p*-cresol (Fiege 2000). *m*-/*p*-Cresol is separated into pure *m*-cresol with co-production of butylated hydroxytoluene (BHT) (Fiege 2000). According to the Stanford Research Institute (SRI 2012), world production of cresols totalled 476 800 metric tons (kt) in 2010. Production was dominated by the United States (149 kt), followed by Western Europe (120 kt), China (66.6 kt) and Japan (54.3 kt). However, information regarding the production levels of individual and mixed

isomers was unavailable in the SRI report (SRI 2012), and the authors note that challenges can arise in identifying the cresol producer when several manufacturers are involved in isolating the crude product to final cresols isolates (SRI 2012).

In Canada, cresols are not intentionally commercially produced; they are produced incidentally as a by-product in various industrial processes throughout various sectors that constitute potential anthropogenic sources of cresols. In recent years, several surveys were carried out to determine the manufacture, import and use quantities of the cresols sub-group in Canada. These surveys included the Canadian DSL Inventory Update (DSL IU) for the three cresol isomers for the 2008 calendar year (Canada 2009a), a questionnaire for the 2011 calendar year as a follow-up to the DSL IU (Environment Canada, Health Canada 2012-2013), and a mandatory survey of mixed cresols for the 2011 calendar year (Canada 2012). All incidental manufacturing quantities and import quantities for cresols are summarized in Table 3.

Table 3: Survey quantities (kg) for the import and incidental manufacture of cresols in Canada

Activity	Source and reporting year	*o*-cresol (95-48-7)	*m*-cresol (108-39-4)	*p*-cresol (106-44-5)	Mixed cresols (1319-77-3)
Incidental manufacture	DSL IU[a] 2008	100 000–1 000 000	100–1000	100–1000	NA
Incidental manufacture	DSL IU follow-up[b] 2011	100 000–1 000 000[c]	NA	NA	NA
Incidental manufacture	S.71[d] 2011	NA	NA	NA	100 000–1 000 000
Import	DSL IU[a] 2008	10 000–100 000	1000–10 000	1000–10 000	NA
Import	DSL IU follow-up[b] 2011	1000–10 000	10 000–100 000	1000–10 000	NA
Import	S.71[d] 2011	NA	NA	NA	10 000–100 000

Abbreviations: NA, not applicable.

[a] Individual cresol isomers (i.e., CAS RNs 95-48-7, 108-39-4 and 106-44-5) were included in the 2009 Canadian Domestic Substances List Inventory Update (DSL IU) survey to identify activities related to the substances in Canada during the 2008 calendar year (Canada 2009a).

[b] In 2012, as a follow-up to the DSL IU survey, a questionnaire was carried out to obtain updated information on activities related to individual cresol isomers during the 2011 calendar year (Environment Canada, Health Canada, 2012-2013).

[c] Calculated based on production quantities (FisherSolve 2012; email from Forest Products and Fisheries Act Division to Environment Canada; unreferenced) and emission factors of O_2 delignification for *o*-cresol (NCASI 2012).
[d] In 2012, mixed cresols (CAS RN 1319-77-3) were included in a mandatory survey pursuant to section 71 of CEPA, to collect information on activities in Canada during the 2011 calendar year (Canada 2012). These companies reported the manufacture and import of mixed cresols in a quantity equal to or above the survey reporting threshold of 100 kg (0.1 tonnes).

Between 100 000 and 1 000 000 kg of mixed cresols were incidentally manufactured in 2011 from three major sectors: steel mills, petroleum refining, and oil and gas exploration (Environment Canada 2013a). Chemical pulp and paper mills across Canada indicated the incidental manufacture of *o*-cresol as being between 100 000 and 1 000 000 kg, with smaller amounts of *m*-cresol and *p*-cresol (100 to 1000 kg each) in 2008 (Environment Canada 2010), and the same range of releases estimated for the 2011 calendar year (NCASI 2012; FisherSolve 2012; email from Forest Products and Fisheries Act Division to Environment Canada; unreferenced), from the kraft pulping process.

Agricultural livestock facilities are a source of cresols because cresols are produced endogenously by animals. No survey data were received from agricultural facilities regarding estimated incidental production quantities. The Canadian livestock sector is dominated by beef production, with dairy a distant second (Speir 2003).

5. Uses

Canada is not a major consumer of cresols relative to other jurisdictions. World consumption of cresols in 2010 totalled 223.4 kt (SRI 2012). The major cresol consumers were Western Europe (73.6 kt), China (59.3 kt) and the United States (29.5 kt), followed by Japan (27.8 kt); together these countries account for 85% of global cresol consumption. The global consumption of cresols forecasted for 2016 is estimated to be 273.8 kt, representing an average annual growth rate of 3.4% from 2010 (SRI 2012).

Internationally, cresols are largely used (i.e., 90% of uses) as chemical intermediates in the production of e.g., antioxidants (in plastics), resins, plasticizers (aryl phosphates) (with applications in a wide range of consumer product for general population use), as well as in synthetic vitamin E, pesticides, dyes, deodorizing and odour-enhancing compounds, fragrances, pharmaceuticals, and other chemicals (e.g., photographic chemicals and explosives) (OECD 2001, 2005).

Cresols added to products account for much smaller proportions of total cresols (less than 1% of production), including bactericides, pesticides, disinfectants, preservatives or stabilizers in cleaning/washing agents and in pharmaceutical products, flavouring agents, fragrances, surface-treatment products, degreasers, paints, solvents, adhesives, binding agents and fillers (hardeners), corrosion

inhibitors, textile scouring, the mining industry (e.g., ore flotation), and impregnation materials (IPCS 1995; OECD 2001, 2005; ATSDR 2008). The International Fragrance Association's (IFRA's) list of fragrance ingredients used in consumer goods worldwide includes *o*-, *m*- and *p*-cresol, and mixed cresols ("Cresol [mixed isomers]") (IFRA 2013).

In general, uses of cresols in Canadian Material Safety Data Sheets (MSDSs) (CCOHS 2013) are aligned with international uses, but are not intended for general population use.

Major uses of individual cresol isomers in Canada based on the results of the DSL IU (Environment Canada 2010) or DSL IU follow-up questionnaire (Environment Canada, Health Canada, 2012-2013) were identified by industry. All three individual isomers find applications in fuel-related products, and engine part cleaners and disinfectants. *o*- and *m*-Cresol are used as laboratory reagents for research of medical devices; *o*-cresol is used in adhesives and sealant substances in electrical components and electronics in auto manufacturing as well as other components in the automotive sector. *p*-Cresol is present in a paint additive (Environment Canada 2010). Based on the information submitted in response to the section 71 Notice in the 2011 reporting year (Canada 2012), mixed cresols find applications in the manufacture of imported automotive components for assembly in finished vehicles; however, the specific function of mixed cresols is unknown (Environment Canada 2013a).

Cresols occur naturally in foods and are also added to food as flavouring agents. In Canada, the *Food and Drug Regulations* do not require the pre-market approval of food flavours (Canada 1986). In the United States, all three cresol isomers are found on the Everything Added to Food in the United States (EAFUS) List (U.S. FDA 2013). The U.S. Food and Drug Administration (FDA) permits the addition of *p*-cresol to foods as a flavouring agent (U.S. CFR 2013). In Europe, *o*-, *m*- and *p*-cresol are permitted for use as food flavouring agents (European Commission 2009). The Food Chemicals Codex published by the United States Pharmacopeia and referenced in the Canadian *Food and Drug Regulations* does not provide specifications for cresols (FCC 2010). However, in 2001, Codex Alimentarius (the international standard-setting body for food) adopted specifications for *o*-, *m*- and *p*-cresol when used as food flavouring agents (CODEX 2012), and the Joint Food and Agriculture Organization of the United Nations / World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) lists specifications for these flavouring agents. JECFA has determined that there is no safety concern when each of the cresol isomers is used as a flavouring agent (JECFA 2001b). Canada, as a participant in both the Codex Committee for Food Additives and JECFA, has had input into the development of this intake assessment and supports it formally (2013 email from the Food Directorate to the Existing Substances Risk Assessment Bureau [ESRAB], Health Canada, unreferenced).

In Canada, mixed cresols are also identified as components of food packaging materials in the internal can coating for all types of food, and have been identified as an incidental additive in lubricants with no food contact. Also, *o*-, *m*- and *p*-cresols are identified in food packaging materials in the internal and external can coatings that can be used for all types of food (2014 email from Food Directorate to Risk Management Bureau, Health Canada; unreferenced).

Mixed cresols are listed in the Natural Health Products Ingredients Database (NHPID) with a medicinal ingredient role in natural health products, as it falls under Schedule 1, item 2 (an isolate) of the *Natural Health Products Regulations* (Canada 2006; NHPID 2014). Mixed cresols and cresol isomers are listed in the NHPID with non-medicinal ingredient roles as flavour enhancers or antimicrobial preservatives (NHPID 2014). Mixed cresols are also listed in the NHPID as homeopathic substances, as "HPUS_Cresolum" (Homœopathic Pharmacopœia of the United States [HPUS]) with a minimum homeopathic potency of 6X, and "EHP_Cresol" (Encyclopedia of Homeopathic Pharmacopoeia [EHP]), with a minimum homeopathic potency of 12CH (NHPID 2011). The monograph of the HPUS describes cresolum as a mixture of the three isomeric cresols (*o*-, *m*- and *p*-cresol), in which the *m*-cresol predominates, and where cresol is obtained from coal tar (2011 email from Health Products and Food Branch [HPFB] to Risk Management Bureau [RMB], Health Canada, unreferenced). Mixed cresol and Cresolum are listed in the Licensed Natural Health Products Database (LNHPD) to be present as medicinal ingredients in currently licensed natural health products for topical and dental use, as well as for oral use as homeopathic medicines (LNHPD 2014).

Mixed cresols are listed in the Drug Product Database (DPD) as an active ingredient in veterinary drugs (DPD 2011). *m*-Cresol is listed in the Therapeutic Product Directorate's internal Non-Medicinal Ingredients Database as present in biologics as an antimicrobial preservative (2011 email from HPFB to RMB, Health Canada, unreferenced). *m*-Cresol is used internationally as a key preservation agent for anti-venoms against snake and scorpion bites or stings, at a concentration that ranges from 0.15 to 0.35% by most manufacturers (Abd-Elsalam et al. 2011).

Cresols are included on the List of Prohibited and Restricted Cosmetic Ingredients (more commonly referred to as Health Canada's Cosmetic Ingredient Hotlist or simply the Hotlist), an administrative tool that Health Canada uses to communicate to manufacturers and others that certain substances, when present in a cosmetic, may contravene the general prohibition found in section 16 of the *Food and Drugs Act* or a provision of the *Cosmetic Regulations* (Health Canada 2013). The Hotlist prohibits "mixed cresols (1319-77-3) and derivatives," where derivatives include all three individual isomers (2013 email from Consumer Product Safety Directorate [CPSD] to RMB, Health Canada; unreferenced). As indicated in the *International Cosmetic Ingredient Dictionary and Handbook*, mixed cresols (from synthetic sources) function as a preservative and fragrance

ingredient in cosmetics (Gottschalck and Bailey 2008), such as in carbolic soap (TSW 2013).

The use of cresols as active ingredients in pest control products was not identified in Canada. However, *p*-cresol is a formulant in pest control products in Canada (2012 email from Pest Management Regulatory Agency [PMRA] to ESRAB, Health Canada; unreferenced). More specifically, *p*-cresol is permitted for use as a fragrance in insecticides and surface cleaners at less than 0.1%. Also, cresol may be present as a micro-contaminant in an active ingredient used as a material preservative for non-food contact material (2013 email, PMRA to ESRAB, Health Canada; unreferenced). Cresols are present in creosote, which is permitted for use in Canada as a heavy-duty wood preservative in industrial settings (e.g., railroad ties) (ATSDR 2003; PMRA 2011).

6. Releases to the Environment

As described in the Section 6, cresols are natural components of many substances and may be found at low concentrations in crude oil, coal tar and brown mixtures. Cresols are naturally occurring in plants, plant oils and food, and are produced by metabolism in mammals. Cresols are products of incomplete combustion and may be produced and released from wildfires associated with lightning, spontaneous combustion and volcanic activity (ATSDR 2008). Cresols have also been found in surface water as a result of volcanic activity (McKnight et al. 1982), although it is unclear whether the cresols originated from wood fires or the eruption (ICPS 1995; ATSDR 2008). Many of these natural sources lead to environmental releases.

Intensive Livestock Operations (ILOs) in Canada represent a focused anthropogenic source of cresols due to concentrated farming practices. In an ILO, cresols may be released where amino acid degradation takes place, including in animals' digestive systems, urine, manure and wastewater (Akdeniz et al. 2013), with subsequent releases following animal grazing (ATSDR 2008) and manure land application (Feilberg et al. 2011). In recent decades, the size of fed-cattle and swine operations has dramatically increased, while the number of operations has diminished (Speir et al. 2003; Canadian Pork Council 2013). In Canada, the greatest concentration of animal units is in the "feedlot alley" of central and southern Alberta (predominantly beef) and along the southern tier of Ontario and Quebec (mostly dairy, beef and swine) (Speir 2003). A number of provincial, municipal and federal regulatory agencies oversee legislation designed to reduce environmental impacts from these operations, including requirements for on-site holding ponds to control surface runoff, as well as manure storage and nutrient removal plans (Caldwell and Toombs 2000; Speir et al. 2003).

Other industrial sites constitute potential anthropogenic sources of cresol releases. Cresols can be incidentally manufactured and released in processing

operations such as petroleum refining, coke-making operations, and kraft pulp digestion (NCASI 2012; Environment Canada 2013a). Some life-cycle stages in the production or uses of cresols are likely to be larger contributors to overall environmental concentrations. Other activities may release cresols but are assumed to have negligible emissions, due to factors such as well-controlled industrial processes or low concentrations of cresols in certain products (Environment Canada 2013a).

In Canada, kraft chemical pulp and paper mills are anthropogenic point sources of cresols released predominantly to air, and to a lesser extent to water (Environment Canada 2013b; NCASI 2012). In a 2001-2003 study conducted by the Québec Ministry of Sustainable Development, Environment and Parks, wastewater discharges from bleached and unbleached kraft mills were analyzed for the presence of cresols (NCASI 2012). Cresols were not detected in effluents collected from mills having secondary treatment, but were present at concentrations of 0.0005 to 0.063 mg/L in mills having primary or no on-site wastewater treatment. Since 1992, the *Pulp and Paper Effluent Regulations* have included enforceable effluent quality requirements for all mills in Canada based on standards achievable using secondary wastewater treatment (Canada 1992). Due to these regulations, pulp and paper mills in Canada provide on-site secondary treatment of effluent prior to discharge or they discharge to publicly-owned wastewater treatment systems.

Cresols were reported in the earlier literature as being produced during coal gasification (Giabbai et al. 1985; Neufeld et al. 1985), coal liquefaction (Fedorak and Hrudey 1986) and shale oil production (Dobson et al. 1985). These references are not recent and may not be representative of current practices and technologies for these sectors. No companies in these industrial sectors reported information on cresol-related activities in the data-gathering surveys.

Based on a 2012 report by Conestoga-Rovers & Associates on the potential presence and releases of substances to the environment from the waste sector, cresols may be present in landfill gas and leachate (CRA 2012).

Cresols are present at relatively low concentrations in vehicular exhaust (Hampton et al. 1982; Johnson et al. 1989), which constitutes a constant source of releases to the atmosphere. Cresols may volatilize from gasoline and diesel fuel used to power motor vehicles (ATSDR 2008). Cresols are also products of the photo-oxidation of toluene (Leone et al. 1985; OECD 2005). As products of incomplete combustion, cresols are emitted to ambient air from tobacco smoke (ATSDR 2008). Other residential combustion activities, such as wood burning in wood stoves and fireplaces, are sources of cresols (Hawthorne et al. 1988, 1989). Residential coal and oil heating may represent an additional source of cresols in home settings (ATSDR 2008). Tire trenches may also be a source of cresols, where cresols are released at low concentrations in the environment (Humphrey and Katz 2001). Cresol-containing consumer products represent

dispersive sources of cresols in residential settings and the environment (OECD 2005) (see Section 13.1.7).

Additional anthropogenic point-source releases of cresols reported in the international literature include rural and suburban septic tanks (ATSDR 2008), stack emissions from municipal waste incinerators (Junk and Ford 1980; James et al. 1984), emissions from the incineration of vegetable materials (Liberti et al. 1983) and fly ash from coal combustion (Junk and Ford 1980), coal- and petroleum-fuelled electricity-generating facilities, municipal solid waste incinerators, and industries with conventional furnace operations or large-scale incinerators (ATSDR 2008).

Anthropogenic releases of a substance to the environment depend upon various losses that occur during the manufacture, industrial use, consumer/commercial use and disposal of the substance. In order to estimate releases to the environment occurring at different stages of the life cycle of the cresols, information has been compiled on the relevant sectors and product lines, as well as emission factors to wastewater, land and air at different life-cycle stages in order to identify the stages that are likely to be the larger contributors to overall environmental concentrations. An emission factor is generally expressed as the fraction of a substance released to a given medium such as wastewater, land or air during a life-cycle stage such as manufacture, processing, industrial application or commercial/consumer use. Sources of emission factors include emission scenario documents developed under the auspices of the Organization for Economic Cooperation and Development (OECD), data reported to Environment Canada's National Pollutant Release Inventory (NPRI), industry-generated data, and monitoring data. Recycling activities and transfer to waste disposal sites (landfill, incineration) are also considered. However, releases to the environment from disposal are not quantitatively accounted for unless reliable information on the rate (or potential) for release from landfills and incinerators is available. In the NPRI reporting year of 2012, nine companies reported releasing cresols to air in a range of a few hundred kg to 10 000 kg, while one company reported releases of cresol to water in a quantity of 11 kg (Table 4; Environment Canada 2013b). The NPRI does not identify the individual isomeric cresol forms but, rather, requires reporting of all cresols (and their salts) under the mixed cresol CAS RN 1319-77-3. Emissions to air and releases to water declared to the NPRI in 2012 are similar to those reported in the previous years. According to NPRI information, kraft pulp mills report significantly higher releases of cresols compared to other industries.

Table 4: Year 2012 NPRI on-site release data (kg) for cresols (CAS RN 1319-77-3) (Environment Canada 2013b)

Sector	Air	Water	Land	Total
Pulp and Paper	19 800	1	0	19 801
Petroleum Refining	1404	0	0	1404

Sector	Air	Water	Land	Total
Chemical Manufacture	800	0	0	800
Totals	**22 004**	**1**	**0**	**22 005**

The information on environmental releases presented here is used to further develop exposure characterization scenarios in order to estimate resulting environmental concentrations. Monitoring data derived from field studies are also considered in determining exposure potential for organisms in the environment.

7. Measured Environmental Concentrations

North American monitoring data for the cresols are summarized in this section. These data were used to identify environmental media where there is a measured presence of cresols, the extent to which cresols are present in these media, and possible point sources of cresol releases into the environment. The data were also used as a basis for comparison with predicted environmental concentration (PEC) estimates.

Air

Few Canadian air monitoring data were found for cresols. Cresols are not included in Canada's National Air Pollution Surveillance (NAPS) network. The available Canadian monitoring data indicate that atmospheric levels of cresols are generally low. For example, cresols were not detected (detection limits ranged from 0.43 to 0.8 µg/m^3) in urban outdoor air samples collected in 2002 and 2003 near 75 homes in Ottawa, Ontario (Health Canada 2003; Zhu et al. 2005).

In the United States, the U.S. Environmental Protection Agency's (EPA's) National Urban Air Toxics Monitoring Program (UATMP) measured *o*-cresol in 28 of 422 samples (detection limit 0.05 µg/m^3) collected in 2001 from 12 urban locations across the U.S. (US EPA 2002). Concentrations of *o*-cresol in the samples ranged from 21 to 813 µg/m^3. *m*- and *p*-Cresols, analyzed together, were detected in 36 of the 422 samples (detection limit 0.04 µg/m^3) at concentrations of 17 to 1900 µg/m^3. The maximum concentration values were recorded at a monitoring station situated near a tar battery plant in a highly industrialized area of Missouri. The next highest concentrations, considered to be more representative of levels in a mixed residential and industrial setting, were 58 and 167 µg/m^3 for *o*- and *m*-/*p*-cresols, respectively. Therefore, higher levels can occur in the vicinity of industrial activity and/or highly urbanized areas, as these present multiple sources of cresols into the atmosphere (see Section 6).

Higher air concentrations have also been reported near large-scale agricultural operations due to natural endogenous production of cresols by animals. McGinn et al. (2003) reported concentrations of 0.003 to 0.029, 0.002 to 0.014 and 0.003

to 0.039 µg/m^3 for *o*-, *m*- and *p*-cresol, respectively, in air samples collected adjacent to three cattle feedlots in Alberta. Concentrations in air samples collected near fields where cattle manure had recently been spread ranged from below detection limits to 0.002 µg/m^3 for all three isomers (detection limits not specified).

Atmospheric degradation processes actively reduce the levels of cresols. Ward et al. (2005) reported a distinct seasonality in cresols measured at two monitoring locations in western Montana. The locations had similar seasonal averages of 0.001 to 0.019 and 0.0005 to 0.042 µg/m^3 for *o*- and *p*-cresol, respectively, despite one site being more urban than the second. The highest levels for both locations occurred in the winter months, with lowest levels in the summer and spring. The higher winter levels were attributed to reduced photochemical degradation resulting from shorter daylight hours and colder temperatures, as well as increased generation of cresols through the use of residential wood combustion for home heating. A spike in cresol levels also occurred during the summer fire season, a result that was considered linked to their presence in by-products of biomass combustion (Ward et al. 2005).

Cresols were reported at levels reaching 0.385 µg/m^3 for *o*-cresol (with an average of 0.047 µg/m^3) and 0.543 µg/m^3 for mixed *m*- and *p*-cresols (average 0.09 µg/m^3) in air samples collected in the summer of 1993 during a severe photochemical smog episode in Los Angeles, California (Fraser et al. 1996, 1998). Background levels at a nearby reference site were 0.0003 and 0.0008 µg/m^3 for *o*- and *m*-/*p*-cresols, respectively. The depletion of cresols in the affected area was determined to occur primarily through atmospheric chemical reactions rather than via downwind transport out of the area (Fraser et al. 1996, 1998).

Water

Some Canadian surface-water monitoring data are available for the cresols. Cresols (*o*- isomer and mixed *m*-/*p*-isomers) were not detected (detection limits 0.2 to 0.4 µg/L) in 30 surface water samples collected from various locations in southern Ontario (Backus et al. 2012). The sampling sites included locations that were close to urban and industrial sources, as well as those situated some distance from urban and industrial areas.

Pakdel et al. (1992) reported concentrations of 29.9 and 4057 µg/L *o*-cresol in 2 of 13 groundwater samples collected in 1988 from an area of known organic chemical contamination near Ville Mercier, Québec. *p*-Cresol was present in the same two samples at 150.7 and 9833 µg/L, with highest levels of both isomers present in a sample collected directly beneath oil waste at the centre of the contamination zone. *m*-Cresol was not analyzed in the study.

Kolpin et al. (2013) reported a *p*-cresol concentration of 10.05 µg/L in one of seven surface water samples collected in 2007 from sites situated close to smallmouth bass (*Micropterus dolomieu*) nesting areas in the Potomac River basin, USA. The study did not analyze for the presence of *o*- and *m*-cresol.

Recent U.S. water monitoring data are available from the U.S. EPA Storage and Retrieval (STORET) database (STORET 2012). *o*-Cresol was detected in 80 of 2112 surface water samples at concentrations of 0.07 to 20 µg/L (mean 2.9 µg/L), while *m*-cresol was measured at 5.8 to 390 µg/L (mean 116 µg/L) in 5 of 217 surface water samples. *p*-Cresol was present in 76 of 1510 surface water samples at concentrations of 0.2 to 737 µg/L (mean 30 µg/L). The samples were collected at various locations across the United States over the period 2000-2009. Detection limits ranged from 2 to 10 µg/L in the studies.

Leachates collected from 19 landfill sites sampled across the United States in 2011 contained a median concentration of 112 µg/L *p*-cresol and a maximum concentration of 7020 µg/L (Masoner et al. 2014). The substance was detected in 10 of the 19 samples (reporting limit 0.4 to 16 µg/L). Andrews et al. (2012) reported concentrations of 35 and 50 µg/L *p*-cresol in two of three landfill leachates collected in Oklahoma in 2009 (detection limit 0.18 µg/L).

Cresols have been detected in some groundwater samples collected from areas of historical industrial contamination in the United States (IPCS 1995). However, a national survey of 47 groundwater sites across 18 states conducted in 2000 did not show cresols to be major contaminants (Barnes et al. 2008). Site selection for the survey focused on areas suspected to be susceptible to contamination from either animal or human wastewaters, such as down-gradient of a landfill, non-sewered residential developments, or animal feedlots. *p*-Cresol was detected in 6 of the 47 samples, in all cases below the reporting level of 1 µg/L. *o*- and *m*-Cresols were not examined in the study.

Sediment

Some Canadian sediment monitoring data are available for the cresols. *o*-Cresol was not detected (detection limits 100 to 500 µg/kg dw) in 30 sediment samples collected from various locations in southern Ontario; however, mixed *m*- and *p*-cresols were measured in four of the samples at concentrations ranging from 400 to 2900 µg/kg dw (Backus et al. 2012). The highest concentrations, 2200 and 2900 µg/kg dw, were measured in samples collected in urban areas that are likely to have multiple potential sources.

Poerschmann et al. (2008) reported concentrations of 2900 to 5800 µg/kg dw *o*-cresol and 8800 to 16 000 µg/kg dw mixed *m*- and *p*-cresols in surface sediments collected near Randle Reef in Hamilton Harbour, Lake Ontario. The area has a long history of intense industrial activity and is known to be contaminated with a variety of pollutants.

p-Cresol was measured at a maximum concentration of 396 µg/kg dw in seven bed sediment samples collected in 2007 from sites situated close to smallmouth bass (*Micropterus dolomieu*) nesting areas in the Potomac River basin, USA (Kolpin et al. 2013).

Recent U.S. monitoring data available from the STORET database also indicate that cresol levels in sediment are generally low (STORET 2012). Much higher concentrations are reported at a small number of sites; however, few details are available on these sampling locations, and it is therefore not possible to identify potential contributing sources to the observed high levels. *o*-Cresol was measured at concentrations of 19 to 14 000 µg/kg dw in 5 of 2700 samples collected from 2000-2006 at various locations across the U.S., while *m*-cresol was present at 84.5 and 450 µg/kg dw in 2 of 194 samples collected over the same period (STORET 2012). *p*-Cresol was detected in 109 of 2623 samples collected from 2000-2008, with concentrations in the samples ranging from 0.3 to 82 700 µg/kg dw. Detection limits for sampling programs submitting data to the STORET database varied widely, with the lowest detection limits in the range of less than 0.3 to 50 µg/kg dw.

Wastewaters and Effluents

Cresols have been measured in some wastewaters, in particular those associated with publicly-owned wastewater treatment plants (WWTPs). Cresols detected in wastewaters may originate from a number of sources, including incidental production during some manufacturing activities and endogenous production by micro-organisms and mammals, including humans (see Section 6). *o*-Cresol was detected in 6 of 275 raw wastewater samples at concentrations of 15.3 to 216.5 µg/L, and was present at low concentrations (3.8 to 7.5 µg/L) in a small number of primary (2 of 39 samples) and final (1 of 227 samples) effluent samples collected from 37 publicly-owned WWTPs in southern Ontario in 1987 (OMOE 1988). The substance was not detected in samples of raw or treated sludge taken from the plants (detection limit 300 µg/L). *m*-Cresol was found in 167 of 275 raw wastewater samples at concentrations of up to 784 µg/L, and was also found in both primary (in 18 of 39 samples) and final (in 7 of 227 samples) WWTP effluents at concentrations ranging from 4.3 to 32.4 µg/L. High levels of *m*-cresol were measured in raw and treated sludge, with concentrations of 233 to 9.6×10^6 µg/kg dw in raw sludge (in 42 of 51 samples) and 7750 to 2.2×10^6 µg/kg dw in treated sludge (15 of 50 samples). Thirteen of the 15 treated sludge samples with detectable *m*-cresol concentrations had levels in the range of 10 000 to 500 000 µg/kg dw, while 34 of the 42 raw sludge samples had levels above 100 000 µg/kg dw. In all but two instances, concentrations in the treated sludge were much lower than those in raw sludge collected from the same plant. For two samples, higher levels were measured in the treated sludge compared with the corresponding raw sludge sample. This may represent an artifact of the sampling procedure or could indicate the active formation of cresols during

wastewater treatment. *p*-Cresol was not detected in any of the treatment plant products (OMOE 1988).

In the U.S., *p*-cresol was included in a nationwide reconnaissance study of organic wastewater contaminants conducted by the U.S. Geological Survey in 1999 and 2000 (Kolpin et al. 2002). The study collected samples from 139 streams across 30 states, but was biased toward streams susceptible to contamination from human, industrial and agricultural wastewater. *p*-Cresol was present in 21 of 85 samples at a maximum concentration of 0.54 µg/L and a median value of 0.05 µg/L (range and detection limits were not provided).

o-Cresol was present at 0.05 to 1.2 µg/L (mean 0.22 µg/L) in 22 of 102 effluent samples collected in 2010 from 52 Oregon publicly-owned WWTPs (Hope et al. 2012). *p*-Cresol was found in 19 samples, at concentrations of 0.10 to 2.6 µg/L (mean 1.0 µg/L). The study did not analyze for the presence of *m*-cresol.

Soil

Soil samples collected in 1988 from an area of known organic chemical contamination near Ville Mercier, Québec contained 0.1 to 8.8 µg/kg dw *o*-cresol and 2.4 to 77.1 µg/kg dw *p*-cresol (Pakdel et al. 1992). Neither isomer was detected (the detection limit was not specified) in soil collected from beneath waste oil in the centre of the contamination zone, although high concentrations of both isomers were measured in water samples collected at this site (see Water section above). The study did not analyze for the presence of *m*-cresol.

Few other North American soil data were found for cresols; however, some information is available from the STORET database: *o*-cresol was not detected in 409 soil samples collected from 2000-2006 at various locations across the U.S., while *p*-cresol was present at 0.19 to 0.23 µg/kg dw in 3 of 363 soil samples collected over the same time period (STORET 2012). Detection limits for the studies varied widely and were not specified for the study reporting the presence of *p*-cresol. Only one entry was found for *m*-cresol over this time period; *m*-cresol was not detected in one sample collected in 2006 (the detection limit was not specified).

Kinney et al. (2008) analyzed soils collected from three agricultural fields in the midwestern United States for the presence of *p*-cresol. The substance was not detected in samples collected from a field that was being fertilized with biosolids from a publicly-owned WWTP, while samples collected from agricultural land amended with swine manure contained a range from below the detection limit to 113 µg/kg dw. Concentrations of 113 to 2200 µg/kg soil dw were detected in samples taken from a field that had received no amendment with biosolids or manure for the previous seven years. A method detection limit (MDL) of 161 µg/kg soil dw was calculated for the study; therefore, the substance was present at levels below the MDL in several samples. Concentrations measured in

samples of the source biosolids and swine manure were 4970 and 30 000 µg/kg dw, respectively, suggesting that these materials may act as sources of *p*-cresol to terrestrial environments. The presence of *p*-cresol in the non-amended soil was unexpected and, while the source could not be confirmed, was attributed to the possible presence of natural sources such as indigenous terrestrial wildlife or soil fauna, or to contamination of the field from up-gradient septic systems (Kinney et al. 2008).

A subsequent study considered three additional agricultural locations, including one just recently amended with biosolids for the first time, a second with an extended history of biosolids amendment, and a third that was used for cattle grazing in addition to receiving routine biosolids amendment (Kinney et al. 2010). Soil concentrations of *p*-cresol were low in the three fields, ranging from not detected to less than 161 µg/kg soil dw (the study MDL), despite high concentrations of 4970 to 29 370 µg/kg dw present in the source biosolids (Kinney et al. 2010).

In both studies, earthworms from each of the test fields were also analyzed for the presence of *p*-cresol; these results are described in the following Biota section.

Fresh biosolids samples collected from five WWTPs within the Greater Vancouver Regional District (now Metro Vancouver) were analyzed for the presence of cresols and a number of other organic and inorganic contaminants (Bright and Healey 2003). *o*-Cresol was detected in two of 31 samples at a maximum concentration of 70 µg/kg dw, while *m*-cresol was present in three of the 31 samples at a maximum level of 460 µg/kg dw (detection limit 50 µg/kg dw). By contrast, *p*-cresol was measured in all of the 31 samples at concentrations ranging from 1300 to 940 000 µg/kg dw (average 140 000 µg/kg dw; median 41 000 µg/kg dw). The researchers reported high variability between levels of *p*-cresol measured at the different WWTP sites and during different time periods and hypothesized that the high incidence and levels of *p*-cresol may have resulted from factors such as *in-situ* production from industrial and natural pre-cursor substances (e.g., petroleum hydrocarbons, amino acid L-tyrosine), extensive use of *p*-cresol in a wide variety of industrial processes and household products, and/or longer half-lives in wastewater sludge and biosolids than those reported for field soils and laboratory microcosms. Environmental biodegradation half-lives for some non-ionic organic contaminants have been reported to be longer in wastewater sludge-amended soils than in other soil systems (Beck et al. 1995). Overall, however, Bright and Healey concluded that the mixing of biosolids with uncontaminated soils during land application would substantially reduce the concentrations of cresols in the amended soils.

Biota

Few data were found on concentrations of cresols in aquatic and terrestrial organisms.

Whole-body concentrations of *p*-cresol in earthworms collected from a field receiving biosolids amendment were 70 to 270 µg/kg dw, while those from a field fertilized with swine manure ranged from not detected to 1290 µg/kg dw (Kinney et al. 2008). The worms were wiped clean and allowed to depurate for 24 hours prior to analysis, in order to ensure that cresols measured in samples originated from tissue rather than ingested soil. Levels from below the detection limit to 125 µg/kg dw were measured in earthworms collected from a field where no amendment activity (biosolids or manure addition) had occurred for the previous seven years. The MDL for the study was calculated as 161 µg/kg dw; therefore, several samples had concentrations which were below the MDL. The presence of *p*-cresol in the worms was regarded as indicating that transfer from source materials (such as biosolids) to soil-dwelling organisms may occur in the environment. However, no clear correlation could be established between *p*-cresol levels measured in the worms and those in the surrounding soil. A subsequent study measured tissue concentrations of 270 to 1185 µg/kg dw *p*-cresol in earthworms collected from agricultural fields amended with biosolids containing 4970 to 29 370 µg/kg dw *p*-cresol (Kinney et al. 2010). Tissue concentrations were below the MDL of 161 µg/kg dw in worms taken from a field that had not received biosolids amendment.

Lebedev et al. (1998) analyzed eggs from 15 species of nesting birds in the Lake Baikal region (Selenga River estuary) of Russia. *o*-Cresol was present at levels above the detection limit (10 µg/kg dw) in 8 of the 15 bird species, with concentrations ranging from 12 to 208 µg/kg dw, while *p*-cresol was found in six species, at concentrations of 10 to 540 µg/kg dw. The study did not analyze for the presence of *m*-cresol. The measured presence of cresols in the eggs was attributed to nearby pollution sources, in particular the Trans-Siberian Railway and the Selenga River (which drains an area of heavy industrialization). Since cresols are readily degradable in the environment and rapidly metabolized in animals, the researchers hypothesized that the substances were being assimilated by birds from water and food (e.g., aquatic invertebrates) in the Lake Baikal area. However, because data for potential prey species and other environmental media were not available, it cannot be definitively established that the presence of cresols in the eggs resulted from trophic transfer from a prey organism to the adult bird and then to the egg.

8. Environmental Fate

Level III fugacity modelling (EQC 2011) simulates the distribution of a substance in a hypothetical, evaluative environment known as the “unit world.” The EQC model simulates the environmental distribution of a chemical at a regional scale (i.e., 100 000 km^2), and outputs the fraction of the total mass in each

compartment from an emission into the unit world and the resulting concentration in each compartment.

A summary of the mass-fraction distribution for the cresols based on individual steady-state emissions to air, water and soil is given in Table 5 (results for individual substances are available in the supporting document, Environment Canada 2015a). The Level III EQC model assumes non-equilibrium conditions between environmental compartments, but equilibrium within compartments. The results in Table 5 represent the net effect of chemical partitioning, inter-media transport, and loss by both advection (out of the modelled region) and degradation/transformation processes.

The results of Level III fugacity modelling suggest that the cresols can be expected to reside in air, water or soil, depending upon the compartment of release.

Table 5: Summary of Level III fugacity modelling results (EQC 2011) for cresols: percentage of substance partitioning into each environmental compartment

Released into:	Air	Water	Soil	Sediment
Air (100%)	33–52	13–15	34–53	0
Water (100%)	0	99.7	0	0.3
Soil (100%)	0	6–9	91–95	0

When released into air, cresols are predicted to distribute into air (33 to 52%), soil (34 to 53%) and water (13 to 15%; see Table 5). A higher proportion of the *o*-isomer is predicted to remain in air, as compared with the *m*- and *p*-isomers, due to the higher vapour pressure of this isomer (i.e., the empirical vapour pressure value of 39.9 Pa for *o*-cresol as compared with 14.7 Pa for *m*- and *p*-cresol at 25°C (Environment Canada 2015a).

When released into water, all three isomers are predicted to remain within the water compartment (greater than 99%), with only a small proportion (0.3%) distributing into sediment. The model predicts that essentially no distribution (less than 0.1%) into air or soil will occur following release into water (see Table 5). This distribution pattern results from the very high water solubility of these substances (i.e., empirical values of 21 500 to 26 000 mg/L at 25°C; see Table 2), which in combination with moderate vapour pressure (14.7 to 39.9 Pa at 25°C) leads to a low Henry's Law constant (0.09 to 0.12 $Pa \cdot m^3/mol$ at 25°C) and therefore a tendency to remain in the water column. However, cresols have been measured at high levels in some sediment samples while being below detection limits in the corresponding overlying surface water (see Section 9), and this suggests that factors other than the hydrophobic partitioning considered by the model may contribute to their presence in sediment. These factors may include the endogenous formation of cresols and/or known historical industrial

contamination, and formation of cresols through the degradation of precursor substances (see Section 6). In addition, non-hydrophobic partitioning may contribute to the distribution of cresols into sediment. Cresols will form relatively strong hydrogen bonds with some inorganic soil components (see below) and such bonding could also occur in sediment. As the EQC model assumes only hydrophobic interactions, the model may not fully account for the partitioning of cresols in sediment and soil.

When released into soil, all three cresol isomers are predicted to remain within this compartment (91 to 95%), with only limited distribution into the water compartment (6 to 9%) and no (less than 0.1%) predicted presence in air or sediment (Table 5). The high water solubility of cresols facilitates dissolution in soil moisture (e.g., pore water); therefore, cresols are expected to have high mobility in soil and may leach through soils into groundwater. However, cresols have also been shown to form relatively strong hydrogen bonds with active sites on inorganic soil surfaces such as clay, particularly in soils containing low amounts of organic carbon (Boyd 1982; Artiola-Fortuny and Fuller 1982; Southworth and Keller 1986). The degree to which these bonds are formed also influences the mobility of these substances through soil.

Despite their predicted distribution into air, particularly when released into this environmental compartment, the short atmospheric half-life of cresols (i.e., empirical half-lives of 0.25–0.40 d; see Section 11.1) suggests that they will have little potential for long-range atmospheric transport.

9. Persistence and Bioaccumulation Potential

9.1 Environmental Persistence

Both empirical and modelled data were considered in the analysis of potential for environmental persistence.

9.1.1 Empirical Data for Persistence

A summary of empirical degradation data for the cresols is presented in Table 6-1 (results for individual substances are available in the supporting document, Environment Canada 2015a).

Table 6-1: Summary of empirical degradation data for the cresols[a]

Medium	Fate process	Degradation value	Degradation endpoint/units	Reference
Air	Atmospheric oxidation	4.2–6.0	Reaction rate constant / $\times 10^{-11}$ $cm^3mol^{-1}s^-$	Atkinson 1989; OECD 2001, 2005

Medium	Fate process	Degradation value	Degradation endpoint/units	Reference
		0.25–0.40	[1]; Half-life / d	
Water	Biodegradation	95–96	Biodegradation at 5 d / %	Pitter 1976
Water	Biodegradation	96–100	Biodegradation at 7–10 d / %	Wellens 1990
Water	Biodegradation	69[b]	Biodegradation at 14 d / %	CHRIP c2010
Water	Biodegradation	65–90	Biodegradation at 20–30 d / %	Buzzell et al. 1968; Bayer AG 1972, 2002
Water	Biodegradation	80–95	Biodegradation at 40 d / %	Desai et al. 1990
Water	Anaerobic biodegradation	0–100	Biodegradation / %	Wang et al. 1988
Water	Biodegradation	0.016–0.073[c]; 0.40–1.8	Rate constant / hr^{-1}; Half-life / d	Van Veld and Spain 1983
Sediment	Biodegradation	0.061–0.12[c]; 0.25–0.46	Rate constant / hr^{-1}; Half-life / d	Van Veld and Spain 1983
Detritus + sediment	Biodegradation	0.044–0.23[c]; 0.12–0.67	Rate constant / hr^{-1}; Half-life / d	Van Veld and Spain 1983
Sediment	Biodegradation	> 90	Biodegradation at 5 d / %	Mueller et al. 1991a, 1991b
Sediment	Biodegradation	> 98	Biodegradation at 56 d / %	Mueller et al. 1991a, 1991b
Soil	Biodegradation	0.5–11	Half-life / d	Namkoong et al. 1988; US EPA 1989
Soil	Biodegradation	< DL[d]	Biodegradation at 5 d	Mueller et al. 1991a
Wastewater sludge	Anaerobic biodegradation	0–100	Biodegradation / %	Boyd et al. 1983
Wastewa	Anaerobic	> 75[e]	Theoretical gas	Shelton and

Medium	Fate process	Degradation value	Degradation endpoint/units	Reference
ter sludge	biodegradation		production at 56 d / %	Tiedje 1984
Wastewater sludge	Anaerobic biodegradation	< 30 – ≥ 80	Theoretical gas production at 60 d / %	Battersby and Wilson 1989

Abbreviation: DL, detection limit.
[a] Degradation endpoint values are for the individual isomers unless otherwise noted.
[b] Degradation endpoint value is for the cresol mixture, CAS RN 1319-77-3.
[c] Degradation endpoint values are for *p*-cresol.
[d] Only *o*- and *m*-cresol were detected in samples; concentrations of both isomers were below the detection limit of 50 µg/L by day 5 of the study.
[e] Degradation endpoint values are for *m*- and *p*-cresol.

9.1.1.1 Biodegradation

Rapid biodegradation of the individual cresol isomers has been reported to occur in water, with at least 65 to 90% removal of the substances occurring within 30 days. Based on the available data, all three isomers meet criteria for ready biodegradation as specified in OECD Test Guideline 301 (OECD 1992); that is, the pass level of 60% biodegradation is reached within the required 10-day window and 28-day exposure duration.

Desai et al. (1990) measured first-order biodegradation rate constants (ln k) of -6.09, -5.77 and -5.86 hr^{-1} for *o*-, *m*- and *p*-cresol in water, resulting in calculated half-life values of 12.7, 9.3 and 10.2 days, respectively. All three isomers degraded rapidly, with 80 to 95% removal occurring over the 40-day exposure period.

Van Veld and Spain (1983) examined biodegradation of *p*-cresol in three types of aquatic test systems by analyzing removal rates in water, sediment and intact eco-cores collected from a river estuary. Eco-cores consisted of an aerobic layer of detritus overlying anaerobic sediment. Rate constants for the water samples ranged from 1.6×10^{-2} to 7.3×10^{-2} hr^{-1}, corresponding to estimated half-lives of 9.5 to 43 hours (0.40 to 1.8 days), while those for the sediment/water test system were 6.1×10^{-2} to 1.2×10^{-1} hr^{-1}, corresponding to estimated half-lives of 5.9 to 11 hours (0.25 to 0.46 days). Half-lives for *p*-cresol in the intact eco-cores ranged from 3.0 to 16 hours (0.12 to 0.67 days), based on degradation rate constants of 4.4×10^{-2} to 2.3×10^{-1} hr^{-1}. A distinct lag phase followed by a period of rapid degradation was observed in some test systems (e.g., some water flasks), while in other systems the biphasic pattern was less distinct and the degradation rate appeared to steadily increase throughout the experiment.

Namkoong et al. (1988) analyzed removal rates for 17 phenolic compounds (including all three cresol isomers) in soil. The soil used in that study was collected from the top 15 cm of the surface of an uncultivated grassland site, and was characterized as a fine sandy loam containing 61.5%, 31.1% and 7.4% sand, silt and clay, respectively. The soil contained 3.25% organic carbon and had a pH of 7.8. Both *o*- and *m*-cresol displayed sudden, rapid removal from the soil, with calculated half-lives of 1.6 and 0.6 days, respectively. A half-life value was not calculated for *p*-cresol, because total removal of the substance occurred within one day.

Biodegradation half-lives of 1.6 to 5.1, 0.6 to 11.3 and 0.5 days were reported for *o*-, *m*- and *p*-cresol, respectively, in aerobic soils (US EPA 1989).

Mueller et al. (1991a) observed greater than 90% removal of *o*-, *m*- and *p*-cresol from field-collected creosote-contaminated sediments incubated for five days in slurry-phase bioremediation flasks, and removal of all isomers to levels below the detection limit of 50 µg/L by the end of the 30-day study period. Only *o*- and *m*-cresol were detected in soil samples collected from the same site. Both substances had degraded to levels less than the detection limit by day five of the study. In a similar study, greater than 98% removal of all three cresol isomers occurred in sediment samples after eight weeks of incubation using solid-phase bioremediation flasks and sediment samples collected from the same creosote-contaminated site (Mueller et al. 1991b).

In standard MITI (Ministry of International Trade and Industry, Japan) testing (OECD 1992), the Chemical Risk Information Platform (CHRIP) (c2010) reported 69.3% biodegradation of the cresol mixture, CAS RN 1319-77-3, with complete removal of *p*-cresol and around 55% removal of *m*-cresol occurring over the 14-day test period. The amount of *o*-cresol degradation was unknown due to the very low concentration of the substance in the mixture (about 0.1%), which made accurate measurement of its disappearance very difficult (CHRIP c2010). The results suggest that biodegradation of the cresol mixture may occur more slowly than that of the individual isomers on their own, although degradation was still sufficiently rapid for the mixture to be considered readily biodegradable (NITE c2004-2010).

Cresols will also undergo anaerobic biodegradation, but at slower rates than those observed in aerobic environments. Shelton and Tiedje (1984) measured a maximum theoretical gas production of more than 75% in test flasks containing *m*- and *p*-cresol incubated anaerobically with an inoculum of 10% digested wastewater sludge over an 8-week period. Based on this, both substances were considered to be fully degradable under anaerobic conditions.

o-Cresol displays greater resistance to anaerobic biodegradation than either *m*- or *p*-cresol. Boyd et al. (1983) reported complete removal of *p*-cresol from an anaerobic wastewater sludge after three weeks, while complete disappearance

of the *m*-isomer occurred after seven weeks. No significant degradation of *o*-cresol occurred during the 8-week incubation period.

p-Cresol was completely degraded (equal to or greater than 80% of theoretical gas production) and *m*-cresol partially degraded (theoretical gas production greater than 30% but less than 80%) under methanogenic conditions with an anaerobic digesting sludge and a maximum exposure period of 100 days (Battersby and Wilson 1989). A period of adaptation, or lag phase, preceded the onset of biodegradation with both isomers. Less than 30% of theoretical gas production was observed with *o*-cresol, and the substance was considered to not biodegrade under the study conditions.

In bench-scale batch testing with mesophilic anaerobic cultures incubated at 37°C, complete mineralization of *m*- and *p*-cresol occurred after 130 days (lag phase 101 days) and 30 days (lag phase 14 days), respectively (Levén and Schnürer 2005). Partial degradation of *o*-cresol occurred, although after 14 days neither the substance nor the degradation intermediate, 3-methylbenzoic acid (CAS RN 99-04-7), were degraded further over the course of the 20-week study.

In batch testing of phenol-enriched methanogenic cultures, *o*-cresol was not significantly degraded during a five-month incubation period, while complete disappearance of *p*-cresol occurred within 192 hours (eight days) following a lag period of approximately 70 hours (three days) (Wang et al. 1988). Degradation of *m*-cresol required a longer period than *p*-cresol, but complete disappearance of the substance was noted after incubation for 1400 hours (58 days).

Smolenski and Suflita (1987) evaluated anaerobic biodegradation of cresol isomers under methanogenic and sulphate-reducing conditions by examining the length of time to onset of metabolism (lag time) for each isomer in samples obtained from a contaminated shallow anaerobic alluvial sand aquifer. *p*-Cresol exhibited the shortest lag times, with biodegradation commencing in less than 10 days under sulphate-reducing conditions (SRC) and 46 days under methanogenic conditions (MC). *m*-Cresol was more stable, with lag times of 43 days (SRC) and 46 to 90 days (MC). *o*-Cresol was the most resistant isomer, with lag times for both SRC and MC exceeding the study duration of 100 and 90 days, respectively. Degradation rates and half-lives were not determined in the study. Based on the longer lag phases for *o*-cresol, the authors hypothesized that this isomer has the greatest potential to be transported the furthest distance from its point of introduction, while *p*-cresol would migrate the least distance.

Anaerobic biodegradation of *o*-cresol may require the presence of an additional substrate that can participate in co-metabolism reactions. A mixed culture of nitrate (NO_3)-reducing bacteria degraded *o*-cresol in the presence of toluene but did not degrade the substance in the absence of toluene or when the culture was grown on *p*-cresol and 2,4-dimethylphenol (Flyvbjerg et al. 1993). Degradation of *o*-cresol began after toluene had been degraded to below 0.5 to 1.0 mg/L, but

continued only for about 3 to 5 days after the depletion of toluene, indicating that the culture had a limited capacity for *o*-cresol degradation once toluene was depleted. The total amount of *o*-cresol degraded was proportional to the amount of toluene metabolized. Based on the study results, the researchers proposed that the mixed culture degraded *o*-cresol by a co-metabolic mechanism in which the enzymes necessary for degradation of *o*-cresol were induced by toluene and not by *o*-cresol.

The need for a suitable co-metabolite to facilitate anaerobic biodegradation of *o*-cresol is further supported by bench-scale research such as that of Charest et al. (1999) and Tawfiki Hajji et al. (1999), in which methanogenic bacteria consortia degraded the substance to levels approaching zero over a period of 25 to 35 days, provided that specific levels of proteose peptone (Charest et al. 1999) or whey (Tawfiki Hajji et al. 1999) were present as co-substrates in the mixture.

Godsy et al. (1983) reported lower concentrations of *o*- and *m*-cresol in groundwater samples collected down-gradient of a coal tar-contaminated aquifer, compared with samples collected directly beneath the contamination source; they attributed the decreased levels to a combination of hydrodynamic dispersion (dilution, dispersion) and methanogenic biodegradation. When adjusted for hydrodynamic influences, losses due to anaerobic biodegradation were 75% for *o*-cresol and 82% for *m*-cresol. Significantly, analyses conducted under laboratory conditions resulted in a similar biodegradation rate for the *m*-isomer but no biodegradation of *o*-cresol. Based on these results, the researchers proposed that anaerobic biodegradation of cresols, including the *o*-isomer, may proceed more readily in the natural environment than in a laboratory setting, possibly because laboratory digestor flasks cannot adequately present the large surface area to microbial growth ratio needed under the low nutrient conditions of anaerobic aquifer conditions (Godsy et al. 1983)

No information was found on the potential of the cresol mixture (CAS RN 1319-77-3) to undergo anaerobic biodegradation.

9.1.1.2 Abiotic Degradation

Cresols will also degrade through abiotic processes, in particular indirect and direct photolysis reactions. Atkinson (1989) reported rapid reaction of cresols with atmospheric hydroxyl (OH) radicals, with rate constants of 4.2×10^{-11}, 6.0×10^{-11} and 4.6×10^{-11} cm^3/molecule/s determined for *o*-, *m*- and *p*-cresol, respectively, at 300K (27°C). Based on a tropospheric OH radical concentration of 5×10^5 molecules/cm^3, this corresponds to estimated half-lives for the *o*-, *m*- and *p*-isomers of 9.6, 6.0 and 8.2 hours, respectively (OECD 2001, 2005). A study by Coeur-Tourneur et al. (2006) derived OH radical reaction rate constants of 4.32×10^{-11}, 5.88×10^{-11} and 4.96×10^{-11} cm^3/molecule/s for *o*-, *m*- and *p*-cresol, respectively; these values agree well with those obtained by Atkinson (1989).

Slower reaction with ozone and NO_3 radicals in the atmosphere has also been reported. Atkinson et al. (1980) examined photo-oxidation reactions of the cresols with gas-phase NO_3 radicals under laboratory-simulated photochemical smog conditions. Greater than 85% disappearance of all isomers occurred over the six-hour test period (estimated from graphical data), with carbon monoxide, peroxyacetyl nitrate and several hydroxynitrotoluenes formed as degradation products. The *m*-isomer displayed much greater reactivity than either the *o*- or *p*-isomers, and was almost completely removed from the test system after 4 hours, with almost complete removal of the other two isomers occurring after about six hours. Rate constants of 1.4×10^{-11}, 1.0×10^{-11} and 1.1×10^{-11} cm^3/molecule/s were subsequently determined for the gas-phase reaction of NO_3 radicals with *o*-, *m*- and *p*-cresol, respectively, at 296K (23°C) (Atkinson et al. 1992).

Cresols can absorb light at wavelengths expected to reach the lower troposphere (i.e., those with λ greater than 290 nm), and may therefore undergo direct photolytic degradation (HSDB 2010).

Based on their chemical structure, cresols are not expected to hydrolyze under environmental conditions (OECD 2001, 2005).

9.1.1.3 Modelling of Persistence

Although experimental degradation data are available for the cresols, quantitative structure-activity relationships (QSARs) were also considered in a weight-of-evidence approach, as described in Environment Canada (2007). The results are summarized in Table 6-2. Given the ecological importance of the water compartment and the fact that cresols can be expected to be released to this compartment, biodegradation in water was primarily examined. As indicated above, cresols do not contain functional groups that can be expected to undergo hydrolysis.

Table 6-2: Summary of modelled data for degradation of cresols

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Atmospheric oxidation	AOPWIN 2010[a]	$t_{1/2}$ = 0.12–0.26 day	≤ 2
Ozone reaction in air	AOPWIN 2010[a]	NA[b]	NA
Hydrolysis in water	HYDROWIN 2010[a]	NA[b]	NA

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
Primary biodegradation (aerobic)	BIOWIN 2010[a] Sub-model 4: Expert Survey (qualitative results)	3.66[c] "biodegrades rapidly"	≤ 182
Ultimate biodegradation (aerobic)	BIOWIN 2010[a] Sub-model 3: Expert Survey (qualitative results)	2.94[c] "biodegrades rapidly"	≤ 182
Ultimate biodegradation (aerobic)	BIOWIN 2010[a] Sub-model 5: MITI linear probability	0.53[d] "biodegrades rapidly"	≤ 182
Ultimate biodegradation (aerobic)	BIOWIN 2010[a] Sub-model 6: MITI non-linear probability	0.66[d] "biodegrades rapidly"	≤ 182
Ultimate biodegradation (aerobic)	TOPKAT 2004 Probability	0.808–0.978[d] "biodegrades rapidly"	≤ 182
Ultimate biodegradation (aerobic)	CATABOL c2004-2008 (biological oxygen demand)	% BOD = 73.2–99.7 "biodegrades rapidly"	≤ 182

Abbreviations: NA, not applicable.
[a] EPI Suite 2000-2011.
[b] Model does not provide an estimate for this type of structure.
[c] Output is a numerical score from 0 to 5.
[d] Output is a probability score.

AOPWIN (2010) estimates atmospheric half-lives of 0.12 to 0.26 days for the cresols, and notes that reaction with atmospheric NO_3 radicals may also be important for this group. Rapid primary and ultimate biodegradation are predicted by BIOWIN (2010), TOPKAT (2004) and CATABOL (c2004-2008). Overall, the modelling results show good agreement with empirical data, and support the conclusion that cresols will degrade rapidly in the environment.

9.1.1.4 Summary on Persistence

Empirical and modelled data indicate that cresols degrade rapidly in the environment, with atmospheric half-lives of less than 1 day and rates of aerobic

biodegradation in the range of 14 days or less. Aerobic biodegradation of the mixture, CAS RN 1319-77-3, proceeds more slowly than that of the individual isomers; however, standard biodegradation testing determined that degradation of the mixture was still sufficiently rapid to suggest that it would not remain for long periods of time in the environment.

While anaerobic biodegradation has been documented for all three isomers, *o*-cresol appears to degrade slowly under anaerobic conditions and may require the presence of a suitable co-metabolite to facilitate biodegradation. This suggests that there could be conditions or circumstances under which the substance remains stable in an anaerobic environment. However, Godsy et al. (1983) demonstrated that *o*-cresol may in fact biodegrade more rapidly in the natural anaerobic environment than under laboratory conditions. Possible explanations for this observed difference between laboratory and field degradation rates include the substantially larger surface area available for microbial degradation in an aquifer, compared with a laboratory digestor (an important factor in low-nutrient conditions), and enhanced cresols degradation through their inclusion in a sequential degradation pathway with other similar phenolic compounds (Godsy et al. 1983). In addition, the rapid biodegradation of all three cresol isomers under aerobic conditions suggests that it is unlikely they will remain sufficiently long in the environment to reach anaerobic zones (OECD 2005).

9.2 Potential for Bioaccumulation

Both empirical and modelled data were considered in the evaluation of the bioaccumulation potential of the cresols.

9.2.1 Empirically determined bioaccumulation

9.2.1.1 Bioconcentration Factor (BCF)

Empirical bioconcentration data for cresols in fish are summarized in Table 6-3. No empirical data were found that describe bioaccumulation in species other than fish. Robust study summaries (RSSs) were completed in order to determine the quality of the studies. Based on the derived BCF values of 2 to 20 L/kg, cresols are determined to have low bioaccumulation potential in aquatic organisms.

Table 6-3: Summary of empirical bioconcentration data for the cresols

CAS RN	Test organism	Kinetic and/or steady-state value (L/kg)[a]	Reference
95-48-7 (*o*-cresol)	Zebrafish *(Brachydanio*	10.7 (2.23 mg/L)[b]	Butte et al. 1987

CAS RN	Test organism	Kinetic and/or steady-state value (L/kg)[a]	Reference
	rerio)		
108-39-4 (*m*-cresol)	Golden Ide *(Leuciscus idus melanotus)*	20 (0.05 mg/L)	Freitag et al. 1985
106-44-5 (*p*-cresol)	Fishes (several species)	2.3 (8 mg/L)	Boling et al. 1982

[a] Values in parentheses represent the test concentrations at which the BCFs were derived.
[b] Reported as a log BCF value of 1.03.

Butte et al. (1987) conducted standard bioconcentration testing on Zebrafish using OECD TG 305E (OECD 1981) and a measured water concentration of 2.23 mg/L of *o*-cresol. A kinetic BCF of 10.7 (log BCF 1.03) was derived from the study.

Freitag et al. (1985) measured the bioconcentration of *m*-cresol in the Golden Ide by exposing the fish to a nominal concentration of 0.05 mg/L for a period of three days and comparing concentrations in the fish tissue with those in the surrounding water. A BCF of 20 was determined from the study.

Cooper and Stout (1982) reported that fish exposed to 8 mg/L *p*-cresol in artificial stream channels for up to 96 hours accumulated the substance rapidly and then quickly eliminated it. The highest concentrations were measured in the liver and intestine, with skin and gill levels similar to those of ambient concentrations. Accumulation in the liver was attributed to sequestration from the blood, while that in the intestine may have resulted from the fish eating soon after dosing ceased. Potential food sources such as small invertebrates were present in the stream channels during the experiment; however, the test fish stopped feeding during dosing and resumed feeding within hours after dosing stopped. An average BCF of 2.3 was calculated from the study (Boling et al. 1982).

9.2.1.2 Bioaccumulation Factor (BAF)

Bioaccumulation factors (BAFs) are measured under field conditions as the ratio of the whole-body burden of chemical taken up from all exposures to that of the ambient water concentrations. Measures of BAF are the preferred metric for assessing the bioaccumulation potential of substances because they incorporate chemical exposures from all routes including the diet, which predominates for substances with log K_{ow} greater than about 4.0 (Arnot and Gobas 2003). As the log K_{ow} for the cresols is approximately 2, accumulation through dietary uptake is not expected to be an important process for these substances, thus estimates of BAF should be very close to estimates of BCF.

No empirical BAF values were found for the cresols, and metabolism-corrected kinetic mass-balance modelling was used to estimate the BAF (see Table 6-4).

9.2.2 Modelling Bioaccumulation

To provide an additional line of evidence for bioaccumulation potential, BCF and BAF estimates were generated using the BCFBAF model in EPI Suite (2000-2011). Both a structure-based model and a three-trophic-level kinetic mass-balance model were used and, with the exception of sub-model 1 of the BCFBAF model, all estimates were corrected for metabolism, as this process represents a fundamental elimination pathway for many chemicals. This correction was performed by deriving metabolism rate constants (k_M) using available empirical BCF study information or a structure-based QSAR method as described in Arnot et al. (2008a, 2008b, 2009). The empirical method is preferred when allowed by data.

Since the metabolic competency of an organism can be related to body weight and temperature (e.g., Hu and Layton 2001; Nichols et al. 2007), the k_M was normalized to the conditions of a middle-trophic-level fish representative of Canadian waters (fish weight = 184 g, lipid content = 6.8%, temperature = 10˚C), in accordance with the procedures outlined in Arnot et al. (2008b). The middle-trophic-level fish was used to represent overall model output as suggested by the model developer, and is most representative of fish weight likely to be consumed by an avian or terrestrial piscivore.

The results of the BCF and BAF modelling of cresols are summarized in Table 6-4.

Table 6-4: Summary of modelled bioaccumulation data for the cresols

Test organism	Model and model basis	Endpoint	k_M (days^{-1})	Value wet weight (L/kg)	Reference
Fish	BCFBAF Sub-model 1 (linear regression)	BCF	Not determined	8.9–12.6	BCFBAF 2010
Fish	BCFBAF Sub-model 2 (mass balance)	BCF	2.3–3.6	5.9–10.2	BCFBAF 2010
Fish	BCF_{max} with	BCF	0.05	37.2–38.0	BBM with

Test organism	Model and model basis	Endpoint	k_M ($days^{-1}$)	Value wet weight (L/kg)	Reference
	mitigating factors				mitigating factors 2008
Fish	BCFBAF Sub-model 3 (Gobas-mass balance)	BAF	2.3–3.6	5.9–10.2	BCFBAF 2010

Abbreviations: k_M, metabolic rate constant; BCF, bioconcentration factor; BAF, bioaccumulation factor.

Modelled BCF and BAF estimates range from 5.9 to 38.0 L/kg, and are in good agreement with empirically derived values of 2.3, 10.7 and 20 L/kg (see Table 6-3). The results indicate that cresols will have low bioaccumulation potential in aquatic organisms.

9.2.3 Metabolism in Aquatic Organisms

Several studies describe the metabolism and clearance of cresols in aquatic species. *m*-Cresol was rapidly taken up and readily eliminated from Dolly Varden char, *Salvelinus malma*, given a single oral dose of radio-labelled compound (Thomas and Rice 1982). After 24 hours, 28.9% of the original dose was determined to have been excreted via the gill and a further 38.1% was excreted via the cloaca. The remaining 29.1% (recovery for the study was 96.1%) was present in the tissues, primarily the gut, gall bladder and muscle.

Layiwola et al. (1983) investigated biotransformation and excretion of *m*-cresol in 12 species of freshwater fish (Bitterling, *Rhodeus sericeus amarus*; Bream, *Abramis brama*; Crucian Carp, *Carassius carassius*; Goldfish, *Carassius auratus*; Gudgeon, *Gobio gobio*; Guppy, *Poecilia reticulata*; Common Minnow, *Phoxinus phoxinus*; European Perch, *Perca fluviatilis*; Common Roach, *Rutilus rutilus*; Common Rudd, *Scardinius erythropthalmus*; Three-spined Stickleback, *Gasterosteus aculeatus*; Tench, *Tinca tinca*). Both urinary and biliary excretion of the parent compound and metabolites occurred over the 48-hour exposure period, with metabolites accounting for 84 to 98% of the total recovered radioactivity in all fish species except the Guppy. Only 55% of the total radio-labelled carbon was recovered as metabolites in the Guppy, as measured through urinary excretion. An analysis of biliary excretion could not be performed for Guppies, because the fish's small size precluded sampling of the bile. Three main metabolites were measured in all species tested: the oxidation product of *m*-cresol, *m*-hydroxybenzoic acid, and the sulfate conjugate, cresyl sulfate, were

present in the urine and bile of all fish species tested; however, the glucuronic acid conjugate, cresyl glucuronide, was present only in bile samples.

Frogs (*Rana temporaria*, *Xenopus laevis*) exposed to a single oral dose of radio-labelled *o*-cresol excreted 90 to 95% of the original dose within 24 hours, with 30% being excreted as the unchanged compound and the remaining 60 to 65% excreted as metabolites (Görge et al. 1987). Sulfation was the primary metabolic pathway in both species, with oxidation to the *o*-hydroxybenzoic acid also taking place. The glucuronic acid conjugate was also present in *Rana* sp. but was not detected in *Xenopus* sp., where a higher amount of the cresyl sulfate was measured.

Rapid and efficient metabolism of cresols further reduces their potential for bioaccumulation in aquatic species.

9.2.4 Bioaccumulation in Terrestrial Organisms

Little information was found on the potential for cresols to bioaccumulate in terrestrial species. The high water solubility and low-to-moderate octanol-air partition coefficient (log K_{oa}) (Table 2) suggest that uptake into organisms through air, water or food is possible. Cresols have been detected in whole-body homogenates of earthworms, *Eisenia fetida*, and in the eggs of several bird species (see Section 9). However, the origin of these cresols is uncertain, and may be endogenous in nature or derived from anthropogenic sources.

Kinney et al. (2008, 2010) considered the measured presence of *p*-cresol in earthworms collected from biosolid- and manure-amended soils, as evidence of transfer from source materials into the worms. However, the substance was not detected in all earthworms taken from amended soils and was also found in worms collected from non-amended soils. Therefore, it is not possible to directly correlate levels measured in earthworm tissue with those in the surrounding soil.

Similarly, Lebedev et al. (1998) attributed the measured presence of *o*- and *p*-cresols in bird eggs collected from a heavily industrialized area of Lake Baikal, Russia, to assimilation by the parent bird of water and food contaminated with cresols from nearby pollution sources. However, no data were available on levels in potential prey species and in abiotic media such as water and sediment taken from the same region; therefore, the occurrence of bioaccumulation in the birds could not be established.

Mink exposed through the diet appear able to rapidly metabolize and excrete cresols (Hornshaw et al. 1986), and a lack of observed effects in birds receiving a single dose of up to 113 mg/kg body weight (bw) (Schafer et al. 1983) suggests that these animals may also possess some metabolic capacity with these substances. These studies are described more fully in Section 12.1. A more in-depth discussion of mammalian cresol metabolism can be found in Section 13.2.

9.2.5 Summary for Bioaccumulation

Empirical BCF values of 2 to 20 indicate that cresols have low bioconcentration potential in aquatic species. Based on log K_{ow} values of around 2, cresols are also not expected to bioaccumulate through dietary uptake. Low modelled BCF and BAF estimates provide further evidence of low bioaccumulation potential for these substances. Low BCF and BAF values also indicate that cresols are unlikely to biomagnify through foodwebs.

The lack of definitive empirical and modelled data to support the occurrence of significant bioaccumulation, together with the observed rapid degradation of cresols and evidence for their metabolism by aquatic and mammalian species, suggests that while uptake of cresols by earthworms may occur, high levels of biomagnification are unlikely in either terrestrial or aquatic biota.

10. Potential to Cause Ecological Harm

10.1 Ecological Effects Assessment

Both empirical and modelled toxicity data were considered for the cresols.

Based on an observed direct relationship between hydrophobicity and toxicity, a polar narcosis mode of action has been proposed for these substances (Schultz et al. 1990, 1996; Cronin et al. 2000; Shen et al. 2000).

10.1.1 Empirical Studies for the Aquatic Compartment

Results from empirical aquatic toxicity studies are summarized in Table 7-1 (results for individual substances are available in the supporting document, Environment Canada 2015b). Only studies that clearly describe the isomeric composition and purity of the test cresol are considered here.

Table 7-1: Summary of empirical aquatic toxicity data (mg/L) for the cresols

Test organism	**Type of test (duration)**	**Endpoint**	**95-48-7 (*m*-cresol)**	**108-39-4 (*o*-cresol)**	**106-44-5 (*p*-cresol)**
Fish	Acute (48, 96 hours)	LC_{50}	6.2–41 (12)	7.6–55.9 (8)	4.4–57.5 (12)
Fish	Chronic (32 days)	NOEC LOEC	n.d.	n.d.	1.35 (1) 2.57 (1)

Test organism	**Type of test (duration)**	**Endpoint**	**95-48-7 (*m*-cresol)**	**108-39-4 (*o*-cresol)**	**106-44-5 (*p*-cresol)**
Daphnia sp.	Acute (24, 48 hours)	EC_{50}	16.7–27.2 (5)	19.2–34.2 (5)	4.9–68.2 (6)
Daphnia sp.	Acute (24, 48 hours)	LC_{50}	9.2–>94.0 (8)	8.9–>99.5 (2)	22.7 (1)
Daphnia sp.	Chronic (21 days)	NOEC LOEC	n.d.	n.d.	1.0 (1) 3.16 (1)
Other invertebrates [a]	Acute (48 hours)	LC_{50}	10–165 (14)	n.d.	n.d.
Algae	Acute (48 hours)	NOEC	34–36 (2)	n.d.	n.d.
Algae	Acute (48 hours)	EC_{50}	n.d.	n.d.	7.8, 21 (1)
Algae	Chronic (96, 168, 192 hours)	NOEC	7–65 (3)	15 (1)	n.d.
Amphibians	Acute (48 hours)	LC_{50}	38–40 (2)	n.d.	n.d.

Abbreviations: EC_{50}, the concentration of a substance that is estimated to cause some effect on 50% of the test organisms; LC_{50}, the concentration of a substance that is estimated to be lethal to 50% of the test organisms; n.d., no data; NOEC, the no-observed-effect concentration, is the highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls; LOEC, the lowest-observed-effect concentration, is the lowest concentration in a toxicity test that caused a statistically significant effect in comparison to the controls.
Note: Numbers in brackets represent the total number of toxicity test endpoint values that are included in the specified range.
[a] Includes acute toxicity data for isopods, amphipods, annelids, flatworms, gastropods, insect larvae, hydra and protozoa.

Acute median toxicity endpoint values range from 4.4 to 57.5 mg/L in fish and 4.9 to greater than 99.5 mg/L in *Daphnia* sp. (see Table 7-1). Some data are also available for other invertebrate species such as non-daphnid crustaceans, insects, worms, gastropods and protozoans, as well as for larval amphibians. Effect values from these studies fall in the range of 10 to 165 mg/L for

invertebrates and 38 to 40 mg/L for larval frogs and salamanders. Mainly no-effects data were found for algal species, with no-observed-effect concentrations (NOECs) ranging from 7 to 65 mg/L. However, acute median effects concentrations (EC_{50}s) of 7.8 and 21 mg/L have also been reported.

In general, trout exhibit the highest acute sensitivity of those species tested, with a lowest median lethal effects concentration (LC_{50}) value of 4.4 mg/L reported for Brown Trout, *Salmo trutta*, exposed for 96 hours to *p*-cresol (Howland 1969). Respective values for the *o*- and *m*-isomers in the same species were 6.2 and 8.4 mg/L, while LC_{50}s for six non-trout species (Common Carp, *Cyprinus carpio*; Fathead Minnow, *Pimephales promelas*; Black Bullhead, *Ictalurus melas*; Channel Catfish, *I. punctatus*; Bluegill, *Lepomis macrochirus*; and Yellow Perch, *Perca flavescens*) were 7.1 to 57.5 mg/L (Howland 1969).

The lowest acute reported effect values for invertebrates are for the water flea *Daphnia magna*, with 24- and 48-hour EC_{50} values of 4.9 (Kühn et al. 1989b) and 7.7 mg/L (Kühn et al. 1989a) determined for *p*-cresol. By comparison, Bringmann and Kühn (1982) measured 24-hour EC_{50} values of 20 and 25 mg/L for *o*- and *m*-cresol, respectively, while lowest acute median lethality (LC_{50}) values of 9.2 (Canton and Adema 1978) and 8.9 mg/L (Bringmann and Kühn 1977) have been reported for these isomers.

Slooff (1983) conducted 48-hour acute lethality tests on 13 species of aquatic invertebrates using 15 test chemicals, including *o*-cresol. Additional short-term testing was performed using the same 15 chemicals and 22 different species of bacteria, algae, protozoans, invertebrates, fish and amphibians (Slooff and Baerselman 1980; Slooff et al. 1983). Lowest LC_{50} values reported for *o*-cresol were 10 mg/L for the stonefly *Nemoura cinerea*, and 21 mg/L for the amphipod *Gammarus pulex* (Slooff 1983). All tests were conducted in a water-only test system; however, test vessels for sediment species such as the amphipod were fitted with a stainless steel meshwork that acted as an artificial substrate, in order to reduce unnatural activity in the test organisms.

Chronic effects data for fish are available only for *p*-cresol. Barron and Adelman (1984) conducted embryo-larval testing on Fathead Minnows exposed to *p*-cresol for 32 days. Growth of the fish was significantly reduced at test concentrations of 2.57 mg/L and above (to the highest test concentration of 4.0 mg/L), with the highest no-observed-effect level (NOEL) occurring at approximately 1.35 mg/L (extrapolated from graphical data). Similarly, a 21-day lowest-observed-effect concentration (LOEC) of 3.16 mg/L (NOEC 1.0 mg/L) reported by Kühn et al. (1989b) for reduced reproduction in the water flea exposed to *p*-cresol represents the only reliable chronic effects data found for aquatic invertebrates.

Only one toxicity study was found that provided data specific to the cresol mixture CAS RN 1319-77-3. Geiger et al. (1990) determined a 96-hour LC_{50}

value of 12.5 mg/L for the Fathead Minnow. However, no information was provided on the composition of the mixture used in the testing.

Considered together, the data indicate that cresols have moderate to low toxicity to aquatic species. The individual isomers display toxicity of a similar magnitude, with the *p*-isomer exhibiting only slightly greater toxicity than the *o*- and *m*-isomers.

Exposure of aquatic ecosystems to cresols could also lead to adverse impacts through the depletion of dissolved oxygen (DO) by the actions of cresol-degrading micro-organisms. Cooper and Stout (1982; Stout and Cooper 1983) conducted controlled outdoor experiments that exposed fish and invertebrates in an experimental stream system to concentrations of 8 mg/L *p*-cresol over periods of 24 to 144 hours. Although the temperature and pH of the test system displayed a normal diurnal cyclic pattern, DO levels fluctuated markedly in a manner that was clearly associated with the addition of *p*-cresol to the system. Large increases in bacterial counts and algal biomass were also highly correlated with the lowest measured DO levels, leading the researchers to hypothesize that the mechanism of effect for the low DO was likely to be increased respiration of organisms (microbes, plants and animals) rather than the inhibition of photosynthesis. Large-scale mortality was seen with some fish and invertebrate species during periods of low DO, with mortality occurring at lower exposure thresholds than would be predicted based on laboratory toxicity tests. Other signs of stress were observed, including gasping for air at the water surface and inhibition of feeding activity. The researchers considered that the indirect effect of reduced DO levels contributed significantly to changes observed in the invertebrate community structure over time, and that this effect could impact the actions of aerobic degradation bacteria.

Some limited information is available on the potential for additional toxicity in mixtures containing more than one cresol isomer. Parkhurst et al. (1979) reported on the contribution of six major coal conversion effluent components, including the three cresol isomers, to toxicity in the water flea *Daphnia magna*. Based on a comparison of individual and combined component toxicities, a simple additivity in the toxicities of the various effluent components was established. However, the authors also noted that other compounds may have been present, and may have contributed to the overall toxicity of the effluent. The results suggested that there is potential for additional toxicity when more than one cresol isomer is present in a mixture.

10.1.2 Empirical Studies for the Terrestrial Compartment

Some limited terrestrial ecotoxicity data are available for the cresols. These are summarized in Table 7-2 (results for individual substances are available in the supporting document, Environment Canada 2015b). In addition, laboratory studies using rodents have been conducted in order to evaluate the potential for

impacts to human health; relevant data from these studies can be found in the Section 13.2.

Table 7-2: Summary of empirical terrestrial toxicity data (mg/kg dw) for the cresols

Test organism	**Type of test (duration)**	**Endpoint**	**95-48-7 (*o*-cresol)**	**108-39-4 (*m*-cresol)**	**106-44-5 (*p*-cresol)**
Lettuce, *Lactuca sativa*	Acute (7 days)	EC_{50}	67	69	n.d.
Lettuce, *Lactuca sativa*	Acute (14 days)	EC_{50}	> 100	96	n.d.
Chinese cabbage, *Brassica rapa*	Acute (5 days)	EC_{50}	54.9[a]	n.d.	n.d.
American Mink, *Mustela vison*	Chronic (28 days)	LC_{50}	> 320[b]	n.d.	n.d.
American Mink, *Mustela vison*	Chronic (6 months)	NOEC LOEC	105[b] > 105[b]	n.d.	n.d.
Ferret, *Mustela putorius furo*	Chronic (28 days)	LC_{50}	> 400[b]	n.d.	n.d.
Red-winged blackbird, *Agelaius phoeniceus*	Acute oral dose	LD_{50}	n.d.	> 113[b]	> 96[b]

Abbreviations: EC_{50}, the concentration of a substance that is estimated to cause some effect on 50% of the test organisms; LC_{50}, the concentration of a substance that is estimated to be lethal to 50% of the test organisms; LD_{50}, the dose of a substance that causes mortality in 50% of the

organisms tested; n.d., no data; NOEC, the no-observed-effect concentration, is the highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls; LOEC, the lowest-observed-effect concentration, is the lowest concentration in a toxicity test that caused a statistically significant effect in comparison to the controls.
Note: Units are in mg/kg dw of soil unless otherwise stated
[a] Units are in mg/L.
[b] Units are in mg/kg body weight.

The acute toxicity of *o*- and *m*-cresol to lettuce, *Lactuca sativa*, was examined in 7- and 14-day static exposure testing using OECD Guideline 208 (OECD 1984b; Hulzebos et al. 1993). Seven-day median effect concentrations (EC_{50}s) for significantly reduced seedling growth were 67 and 69 mg/kg dw of soil for *o*- and *m*-cresol, respectively, while 14-day EC_{50} values were greater than 100 and 96 mg/kg dw, respectively. All values were calculated based on nominal test concentrations. The observed increase in EC_{50} values between 7 and 14 days was attributed to disappearance of the test substances from the soil, leading to decreased exposure levels and enabling the plants to recover (Hulzebos et al. 1993).

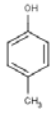
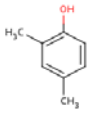
Feng et al. (1996) exposed seeds of the Chinese Cabbage, *Brassica rapa*, to aqueous solutions of *o*-cresol for a period of five days, and recorded root elongation of seeds in the test containers and controls. A five-day EC_{50} of 54.9 mg/L was calculated based on the concentration at which mean root length in the test containers was 50% of that in the control.

Hornshaw et al. (1986) evaluated the toxicity of *o*-cresol to American Mink and Ferrets using dietary LC_{50} and reproduction tests. No overt signs of toxicity and no mortalities were observed for either species over the 28-day LC_{50} study period, up to the highest test concentrations of 2520 parts per million (ppm), equal to 320 mg/kg bw/day (d) for mink, and 4536 ppm, equal to 400 mg/kg bw/d for Ferrets. Based on feed consumption, body weight data and hematologic parameters, mink were found to be more sensitive to *o*-cresol than Ferrets. For this reason, reproduction testing was conducted only with mink. Test animals in the mink reproduction study received dietary exposures to *o*-cresol over a six-month period from two months prior to mating to weaning of the offspring at six weeks post-partum. Males at the highest test concentration of 1600 ppm, equal to 105 mg/kg bw/d, had statistically lower body weight gains relative to the controls; however, the difference was not considered to be ecologically relevant. No other significant effects on body weight and feed consumption were seen among the test animals. No significant results were observed in reproductive indices, including gestation time, average birth weight, young survival and mean litter size. Based on the study results, the researchers concluded that because cresols are easily metabolized and excreted by mammals, both mink and Ferrets were able to excrete enough *o*-cresol ingested at any one feeding during the day to prevent a toxic dose from being reached.

Acute oral toxicity testing was conducted for *m*- and *p*-cresol using Red-winged Blackbirds, *Agelaius phoeniceus* (Schafer et al. 1983). Median lethal dose (LD_{50}) values of greater than 113 and greater than 96 mg/kg bw were determined for *m*- and *p*-cresol, respectively.

The measured presence of cresols in some terrestrial species, including earthworms and the eggs of some birds (see Section 9) provides evidence for potential uptake and exposure. Kinney et al. (2008, 2010) reported maximum concentrations of 1.290 and 1.185 mg/kg dry weight (dw) *p*-cresol in earthworms, *Eisenia fetida*, collected from manure- or biosolids-amended soils, respectively, while worms collected from non-amended soils contained a maximum concentration of 0.125 mg/kg dw. No toxicity data were found for cresols in earthworms. However, some limited data are available for two structurally and chemically similar substances; these data will be examined here as a means of estimating the potential for effects. Relevant physical and chemical properties for the two analogue substances, phenol and 2,4-dimethylphenol, are described in Table 7-3, along with those of the three cresol isomers.

Table 7-3: Comparison of physical and chemical properties of cresols, phenol and 2,4-dimethylphenol

Property **(CAS RN)**	***o*-cresol** **(95-48-7)**	***m*-cresol** **(108-39-4)**	***p*-cresol** **(106-44-5)**	**Analogue: phenol** **(108-95-2)**	**Analogue: 2,4-dimethyl-phenol (105-67-9)**
Chemical structure					
Chemical formula	C_7H_8O	C_7H_8O	C_7H_8O	C_6H_6O	$C_8H_{10}O$
Molecular mass (g/mol)	108.14	108.14	108.14	94.11	122.17
Water solubility (mg/L)	2.6×10^4	2.27×10^4	2.15×10^4	8.3×10^4	7.9×10^3
Log K_{ow}	1.95, 2.17	1.96	1.94	1.46	2.30
Log K_{oa}	6.26	6.42	6.33	6.33	6.71

Source: TOXNET 2012

Acute LC_{50} values of 270 (Environment Canada 1995) and 401 (Neuhauser et al. 1985) mg/kg soil dw have been reported for earthworms, *Eisenia fetida*, exposed to phenol in 14-day artificial soil testing (OECD 1984a). In a 56-day growth and reproduction study, no adverse effects were noted in *E. fetida* at a test concentration of 3900 mg/kg soil dw, while exposure to the next-highest concentration of 4900 mg/kg soil dw resulted in a 26% decrease in cocoon production (Neuhauser and Callahan 1990; Efroymson et al. 1997).

No comparable toxicity data were found for 2,4-dimethylphenol. However, Neuhauser et al. (1985) determined 2-day *E. fetida* LC_{50} values of 2.2 and 5.0 $\mu g/cm^2$ for 2,4-dimethylphenol and phenol, respectively, using the filter paper contact test described in OECD (1984a). This test method does not provide results that are readily comparable to a field setting, because it does not incorporate consideration of soil conditions. However, the lower LC_{50} obtained for 2,4-dimethylphenol suggests that the hazard potential of this substance to earthworms is similar to, and possibly greater than, that of phenol.

10.1.3 Modelled Results

Although empirical aquatic toxicity data are available for the cresols, modelled estimates based on QSARs were also considered in a weight-of-evidence approach to evaluating the potential for adverse effects in organisms (Environment Canada 2007). Modelled ecotoxicity values were considered reliable because they were within all model domains of applicability. Modelled values used in the analysis of aquatic hazard potential are summarized in Table 7-4. No reliable modelled estimates are available for terrestrial species.

Table 7-4: Summary of modelled aquatic toxicity data for the cresols

Test organism	Type of test (duration)	Endpoint	Toxicity value (mg/L)	Reference
Fish	Acute (96 hours)	LC_{50}	10.3–74.1[a]	ECOSAR 2009
Fish	Acute (96 hours)	LC_{50}	36.8–53.0	TOPKAT 2004
Fish	Acute (96 hours)	LC_{50}	24.8–25.3	OASIS Forecast 2005
Fish	Acute (96 hours)	LC_{50}	17.6	AIEPS 2003–2007

Test organism	Type of test (duration)	Endpoint	Toxicity value (mg/L)	Reference
Fish	Chronic (30 days or duration not specified)	ChV	1.1–7.0[a]	ECOSAR 2009
Daphnia	Acute (48 hours)	EC_{50}	14.8–20.2	TOPKAT 2004
Daphnia	Acute (48 hours)	LC_{50}	5.2–43.1[a]	ECOSAR 2009
Daphnia	Acute (48 hours)	LC_{50}	55.8–58.8	OASIS Forecast 2005
Daphnia	Acute (48 hours)	LC_{50}	7.5	AIEPS 2003–2007
Daphnia	Chronic (21 days)	ChV	1.0	ECOSAR 2009
Algae	Acute (72 hours)	EC_{50}	12.2	AIEPS 2003–2007
Algae	Acute (96 hours)	EC_{50}	19.0–23.9[a]	ECOSAR 2009
Algae	Chronic (21 days)	EC_{50}	11.9[b]	ECOSAR 2009
Algae	Chronic (not specified)	ChV	7.0–11.2[a]	ECOSAR 2009

Abbreviations: EC_{50}, the concentration of a substance that is estimated to cause some effect on 50% of the test organisms; LC_{50}, the concentration of a substance that is estimated to be lethal to 50% of the test organisms; NOEC, the no-observed-effect concentration, is the highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls; LOEC, the lowest-observed-effect concentration, is the lowest concentration in a toxicity test that caused a statistically significant effect in comparison to the controls; ChV, the chronic value, is the geometric mean of the NOEC and LOEC.

[a] Range includes values derived using ECOSAR (the software program Ecological Structure Activity Relationships) classes for phenols and neutral organics.

[b] Estimated 21-d EC_{50} for *Lemna gibba* testing in the phenolics SAR substance class; no corresponding value was available for the neutral organics substance class.

The software program Ecological Structure Activity Relationships (ECOSAR) (2009) provides aquatic toxicity estimates for cresols in the phenolics and neutral organics substance classes. When considered in the phenolics substance class, ECOSAR (2009) predicts acute toxicity endpoint values of 10.3 to 14.6, 5.2 and 23.9 mg/L for fish, *Daphnia* and algae, respectively, and chronic values of 1.1, 1.0 and 11.2 to 11.9 mg/L, respectively (Environment Canada 2014a). The corresponding acute values in the SAR for neutral organic substances are 74.1, 43.1 and 19.0 mg/L for fish, *Daphnia* and algae, respectively, with chronic values of 7.0 mg/L for fish and algae. No reliable estimate of the *Daphnia* chronic value was available in the neutral organics substance class. Other models (TOPKAT 2004, OASIS Forecast 2005 and AIEPS 2003–2007) predict acute toxicity values in the range of 17.6 to 53.0, 7.5 to 58.7 and 12.2 mg/L for fish, *Daphnia* and algae, respectively (Table 7-4). In general, modelled estimates tend to be slightly higher than the corresponding empirical values; however, there is good agreement between the empirical and modelled data in attributing moderate toxicity to the cresols in aquatic species.

10.1.4 Derivation of the Predicted No-Effect Concentration (PNEC)

10.1.4.1 Aquatic Compartment

The lowest toxicity endpoint value reported for a water column species is a 32-day LOEC of 2.57 mg/L, measured for reduced growth in Fathead Minnows exposed to *p*-cresol (Barron and Adelman 1984). The data presented in this study were reviewed and deemed to be of acceptable quality for use in the assessment. The value of 2.57 mg/L was therefore selected as the Critical Toxicity Value (CTV) for use in the evaluation of potential adverse effects in aquatic species. An Assessment Factor (AF) of 5 was applied to the CTV in order to account for some species sensitivity differences for baseline polar narcosis. The AF of 5 was selected based on the relative robustness of the empirical toxicity database for cresols and the presence of toxicity data for more than three trophic levels. The resulting PNEC is 0.51 mg/L.

10.1.4.2 Sediment Compartment

Slooff (1983) reported a 48-hour LC_{50} of 21 mg/L for the amphipod *Gammarus pulex*, which is selected as the CTV for sediment organisms. A lower LC_{50} of 10 mg/L was reported for the stonefly *Nemoura cinerea*; however, the amphipod associates more closely with the sediment bed throughout its life cycle and is therefore considered to better represent sediment-dwelling organisms. Although this testing was conducted as water-only testing, the results are considered to be meaningful for sediment organisms, because the high miscibility of cresols in water suggests that pore water will be a significant exposure route for sediment

species. An AF of 10 was applied to the CTV based on the relative robustness of the empirical toxicity database and to extrapolate from acute to chronic endpoints. The resulting PNEC is 2.1 mg/L.

10.1.4.3 Terrestrial Compartment

Hulzebos et al. (1993) reported a lowest EC_{50} of 67 mg/kg dw (nominal) for lettuce, *Lactuca sativa*, exposed for seven days to soil concentrations of *o*-cresol; this value is selected as the CTV for terrestrial plants. Given the paucity of terrestrial effects data, an AF of 100 is applied to the CTV in order to account for extrapolation from laboratory to field conditions and for inter- and intra-species variability in sensitivity. The resulting PNEC is 0.67 mg/kg dw. This PNEC is specific to terrestrial plants and does not apply to PNEC soil-dwelling species such as earthworms.

No effects data were found for cresols in soil-dwelling organisms; however, data are available for a chemically similar substance, phenol. A lowest LC_{50} of 270 mg/kg soil dw was reported for earthworms, *E. fetida*, exposed to phenol for 14 days (Environment Canada 1995); this value will be used to estimate a CTV for cresols in this species. Applying an AF of 100 to account for some inter- and intra-species variability and to extrapolate to chronic endpoints yields a PNEC value of 2.7 mg/kg dw for soil-dwelling organisms.

For terrestrial wildlife, a lowest effect level of 1600 ppm, equal to 105 mg/kg bw/d, was reported for male mink exposed for six months to *o*-cresol in the diet (Hornshaw et al. 1986). The observed endpoint of statistically lower body-weight gains relative to the control animals was not considered ecologically relevant. No other statistically significant results were observed in the study. Similarly, acute endpoint values could not be determined in oral toxicity testing with *m*- and *p*-cresol in blackbirds (Schafer et al. 1983). For this reason, a PNEC for wildlife cannot be determined for the cresols.

10.1.5 Summary of Ecological Effects

The available empirical and modelled data indicate that cresols are, at most, moderately toxic to aquatic organisms, with the *p*-isomer generally displaying slightly higher potency than the other two isomers, and fish exhibiting the greatest sensitivity. There is also some evidence for additivity in the toxicities of the individual isomers, suggesting that there may be additional toxicity in mixtures containing more than one cresol isomer.

In addition to direct toxic effects, there is also potential for indirect toxicity through the depletion of DO in receiving water bodies. This effect likely results from the ability of micro-organisms to rapidly biodegrade cresols under aerobic conditions, and suggests that adverse effects could occur under some environmental

conditions, such as during a large release of a cresol-containing mixture into water having a limited or infrequent oxygen exchange.

The terrestrial toxicity database is not large; however, the available information suggests that cresols are unlikely to have high hazard potential in terrestrial species.

10.2 Ecological Exposure Assessment

The ecological exposure assessment of the cresols examined potential exposure levels in air, soil, water and sediment. The assessment for the environment focused on industrial sources of cresols, such as those originating through incidental production during manufacturing and industrial processing activities. Factors relevant to key industrial life-cycle stages of the cresols have been considered, uncertainties have been recognized, and assumptions have been made during different life-cycle stages, subject to the availability of information. Exposure scenarios for media of potential concern have been developed, including the determination of applicable predicted environmental concentrations (PECs).

The chemical properties and reported uses of cresols indicate that anthropogenic releases into air or water could occur during both consumer and industrial applications. Cresols released into air are expected to degrade rapidly through reaction with photochemically-produced atmospheric hydroxyl radicals. Some deposition to soil or water could also occur. Cresols released into water are expected to primarily biodegrade, particularly under aerobic conditions. Release of cresols from consumer applications is expected to be diffuse and, for this reason, industrial sources are deemed to provide the highest potential for more concentrated releases into the environment.

As noted in Sections 6 and 8, intensive livestock operations (ILOs) may represent a source of cresols into the environment. Cresols originating from these operations may be released into air or introduced into soil through the land application of manure. Release into surface waters could also occur, for example through soil runoff during rainfall events. However, no information on levels of cresols produced and potentially released from ILOs in Canada directly to environmental media was submitted during the data-gathering surveys. The published literature indicates that cresols are primarily measured at ILOs in the context of air emissions (See Human Health Exposure Assessment – Intensive Livestock Operations (ILOs)), although some levels in manure have also been reported (e.g., Kinney et al. 2008, 2010). There is a paucity of data relating to the measured presence of cresols originating from ILOs in runoff to surface waters and in soil from the land application of ILO-derived manure. A number of provincial, municipal and federal regulatory agencies oversee legislation designed to reduce environmental impacts from these operations, including requirements for on-site holding ponds to control surface runoff, as well as

manure storage and nutrient removal plans (Caldwell and Toombs 2000; Speir et al. 2003). Based on these considerations, other industrial sources of cresols are deemed in this assessment to present the most significant exposure potential for cresols to the environment. These industrial sources were used in the ecological exposure assessment in order to provide the highest estimates of potential exposure concentrations to anthropogenic sources of cresols.

10.2.1 Identification of Exposure Scenarios

Exposure characterization is focused on scenarios expected to result in the highest levels of exposure in the environment. In general, the magnitude of releases is a direct function of the quantity of a substance manufactured or used and its applicable emission factors. In cases where industrial releases are similar in total quantity to consumer and/or commercial releases, the former normally results in higher levels of environmental exposure than the latter. This is because industrial releases are concentrated at a limited number of sites, while consumer and/or commercial releases are generally dispersed.

10.2.1.1 Air

According to NPRI data from 2012, three industrial sectors are responsible for air emissions of mixed cresols (see Table 4). These sectors are: Pulp, Paper and Paperboard Mills; Basic Chemical Manufacturing; and Petroleum Refining and Coal Product Manufacturing. Overall, the Pulp, Paper and Paperboard Mills sector reported significantly higher releases of cresols to air compared with other industries. Emissions from Pulp, Paper and Paperboard Mills industries will therefore be used to assess the risk of cresols resulting from industrial releases to air.

10.2.1.2 Soil

Cresols released into air could potentially reach soil through wet or dry deposition. Given the evidence for rapid degradation of cresols in both air and soil (refer to Section 11.1), soil concentrations of cresols originating from air deposition are expected to be low. The available Canadian and U.S. monitoring data provide support for this. Cresols are rarely present above detection limits in soil samples collected through routine monitoring, and were not detected in over 400 soil samples collected from various locations in the United States over the period 2000-2006 (STORET 2012). Where higher concentrations are measured, the source is associated with sites of historical contamination rather than air deposition. For example, cresols were measured in soil samples collected in 1988 from a site near Ville Mercier, Québec (Pakdel et al. 1992; refer to Section 9). However, the samples were taken from a known dumping area for organic wastes and therefore the source was most likely through soil application of waste products rather than deposition from air. For this reason, an exposure scenario

for the soil compartment resulting from release of cresols to air will not be developed.

There is, however, potential for cresols to enter soil through the land application of biosolids. Very high cresol levels have been measured in some biosolids, although a direct correlation has not been established between concentrations in the biosolids and those in biosolid-amended soil. For example, Kinney et al. (2008, 2010) measured cresol concentrations of 5 to 29 mg/kg dw in WWTP biosolids, but found only low concentrations of less than 0.2 mg/kg dw in soils amended with these biosolids. Furthermore, a concentration of 2.2 mg/kg dw was measured in soil collected from a site that had not received biosolids amendment. The source of these cresols could not be confirmed, but was attributed by the researchers to the possible presence of natural sources such as indigenous terrestrial wildlife or soil fauna, or contamination of the site from up-gradient septic systems (Kinney et al. 2008). However, given the potential for high exposure levels from biosolids application, a PEC was developed using known manufactured quantities and conservative assumptions, in order to quantitatively evaluate the potential for soil organisms to be exposed to cresols through this exposure route.

10.2.1.3 Water

In the kraft pulp process, cresols can be found in air from steam distillation, and in wastewater from steam condensation. A significant proportion of cresols formed during processing are recovered and incinerated in a recovery furnace at the kraft pulp facility (NCASI 2012). NPRI data from 2012 show very limited release of cresols to water, with only one company reporting releases to water at a maximum annual release quantity of 1 kg. Industry-specific information indicates that *o*-cresol (CAS RN 95-48-7) can be present in wastewater, but will be efficiently removed in on-site wastewater treatment and will not enter receiving water bodies (Environment Canada 2013a; NCASI 2012).

In a 2001-2003 study conducted by the Québec Ministry of Sustainable Development, Environment and Parks, wastewater discharges from bleached and unbleached kraft mills were analyzed for the presence of cresols (NCASI 2012). Cresols were detected only in effluents collected from mills having primary or no on-site treatment with concentrations ranging from 0.0005 to 0.063 mg/L. Since 1992, the *Pulp and Paper Effluent Regulations* have included enforceable effluent quality requirements for all mills in Canada based on standards achievable using secondary wastewater treatment (Canada 1992). Due to these regulations, pulp and paper mills in Canada provide on-site secondary treatment of effluent prior to discharge or they discharge to publicly-owned wastewater treatment systems. Given this information, releases of cresols to water from this industry sector are expected to be low. The highest measured effluent concentration (0.063 mg/L) was used to provide an estimate of the cresol concentration entering near-source receiving waters. It is recognized that this is a

conservative value, as it does not account for removal through additional downstream wastewater treatment.

10.2.1.4 Sediment

The available monitoring data indicate that cresols are generally not detected in sediment samples, but that, when they are detected, they may occasionally occur at relatively high concentrations (see Section 9). The sites where elevated concentrations of cresols were found are likely influenced by production of cresols from endogenous sources and/or associated with areas of known historical industrial contamination. In addition, corresponding aqueous concentrations of cresols at a number of these sites in the Canadian environment were below detection limits, despite high sediment concentrations and high water solubility of cresols, which places further weight on the likely contribution of endogenous production within the surface sediment. Therefore, a PEC for the sediment compartment was developed by applying Equilibrium Partitioning (EqP) methods, along with using the MDL from a comprehensive Canadian monitoring dataset.

10.2.1.5 Products

Cresols have been reported to occur as minor or trace components in some industrial products, and could be transferred from these products into consumer products. For example, cresols can be found at low concentrations of about 0.008 weight percent (wt. %) and 0.015 wt. % in fuel, and may also be present in some construction materials (Environment Canada 2013a). Given the very low concentration of cresols present in these products, they are not considered to contribute significantly to overall environmental exposure.

10.2.2 Estimates for Predicted Environmental Concentrations (PECs)

10.2.2.1 Air

PECs in air were estimated based on information received from industry stakeholders relating to quantities of cresols in Canada, as well as sector-specific industrial data. Release quantities reported to the NPRI were used as the basis to develop PECs, together with site-specific or published emission factors. These data are considered to be representative of industrial activities in a given sector and therefore can be used as a measure of potential releases to air.

Based on NPRI data for the 2012 calendar year, a single pulp and paper facility in Alberta reported a highest release quantity of 10 400 kg to air (Environment Canada 2013b); this quantity is used to estimate a PEC for cresols in air. Typically, cresols can be emitted to air via ventilation systems or captured and incinerated in recovery furnaces. For a conservative approach, the modelling assumed that all emissions were released directly to air via a venting system.

As a first-tier approach, the U.S. EPA model SCREEN3 was selected to estimate a generic 1-hour maximum air concentration surrounding an industrial facility (SCREEN3 1995). For exposure events occurring over the span of several years, i.e., chronically, it can be expected that the direction of the prevalent winds will vary and is less likely to mimic wind direction for a single 1-hour event. Multiplication factors can be applied to conservatively estimate 24-h and annual averaging periods, as discussed in the SCREEN3 Model User's Guide (US EPA 1995) and Screening Procedures for Estimating the Air Quality Impact of Stationary Sources (Revised) (US EPA 1992).

The selected scenario is designed to provide an estimate based on conservative assumptions regarding the amount of substance used and released by the facility, and the facility and environmental setting where the releases occur. Inputs used to calculate PECs in the vicinity of the facility are presented in . Releases were modelled as “point” releases to represent the focused release of cresols from a central vent at a chemical kraft pulp and paper facility. Assuming a release rate of 0.33 g/s, SCREEN3 estimates that a maximum 1-h concentration of 0.076 mg/m^3 is obtained at 100 m from the source, with decreasing concentrations of 0.058, 0.030 and 0.014 mg/m^3 predicted to occur at downstream distances of 200, 500 and 1000 m, respectively (Appendix A).

Comparison of the derived PECs with concentrations reported in air monitoring studies indicates that the estimated exposure values are within the range of measured air concentrations reported at various locations throughout the United States (see Section 9), although ambient levels are mostly lower than the estimated PECs (i.e., generally equal to or less than 0.001 mg/m^3). No Canadian air monitoring data were found; however, it is expected that cresol concentrations in Canadian air will be comparable to those in the United States.

10.2.2.2 Soil

The approach used to develop a soil PEC for the land application of wastewater biosolids was based on that described in the European Chemicals Agency (ECHA) (2010), and considers the quantity of biosolids that could accumulate within the top 20-cm layer (ploughing depth) of soil over 10 consecutive years. This method assumes no loss due to degradation, volatilization, leaching or soil runoff once the biosolids are applied to the soil. As cresols have been demonstrated to actively biodegrade, this assumption will lead to a conservative soil PEC.

A total manufactured quantity of cresols in the range of 100 000 to 1 000 000 kg was reported for the 2011 calendar year (Environment Canada 2013a); this was used as a starting point for calculating the potential concentration in WWTP biosolids. Factors were applied to this total quantity in order to estimate the daily quantity of cresols released to sewers from an industry, assuming all cresols manufactured were subsequently released into sewers (a very conservative

assumption), and in order to account for adsorption and degradation losses at the receiving WWTP. The daily quantity of biosolids produced was then calculated by assuming all treatment plant sludge was converted to biosolids. The resulting biosolids concentration was calculated as 0.65 mg/kg dw. This PEC represents the predicted environmental concentration of cresols resulting from industrial activities associated with the direct import and use of the substances themselves and does not account for other cresol sources, notably endogenous production and production through degradation of other organic substances (e.g. toluene; see Sources section).

The annual quantity of cresols entering soil through biosolids land application is a function of the concentration present in the biosolids and the biosolids application rate. In Canada, land application of biosolids is regulated by individual provinces and territories. Based on a highest allowable application rate of 8.3 tonnes/ha-yr (Alberta Environment 2001), and assuming an application period of 10 consecutive years over the top 20 cm of soil (ECHA 2010), the soil PEC amounts to 0.00023 mg/kg dw. As indicated, this PEC value is conservative. The value is also comparable with most monitoring data, which report concentrations in the range of below detection limits to about 0.08 mg/kg dw (n = greater than 400 samples; see Section 9). The derived PEC is much lower than the highest concentration of 2.2 mg/kg dw measured for *p*-cresol at a reference site that was not known to have received amendment with either biosolids or manure for a period of at least seven years. As noted above, the source of this higher than expected concentration could not be identified and may be attributable to factors such as a concentration of natural sources or contamination from an up-gradient septic system (Kinney et al. 2008). The results suggest that biosolids may not always be the major source of cresols to soil.

10.2.2.3 Water

A PEC for surface water was derived using the effluent concentration of 0.063 mg/L reported for cresols present in primary WWTP effluent from a Québec kraft pulp mill (NCASI 2012). A dilution factor of 10 was applied to this value in order to estimate the concentration present in receiving waters situated near a discharge point. The resulting surface water PEC is 0.0063 mg/L. It is recognized that the highest measured value is a conservative estimate of potential exposure, as it does not account for further treatment of effluent from this pulp mill that is known to take place at an off-site WWTP prior to discharge to the environment.

10.2.2.4 Sediment

An EqP was applied to the surface water PEC value of 0.0063 mg/L in order to derive an estimated PEC for the sediment compartment, based on cresols released to the aquatic environment from a primary WWTP discharging kraft pulp mill effluent.

Based on the principles of hydrophobic interactions,

$$PEC_{sediment} = PEC_{water} \times K_{oc} \times f_{oc\ sediment} \quad (1)$$

where:

$PEC_{sediment}$ = Predicted exposure concentration in sediment (mg/kg dw)

PEC_{water} = Predicted exposure concentration in water (mg/L) = 0.0063 mg/L

K_{oc} = organic carbon-water partition coefficient (L/kg) = 35.04 (average empirical value; Environment Canada 2014a)

$f_{oc\ sediment}$ = fraction of organic carbon in sediment (unitless)

The fraction of organic carbon (OC) present in sediment ($f_{oc\ sediment}$) is expected to vary substantially between locations; an average value of 3% OC was used to represent Canadian sediments.

The resulting $PEC_{sediment}$ value is 0.01 mg/kg dw of sediment. This estimated exposure value is lower than most monitoring data (including detection limits), which indicates that cresols are generally present at only low levels in sediment. However, as noted in Section 10, cresols have been detected at higher concentrations in a small number of sediment samples, although the incidence of these high concentrations is low. For example, mixed *m*-/*p*-cresols of up to 2.9 mg/kg dw were measured in four of 30 sediment samples collected in southern Ontario in 2011 (Backus et al. 2012). Three of the samples had concentrations of 2.2 to 2.9 mg/kg dw (representing two sites), while the concentration in the fourth sample was 0.4 mg/kg dw. In addition, Poerschmann et al. (2008) reported values as high as 5.8 mg/kg dw in a heavily industrialized harbour. Detection limits for the Backus et al. (2012) study ranged from 0.1 to 0.5 mg/kg dw, indicating that the concentration measured in the fourth sample was in the range of the analytical detection limits. *o*-Cresol was not detected in any of the 30 samples. The results indicate that cresols are generally present at low levels in sediment, although higher levels may be found at a small number of locations. The sites where elevated concentrations of cresols were found are likely influenced by production of cresols from endogenous sources and/or associated with areas of known historical industrial contamination. In addition, corresponding aqueous concentrations of cresols at these Canadian sites were below detection limits despite high sediment concentrations and high water solubility of cresols, which places further weight on the likely contribution of endogenous production within the surface sediment. Based on the preponderance of data indicating low sediment levels, the sediment PEC value of 0.5 mg/kg dw is considered to be a reasonable estimate of potential concentrations at most locations in Canada. This value was selected as the highest limit of detection from the most

comprehensive monitoring dataset available for cresols in Canadian sediment (Backus et al. 2012).

10.3 Characterization of Ecological Risk

The approach taken in this ecological screening assessment was to examine various supporting information and develop conclusions based on a weight-of-evidence approach and using precaution as required under CEPA. Lines of evidence considered in the assessment of the cresols relate to information on the persistence, bioaccumulation potential, toxicity and environmental presence of these substances.

Cresols degrade rapidly in the environment, with atmospheric half-lives of less than one day and aerobic biodegradation half-lives in the range of 14 days or less. Anaerobic biodegradation proceeds more slowly; however, there is evidence that cresols may biodegrade more rapidly in natural anaerobic environments than under laboratory conditions. Therefore, biodegradation half-lives derived from laboratory testing may underestimate the rate at which these substances are removed from low oxygen environments. Considering both aerobic and anaerobic degradation rates, but assigning greater weight to aerobic degradation due to the greater ecological relevance of the aerobic environment, cresols are considered to have low persistence. This low persistence is expected to reduce the frequency and duration of exposure to cresols for organisms in the environment.

Based on a maximum empirical BCF of 20, and modelled BCF and BAF values of 38 or less, cresols have low bioaccumulation potential in aquatic species. No bioaccumulation data were found for terrestrial organisms. Cresols have been measured in some earthworm and birds' egg samples; however, the origin of the cresols in these samples is unclear and cannot be definitively linked to either endogenous production or assimilation from nearby industrial pollution sources. The rapid degradation of cresols, along with evidence of metabolic capacity in fish, micro-organisms and mammals, suggests that accumulation and biomagnification of these substances are unlikely. Therefore, cresols are considered to have low bioaccumulation potential in both aquatic and terrestrial species. This low bioaccumulation potential is expected to reduce the overall body burden of cresols in organisms, thereby reducing the potential for adverse effects.

Cresols display moderate toxicity in aquatic species, with lowest empirical acute endpoint values in the range of 4 to 5 mg/L and lowest chronic effect values of 2 to 3 mg/L. Modelled estimates are slightly higher than the corresponding empirical values. The individual isomers are generally similar in toxicity, although the *p*-isomer is slightly more toxic to some species. There is some evidence for additional toxicity in aquatic organisms when more than one cresol is present in a mixture. However, the available data are not definitive in this regard. For

example, the endpoint value for the one fish toxicity study conducted on the cresol mixture (Geiger et al. 1990) is only slightly below the range of values obtained for studies conducted using the same fish species and individual isomers. As well, the study by Parkhurst et al. (1979), which reported on the toxicity of individual cresol isomers within a complex mixture, could not eliminate the possible contribution of unidentified substances in the mixture. Still, the potential for additional toxicity should be considered in instances where more than one cresol isomer is present in a mixture. However, it is also important to note that a number of species have demonstrated the capacity to rapidly and efficiently metabolize and excrete cresols, and this is expected to mitigate the potential for effects.

In addition to direct toxic effects, there is also a potential for adverse ecosystem effects resulting from the depletion of DO following large-scale release of cresols into waters with limited oxygen exchange. The oxygen depletion likely results from rapid aerobic biodegradation of cresols by micro-organisms in the aquatic ecosystem and may result in mass mortality of organisms in affected areas. Typical releases of cresols to the environment from industrial and commercial/consumer activities would not be expected to result in acute oxygen depletion.

Although only limited terrestrial ecotoxicity data are available, the information suggests that cresols are unlikely to have high hazard potential in terrestrial species. The lowest effect level for terrestrial plants is a seven-day EC_{50} of 67 mg/kg dw for significantly reduced seedling growth in lettuce, *Lactuca sativa*, while that for soil-dwelling invertebrates is a 14-day LC_{50} of 270 mg/kg dw for earthworms, *Eisenia fetida*. The latter endpoint value was derived using data from a suitable analogue substance, phenol.

Mammalian species exposed through the diet appear able to rapidly metabolize and excrete cresols, thereby reducing the potential for buildup of high internal body burdens. An observed lack of effects in blackbirds suggests that these organisms may also have the capacity to metabolize cresols. Considered in the context of reported tissue concentrations in earthworms and birds' eggs, this evidence for metabolic capacity suggests that cresols ingested in the diet of predators or foragers will be rapidly metabolized and removed from the animal before toxic body burdens can be reached. As well, the levels reported to occur in animals (a maximum of 0.5 mg/kg dw in birds' eggs and 1.3 mg/kg dw in earthworms) are well below those expected to elicit adverse effects in the animals, and may in fact result from natural metabolic production rather than from exposure to industrial sources.

Based on certain assumptions and reported use patterns, cresols are expected to be released primarily to air, with releases also occurring to surface waters and soil. A conservative PEC in air of 0.076 mg/m^3 was calculated for a distance of 100 m from the source of the highest reported (i.e., NPRI) industrial releaser of

cresols to air. This value is substantially lower than the lowest-observed-adverse-effect concentration (LOAEC) of 9 mg/m^3 reported for adverse morphological changes to respiratory tissue in mice exposed to *o*-cresol via inhalation for five days each week over a four-month period (Uzhdavini et al. 1972; see Section 13.2). These results indicate that potential air concentrations of cresols resulting from industrial-source releases are much lower than levels expected to elicit adverse effects in mammals.

A soil PEC of 0.00023 mg/kg dw was calculated for the concentration of cresols that could be present in soil from the land application of biosolids. This PEC value is very conservative because it assumes no loss through biodegradation, volatilization, leaching or soil runoff once the biosolids are applied to the soil. The PEC is also only representative of cresols present in biosolids through the industrial applications of the substances themselves and does not incorporate consideration of cresols produced through endogenous production or as degradation products from other organic substances. The PEC was compared with terrestrial PNECs in a risk quotient (RQ) analysis (RQ = PEC / PNEC) in order to quantitatively evaluate the potential for ecological harm from this exposure route. A PNEC of 0.67 mg/kg dw was determined for terrestrial plants, based on a seven-day EC_{50} of 67 mg/kg dw for reduced seedling growth in lettuce, *Lactuca sativa* (Hulzebos et al. 1993), while a PNEC for soil-dwelling organisms of 2.7 mg/kg dw was calculated using a 14-d LC_{50} of 270 mg/kg soil dw for earthworms, *Eisenia fetida*, exposed to a suitable analogue substance, phenol (Environment Canada 1995). The resulting RQs are 0.0003 and 0.00008 for terrestrial plants and soil-dwelling species, respectively, indicating that adverse effects are unlikely to occur in soil organisms exposed to cresols through the land application of biosolids.

For the pelagic compartment, a surface water PEC of 0.0063 mg/L was determined as the highest predicted concentration present in receiving waters. Comparing the PEC value with a PNEC of 0.51 mg/L, derived from the 32-day lowest effect value for Fathead Minnow (Barron and Adelman 1984), yields an RQ of 0.012. This RQ indicates that cresols released into surface waters from WWTPs are unlikely to harm aquatic organisms.

For the sediment compartment, a PEC of 0.5 mg/kg dw was selected based on the highest limit of detection from the most comprehensive monitoring dataset available for cresols in Canadian sediment (Backus et al. 2012). According to the principles of EqP, the corresponding predicted surface water concentration (i.e., the PEC) would be approximately 0.5 mg/L (using equation 1 from the Sediment section). For comparison, a PNEC of 2.1 mg/L for sediment organisms was calculated based on a 48-hour LC_{50} of 21 mg/L for the amphipod *Gammarus pulex*, exposed in water-only testing (Slooff 1983). However, all sites measured in the Backus et al. (2012) study had actual measured water concentrations below the MDL of 0.0004 mg/L (which was in agreement with other available surface water monitoring data). Thus, aqueous concentrations associated with a

sediment PEC of approximately 0.5 mg/kg dw were in fact much lower than the PNEC of 2.1 mg/L, indicating that adverse effects to sediment organisms are unlikely.

An important qualification regarding the derivation of PEC values used in the quantitative analyses is that, in all cases, PECs were calculated using quantity information regarding industrial sources, including the NPRI or monitoring data that included analysis for all cresol isomers (i.e., *o*- and *m/p*-cresol). Therefore, these predicted concentrations represent the potential contribution of industry-related sources to the total amount of cresols entering the environment. As well, these PECs consider only the industrial loading from cresols themselves and do not account for the potential presence of cresols resulting as biodegradation products of other organic compounds. As discussed in the Sections 8 and 11.1, cresols are formed as transformation products during the degradation of aromatic organic compounds such as toluene. Cresols are also present in organic substances produced during incomplete combustion, including coal tar and petroleum. Therefore, some proportion of the cresols measured in environmental samples may originate from other industrial activities in which cresols are formed as degradation products.

There is also extensive natural production of cresols (see Section 6) as confirmed by the very high concentrations measured in animal manure. Cresols may enter the environment from a number of additional sources, including WWTPs and large-scale agricultural operations, as well as from natural sources that are not associated with anthropogenic activity. The high levels of cresols measured in WWTP sludge and biosolids may in fact be due to endogenous production as *p*-cresol is the dominant isomer measured and this isomer is also the main isomer produced endogenously by mammals and micro-organisms and during the biodegradation of various organic compounds including naturally occurring substrates. Conversely, *o*-Cresol and, to a lesser extent, *m*-cresol are more commonly associated with direct industrial sources (see Table 3, Sources section). However, even if the highest concentration found in biosolids (~940 mg/kg dw) was extrapolated to estimate cresols concentrations in amended soils, the resultant concentration estimate for amended soils would still be below the PNECs derived in this assessment for the terrestrial compartment.Cresols are generally present at low levels or below detection limits in environmental samples, which given the number of potential natural and anthropogenic sources, indicates that degradation processes are largely effective at removing these substances. A number of factors may contribute to the occasional high concentrations of cresols observed in some samples, including high loading from multiple nearby anthropogenic and/or natural sources of cresols and their precursors, slower biodegradation of cresols due to limited oxygen exchange and anoxic/anaerobic conditions, or oxygen depletion from rapid microbial degradation leading to the inhibition of cresol biodegradation. It is possible that organisms residing in these areas of high concentration, such as sediment species in areas where high levels of cresols have been measured in monitoring

programs, may be adversely affected by the presence of the cresols. However, it is unclear why surface water samples collected concurrently at these locations did not contain detectable levels of cresols. The low persistence of cresols indicates that they are most likely to be near-source contaminants, and their removal from the environment may be closely linked to local conditions that affect oxygen availability, such as proximity to the soil surface in terrestrial settings or the degree of underwater mixing in aquatic systems.

In summary, high aerobic biodegradation rates and low bioaccumulation potential suggest that organisms will have low exposure to cresols. The available information indicates that the contribution of industrial-source cresols to environmental levels is low, which is further supported by RQ analyses which determined that PECs derived from these sources will be much less than the lowest no-effect levels measured in organisms. Although cresols demonstrate low to moderate toxicity, a number of aquatic and terrestrial species have demonstrated a capacity to effectively metabolize and excrete these substances, thereby reducing the potential for effects. Overall, monitoring data indicate that levels of cresols in the Canadian environment are generally low. Although cresols can be present at high concentrations in some environmental samples, and it is possible that organisms residing in the vicinity of these locations may be adversely impacted by the presence of the cresols, the low persistence and bioaccumulation potential, moderate to low toxicity, and predominantly low environmental presence reduce the overall level of concern for cresols in the Canadian environment. It is therefore concluded that *o*-, *m*-, and *p*-cresols and mixed cresols do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have immediate or long-term harmful effects on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

10.4 Uncertainties in Evaluation of Ecological Risk

Variability in the reported composition of the mixed isomer CAS 1319-77-3 incorporated some uncertainty into the analysis of potential for ecological risk; however, this uncertainty was considered to have a minimal impact on the overall determination of potential for ecological harm. Most ecotoxicity and monitoring data are specific to an individual isomer or, in the case of the monitoring data, mixed *m*- and *p*-isomers. However, PECs were calculated based on a consideration of all isomers together.

The potential for indirect adverse effects through rapid oxygen depletion is also an uncertainty. Mesocosm studies suggest that this impact could occur in near-field areas following large-scale release of cresols into water bodies having limited or infrequent oxygen exchange. Such an occurrence has not been documented outside of controlled study conditions, but remains theoretically

possible. The available information on sources and releases of cresols in Canada indicates that the potential for this effect is low.

Higher concentrations of cresols have been reported for a limited fraction of environmental samples collected in areas of southern Ontario. The extent to which endogenous sources of cresols contribute to the environmental presence of these substances could be clarified by increasing the size and scope of the environmental monitoring database.

Finally, the measured presence of cresols in earthworms and birds' eggs confirms that these substances are bioavailable, but does not establish their source or bioaccumulation potential in terrestrial species. A direct correlation between levels measured in organisms and those present in the surrounding media has not been determined. Furthermore, there is evidence for the natural production of cresols by animals, and it is possible that these processes influence levels detected in the tissues. Based on the observed rapid microbial biodegradation of cresols, as well as their metabolic breakdown in some vertebrates, it is considered unlikely that cresols will bioaccumulate in terrestrial organisms.

11. Potential to Cause Harm to Human Health

11.1 Exposure Assessment

Cresols are both naturally occurring and manufactured organic chemicals, and are produced endogenously by mammals and micro-organisms. Exposure potential to cresols has been reviewed previously (e.g., IPCS 1995; OECD 2001, 2005; ATSDR 2008).

Data pertaining to concentrations of cresols in ambient air, indoor air, air near-point sources, soil, drinking water, food, consumer products and humans were identified for Canada and elsewhere, and relevant studies are presented in this section.

Based on the available information, the general population of Canada is exposed to cresols mainly from the ingestion of food. Inhalation of air near industrial sites is an additional minor source of exposure. Upper-bounding estimates of total daily intake of cresols ranged from 0.48 µg/kg bw/d for breastfed infants (0–6 months to 22.8 µg/kg bw/d for non-formula-fed infants (0–6 months) (see Appendices B and C). Food was the primary source of exposure.

11.1.1 Ambient Air

In general, cresols do not persist in air (i.e., they have short half-lives) due to their reactivity with hydroxyl and nitrate radicals in the day and night, respectively. Scavenging by water may further reduce cresols' atmospheric residence time (see Section 11.1).

Canadian ambient air monitoring data for cresols are very limited (see Section 9). Several U.S. studies (e.g., Leuenberger et al. 1985; Fraser et al. 1996, 1998; Ward et al. 2005) have reported cresols in ambient air. In general, concentrations of cresols in these studies do not differ widely from those measured in Canada (Health Canada 2003; Zhu et al. 2005), with the exception of the 2001 monitoring of a highly industrialized site within the UATMP conducted by the U.S. EPA (US EPA 2002).

Based on the available data set for cresols in ambient air, a study of residences in Ottawa (Health Canada 2003; Zhu et al. 2005) was considered the most appropriate for characterizing general population exposure for Canadians via ambient air. The detection limits for *o*- and *m*-/*p*-cresol (0.43 and 0.80 µg/m^3, respectively, summed as 1.23 µg/m^3) were selected for deriving upper-bounding intake estimates of cresols in ambient air for the general population of Canada.

11.1.2 Point Source Emissions to Air

Point source releases of cresols in Canada include kraft pulp and paper mills, agricultural operations (ILOs) and potentially other operations, as described further below.

11.1.2.1 Pulp and Paper Mills

In Canada, kraft pulp and paper mills are a source of cresols to air (Environment Canada 2013b), as indicated in Section 8.

The SCREEN3 dispersion model was used to determine concentrations of *o*-cresol (the predominant isomer released) for residents living within the vicinity of a chemical kraft pulp and paper mill (see section 12.2.2.1). An upper-bounding emission rate of 10 400 kg/year for *o*-cresol from a kraft pulp and paper mill was used (Environment Canada 2013b). This scenario was identified as representing the upper-bounding scenario for point source releases to air. The release type selected in the model was the "point" releases, to represent the focused release of cresols from a central vent at a chemical kraft pulp and paper facility. The model output provided one-hour *o*-cresol dispersion concentrations at various distances from the mill, which were adjusted to one year by applying a multiplication factor of 0.1 (i.e., the upper bound of 0.08 ± 0.02 µg/m^3) (US EPA 1992, 1995), to represent long-term exposure of the general population to cresol in the air from pulp and paper mills. Relevant input parameters and outputs for SCREEN3 modelling scenarios are presented in Appendix A.

Map analysis shows that residential homes exist at a distance of 600 m from the release site (2013 email from Forestry Products and Fisheries Acts Division, Environment Canada, to ESRAB, Health Canada; unreferenced), corresponding to an estimated exposure concentration of 2.49 µg/m^3. This value is considered adequately conservative for deriving upper-bounding estimates of exposure for Canadians residing near pulp and paper mill facilities.

11.1.2.2 Intensive Livestock Operations (ILOs)

ILOs represent a focused source of industrial production of cresols, as described in Sections 6 and 8. Exposure from this source is expected to be variable, given the wide range of ILOs that exist in Canada. However, based on available information, exposure concentrations for nearby communities are expected to be within the same order of magnitude as concentrations estimated for the pulp and paper mill scenario.

While several studies have reported on *p*-cresol as an important odourant emitted from ILOs (Ni et al. 2012), only a limited number of studies have measured cresol concentrations downwind from ILOs for general population human-health considerations. One Canadian study (McGinn et al. 2003)

measured 14 volatile compounds, including all three cresol isomers, near three beef cattle feedlots in Lethbridge, Alberta. Feedlot capacities of 6000, 12 000, and 25 000 heads were monitored and compared. Samples were collected in 1999 from main towers located approximately at 3, 100 and 200 m from feedlot perimeters. However, the height of the sampling apparatus on the towers was not specified, which is an uncertainty in this study with respect to the breathing height zone for human exposure. The maximum gas concentration (average over a sampling period of 2 to 3 days) for *o*-, *m*- and *p*-cresol was 0.029, 0.014 and 0.039 µg/m^3, respectively. The *o*- and *p*-cresol maximum values were associated with the 12 000-head feedlot, and the authors note that this was likely due to the higher anaerobic conditions in the manure pad at that lot (McGinn et al. 2003). In other U.S. studies, Wright et al. (2005) detected *p*-cresol 2 km downwind from a commercial cattle feedyard, and Koziel et al. (2006) detected *p*-cresol 16 km downwind from a beef cattle feedlot in Texas; however, the authors did not report cresol concentrations. Buser et al. (2007) observed the highest *p*-cresol concentrations at the property line, i.e., 0.30 µg/m^3, although a sample obtained 13 km downwind of a feedyard following a rain event had a noticeable odour and an elevated *p*-cresol concentration (Buser et al. 2007). Monitoring studies (primarily from the U.S.) of cresols surrounding or downwind from ILOs are summarized in Appendix D.

11.1.2.3 Other Point Sources

Releases of mixed cresol from petroleum refineries and the coke-making process in steel mills have been reported to the NPRI (Environment Canada 2013b) and/or surveys (Environment Canada 2013a). In the international literature, older references report that cresols are produced during coal gasification (Giabbai et al. 1985; Neufeld et al. 1985), coal liquefaction (Fedorak and Hrudey 1986) and shale oil production (Dobson et al. 1985). However, it is likely that technologies have changed considerably since that time.

Landfill gas is expected to be an anthropogenic source of cresols in Canada (CRA 2012). All three isomers of cresol have been identified, but not quantified, in landfill gas from the United Kingdom (Dottridge et al. 2002). Also, as products of incomplete combustion, cresols are emitted to ambient air during the combustion of municipal waste (Jay and Stieglitz 1995), coal (Junk and Ford 1980) and wood (Hawthorne et al. 1988, 1989). Therefore, exposures near municipal solid waste incinerators, coal- and petroleum-fuelled electricity-generating facilities, and industries with conventional furnace operations or large-scale incinerators may be more elevated (ATSDR 2008). *p*-Cresol was identified in the air adjacent to municipal incinerators, waste collection centers, wastewater treatment plants around Southampton, England, in concentrations ranging from less than 0.1 to 24.5 µg/m^3 (Leach et al. 1999). These point sources, however, are not expected to generate greater exposures than the upper-bounding scenario identified.

11.1.3 Indoor air

Cresols were measured in indoor air samples in the study of Ottawa residences (Health Canada 2003; Zhu et al. 2005), and were detected at slightly higher frequencies than in outdoor air samples. However, cresols were still not widely occurring compounds measured in indoor air. Seventy-five homes were sampled, where 10 had at least one smoking participant and the remainder had no smoking participants. Both *o*-cresol and *m*-/*p*-cresol were detected in 6% of homes (detection limits of 0.43 and 0.8 µg/m^3, respectively). When detected, *o*-cresol and *m*-/*p*-cresol concentrations ranged from 0.44 to 4.50 µg/m^3 and 0.8 to 10.17 µg/m^3, respectively. The corresponding mean and 95th percentile for *o*-cresol were both 0.54 µg/m^3, while, for *m*-/*p*-cresol, the mean and 95th percentile were slightly higher at 1.01 and 1.23 µg/m^3, respectively (Health Canada 2003).

VOCs, including *m*-/*p*-cresol (cited as "*p,m*-Cresol"), were investigated in 15 single-family houses in southwest Michigan to determine their potential migration from attached garages (Batterman et al. 2007). Of the 47 VOCs targeted, 39 analytes were detected either indoors, in the garage, and/or in the ambient air over a four-day sampling period; however, *m*-/*p*-cresol was not among the analytes detected. No samples were above the reported MDL of 1.596 µg/m^3 for *m*-/*p*-cresol.

Coal, oil or wood as heating sources in residential settings are potential sources of cresols in indoor air (ATSDR 2008). Cresols have been measured in both the gas and particle phases of smoke released from burning pine, oak and eucalyptus (Schauer et al. 2001), and in residential wood smoke and stoves (Hawthorne et al. 1988, 1989). As incomplete combustion products, cresols may be emitted into the air during the combustion of cigarettes. According to the literature, individuals who smoke or who live with smokers are exposed to higher concentrations of cresol in the air, due to active and/or passive inhalation of tobacco smoke (Nazaroff and Singer 2004; ATSDR 2008). Monitoring data from the Ottawa Study involving 75 homes (Health Canada 2003; Zhu et al. 2005) were deemed an adequate representation of overall exposure from all sources of combustion. Homes in this study included those with wood stoves, fireplaces, and smoking participants, although no trend was observed between the detection of cresols and the presence or absence of these combustion activities recorded in the questionnaire (2013 email from Environmental and Radiation Health Sciences Directorate [ERHSD] to ESRAB, Health Canada; unreferenced). It is also likely that other combustion activities (such as cooking and candle burning) took place in the indoor environment and would be reflected in the monitoring data set.

As such, the study of Ottawa residences (Health Canada 2003) was considered to represent the most relevant and realistic study for characterizing general population exposure via indoor air. Specifically, the 95th percentiles of *o*-cresol and *m*-/*p*-cresol (0.53 and 1.22 µg/m^3, respectively, summed as 1.75 µg/m^3)

were selected for deriving upper-bounding intake estimates of cresols in indoor air for the general population of Canada.

11.1.4 Soil

Any anthropogenic or natural release of cresol to soil, with the exception of massive quantities from spills, is expected to be rapidly degraded (ATSDR 2008). Cresols monitoring in soil is described further in Section 9.

Canadian monitoring of cresols in soil was identified for a contaminated site, near Ville Mercier, Québec (Pakdel et al. 2002). A contaminated site, however, was not considered appropriate for estimating soil exposure for the general population. One study conducted in the United States monitored *p*-cresol in soil samples (n=6) from a non-amended field in 2005 (Kinney et al. 2008). Concentrations ranged from below the MDL to 2200 µg/kg soil dry weight (dw) (MDL of 161 µg/kg soil dw). This field had received no amendment with biosolids or manure for the previous seven years, and therefore, the presence of *p*-cresol in the non-amended soil was unexpected. Although the source could not be confirmed, *p*-cresol was attributed to the possible presence of natural sources such as indigenous terrestrial wildlife or soil fauna, or to contamination of the field from up-gradient septic systems (Kinney et al. 2008).

A soil PEC of 0.00023 mg/kg dw was estimated for land application of biosolids on an agricultural field using conservative approaches, as detailed further in Section 12.2.2.2. This value is consistent with the monitoring data within the U.S. EPA Storage and Retrieval (STORET) database, where cresols were not detected in 409 samples.

Agricultural soil represents a soil type that could realistically be ingested by the general population, particularly via food such as fresh produce. The value estimated for Canadian soil (0.00023 mg/kg dw) was deemed appropriate for deriving upper-bounding intake estimates of cresols in soil for the general population of Canada. No cresol monitoring in dust was identified for general population exposure; however, the soil concentrations were deemed adequately conservative for estimating cresol exposure from both soil and dust.

11.1.5 Drinking Water

Cresol levels in drinking water are generally low. This may be due in part to rapid degradation of cresols in surface waters and aerobic environments (ATSDR 2008).

Cresols were included in municipal drinking water surveillance programs for Toronto and Montreal, two highly urbanized cities. None of the cresol isomers were detected (detection limit of 3.0 ng/L) in Toronto tap water samples collected in November and December of 1988 (City of Toronto 1990). Subsequently, *Water*

Quality Quarterly Reports were issued between July 2000 and September 2003 by Toronto Water, and cresols were consistently below the detection limit of 0.0004 mg/L (City of Toronto 2003). The reports have now been replaced with the *Drinking Water Systems Annual Report* (City of Toronto 2012), which do not include cresols (Toronto Water 2012). In a report on Montreal drinking water, all three individual cresol isomers were below the limit of detection of 0.5 µg/L in 2000 (Bernier et al. 2000).

Cresols (cited as "(methyl phenols (cresols)") (no isomer-specific data) were not detected in tap water from: Calgary, Alberta in 1991 (ETL 1991); Windsor, Ontario in 1992 (ETL 1992); and Ville-Mercier, Québec in 1995 (ETL 1995), as part of a background study carried out in the 1990s by Health Canada (specified in the report as Health and Welfare Canada) (see the Food and Beverages section in Appendix E for details on this study).

In the United States, cresols have not been shown to be widely occurring in drinking water and surface water. In the summer of 2001, Focazio et al. (2008) sampled untreated sources of drinking water in the United States to provide new data and insights on the environmental presence of some pharmaceuticals and other organic waste chemicals, such as cresols, in these waters. The sampling sites included 25 ground- and 49 surface-water sources of drinking water, serving populations ranging from one family to over 8 million people. *p*-Cresol (cited as "para-cresol") was detected above the reporting level of 1 µg/L in 2.7% of the 73 samples; as such, "a maximum concentration was not determined" (Focazio et al. 2008). *p*-Cresol (cited as "4-methyl phenol") was detected in 24% of the total surface water samples (n = 85) collected from sites in the United States that were susceptible to contamination, i.e., downstream of intense urbanization and livestock production (Kolpin et al. 2002). The median for detectable concentrations of *p*-cresol in this study was low (0.05 µg/L)—near the detection level of 0.04 µg/L. The maximum concentration of *p*-cresol was also low at 0.54 µg/L (Kolpin et al. 2002).

Canadian monitoring of cresols in groundwater was identified for a contaminated site, near Ville Mercier, Québec (Pakdel et al. 2002) as described in Section 9. A contaminated site, however, was not considered appropriate for estimating drinking water exposure for the general population.

The detection limit of all three cresols for the City of Montreal drinking water monitoring (0.5 µg/L; Bernier et al. 2000) is used for estimating general population exposure via drinking water. This value represents a relevant and realistic concentration for deriving upper-bounding intake estimates of cresols in drinking water for the general population of Canada.

11.1.6 Food and Beverages

Cresols are naturally present in food and can also be added to food as flavouring agents. Cresols have been detected in a wide variety of foods and beverages, including fruits, vegetables, dairy products, flour products, various beverages and alcohol, generally at low levels.

The information on cresols measured in food purchased or grown in Canada provides some indication of exposure for the general population in Canada. Cresols (cited as “methyl phenols (cresols)”; no isomer-specific data) were among the compounds targeted in a series of studies carried out in the 1990s by Health Canada (specified in the report as Health and Welfare Canada) to establish the background concentrations of various parameters in foods purchased in Canada. Enviro-Test Laboratories (ETL) was contracted to collect and analyze approximately 35 food groups in grocery stores within the vicinity of three Canadian cities: Calgary, Alberta in 1991 (ETL 1991); Windsor, Ontario in 1992 (ETL 1992); and Ville-Mercier, Québec in 1995 (ETL 1995). For each community, a “grocery list” from four different retailers was purchased, and grouped for composite analysis for each food group. Based on the ETL surveys, cresols were detected at low levels in samples from Calgary and Windsor in a small number of food groups, including dairy products, meats, soups, flour products, pasta, soft drinks, coffee/tea and alcohol. Cresols were not detected in any of the Ville-Mercier samples. The levels of cresols detected in foods from Calgary and Windsor were comparable and were low (all less than 1.4 µg/g). All values are summarized in Appendix E.

Internationally, cresols have been detected in a wide range of foods, based on the compilation of international food monitoring studies by the Netherlands Organization for Applied Scientific Research (TNO). These foods include: eggs; various dairy products (various cheeses, various milks [e.g., goat’s, sheep’s, water buffalo’s, skim milk powder] and butter); fruit (bilberries, heated blackberries, black currant buds, chempedak, cherimoya, cherries, cranberries, plums, pineapple, rambutan juice, raspberries, rhubarb, elderberry juice, grapes, mango pulp, Chinese quince, dwarf quince, and tamarind pulp); vegetables (asparagus, barley, beans, cardamon, cassia leaf, kumazasa, lamb’s lettuce, mushrooms and truffles, roasted onions, pepper, soybeans and tomatoes); some cereal products (rye bread, buckwheat and rice); various meat and poultry products (grilled/roasted beef, chicken, boiled mutton, bacon, ham and uncured pork); several fish species (smoked cuttlefish, mackerel, tuna, sardines, herring, salmon, cod, swordfish, bream, trout, cod, katsuobushi and trassi); squid; nuts (Brazil nuts and filberts); and honeys, licorice and vanilla (Bourbon and Tahitian). Based on the same database, cresols have been detected in alcoholic beverages, including beer, various spirits (brandies, malts, rum, sherry, tequila and whiskeys) and wine (red, rose, white and botrytised); and in coffees, teas (black, green, fermented and rooibos), mate, and roasted cocoa beans (TNO 2013).

Cresol dietary intake estimates for the general population of Canada were determined based on Health Canada–sponsored monitoring studies (ETL 1991, 1992) and the 1970–72 Nutrition Canada Survey food ingestion rates (Health Canada 1998). No monitoring of breast milk or formula was identified or included. The details of the assessment are discussed below and presented in Appendix B.

Total daily intake of cresols from food ranged from 2.93 µg/kg bw/d for adults (≥ 60 years) to 22.3 µg/kg bw/d for non-formula-fed infants (0–6 months), representing a range of 90 to 98% of total daily intake from all sources in the ambient urban environment. The butter/cheese food item (200 µg/kg), representing the dairy products food commodity type, accounted for the highest intake for the non-formula-fed infants.

This dietary intake is an upper-bound estimate based on concentrations of cresols likely to be naturally found in foods. Cresols could be present in food as a result of its use as a flavouring agent, but cresols as flavouring agents contributes insignificantly to the overall estimate of cresols intake from food (2013 email from Food Directorate to ESRAB, Health Canada; unreferenced). The JECFA cresol-intake estimates as flavouring agents were estimated to be approximately 1000 to 15 000 times less than the JECFA cresol intake estimates of naturally occurring cresols. The JECFA assessment of cresols as a food flavourant estimated current levels of intake in the United States of *o*-cresol (Substance No. 691), *m*-cresol (Substance No. 692) and *p*-cresol (Substance No. 693) to be 0.001, 0.001 and 0.02 µg/kg bw/d, respectively (JECFA 2001a). *Fenaroli's Handbook of Flavor Ingredients* (*6th Edition*) (Burdock 2010) also estimated relatively low annual consumption of *o*-, *m*- and *p*-cresol as flavouring agents, specifically 0.00098, 0.00141 and 0.01412 µg/kg bw/d, respectively, which is consistent with the JECFA (2001a) estimates.

11.1.7 Consumer Products

Cresols are subject to the Canadian VOC-related regulations under CEPA, limiting VOCs in, for example, architectural coatings and certain products (Canada 2008, 2009b, 2009c). Furthermore, *o*-cresol (no information is available on other isomers) was not detected in 58 building materials from 50 homes in Québec City, Québec that were examined by the National Research Council Canada (NRC 2011). Additionally, there were no household products with cresols as an ingredient in the U.S. Household Products Database (HPD 2013).

Very few Canadian consumer products containing cresols for general population use were identified, based on several recent industry surveys (Canada 2009a, 2012; Environment Canada, Health Canada 2012-2013). Cresols were identified as substances used in the automobile manufacturing sector, including in adhesives and sealants in the electrical and electronic components of cars, and

in other unidentified auto parts; however, these uses are not expected to result in general population exposure.

With respect to cosmetics, cresols appear on Health Canada's List of Prohibited and Restricted Cosmetic Ingredients (see Section 7). One monitoring study reported the detectable presence of naturally occurring cresols in peppermint oils (*o*-cresol: 1 ppm; and *p*-cresol: 2 ppm [TNO 2013]). Peppermint oils may be used in the formulation of cosmetic products in Canada, but exposure to cresols is expected to be negligible.

The international literature (OECD 2005) has highlighted a number of applications of cresols as intermediates in consumer products (e.g., dyes, fragrances, synthetic vitamin E, etc.; see Section 7); however, exposure to residual levels of cresol in products is expected to be negligible.

11.1.8 Biomonitoring Data

According to the ATSDR (2008), no biomarkers that uniquely implicate exposure to cresols have been identified in humans or non-human organisms. Cresols occur naturally in human and animal tissues, fluids and urine (ATSDR 2008). Healthy humans excrete an average of about 50 mg (Bone et al. 1976; Renwick et al. 1988) to 87 mg (Ciba-Geigy 1984) of *p*-cresol in the urine per day. Free *p*-cresol that is formed in this way is absorbed from the intestine and eliminated in the urine as conjugates (IPCS 1995). Endogenous *p*-cresol is produced from tyrosine (an amino acid present in most proteins) by anaerobic bacteria in the intestine (Bone et al. 1976). Cresols are also metabolites of other aromatic compounds, such as toluene (ATSDR 2008). The use of cresols as a biomarker of exposure to cresol would require a considerable elevation to exceed biological background levels and potential confounding from conversion of other environmental agents (ATSDR 2008).

In a study conducted within the area of a large electric power facility in Perm, Russia, an analysis of children's biological media for the cresol isomers and phenol was conducted, and mean concentrations of *o*-, *m*- and *p*-cresol were found to be 6 to 11 times higher in blood and 0 to16 times higher in urine compared to control groups (Zaitseva et al. 2011). In this study, Zaitseva et al. (2011) showed a correlation between eosinophilia and the level of total cresols in the blood of children, but there are no experimental animal or human data to corroborate this as an effect. Also, Zaitseva et al. (2011) did not provide details on the duration of the study or number of children sampled, including the control groups.

11.1.9 Confidence in Exposure Database

Representative, robust Canadian monitoring data were available for cresols in ambient air, indoor air and food, resulting in high confidence in the upper-

bounding intake estimates from these media. As such, confidence is also high that food is the primary source of exposure to cresols for Canadians.Monitoring of cresols in groundwater, soil and dust in Canada is limited. Groundwater as a source of cresol exposure is an uncertainty in this assessment. Confidence is high that soil and dust are minor contributors to total cresol intakes, given the use of conservative monitoring data resulting in negligible exposure estimates.No data were identified for cresols in breast milk and formula, representing an uncertainty in the dietary intake assessment for infants. Cresols monitoring in Canadian alcohol was limited and is an additional uncertainty.

Due to the absence of monitoring data for this industry, SCREEN3 modelling of air concentrations was applied and was based on conservative Canadian emission factors. Uncertainties remain for exposures from other point sources, particularly from ILOs. Only one representative Canadian air monitoring study of a large-scale cattle operation was identified; however, several limitations were noted. Agricultural monitoring studies in the United States were identified, but data were highly variable and were not all recent and/or were lacking specificity. However, trends over the past 15 years for Canadian swine ILOs show considerable increases (Canadian Pork Council 2013). Other point sources, such as some petroleum refining–related industries and incineration, were identified. However, the cited older international literature likely reflects a conservative source, because control strategies implemented over the last 30 years have likely lowered environmental emissions.

Some uncertainties remain regarding residual levels of cresols as intermediates in some final applications, although, in general, exposures are expected to be negligible.

Additional uncertainties remain regarding the variability in grade, scope, composition, source and nomenclature of CAS RN 1319-77-3 between references cited in this assessment.

11.2 Health Effects Assessment[2]

Toxicity studies based on any of the *o-, m-* or *p*-cresol isomers or on a mixture of isomers were taken into consideration to characterize the overall health effects associated with cresols. As shown in Section 4, these substances are being

[2]A tabulated summary of health effects studies considered in this assessment can be found in the Supporting Document (Health Canada 2015).

assessed as a single sub-group because they possess similar physical and chemical characteristics and display comparable environmental and toxicological properties.

11.2.1 Chronic Toxicity/Carcinogenicity

Each of the three individual isomers was given the classification C (possible human carcinogen) for carcinogenicity by the U.S. EPA in 1991 (US EPA 1991a, 1991b, 1991c), based on an increased incidence of skin papillomas in mice in an initiation-promotion study (Boutwell and Bosch 1959). *o*-, *m*- or *p*-cresol were applied together as a 20% solution in benzene applied to skin of mice twice weekly for 12 weeks; the skin of the animals received a single dermal application of the established genotoxic skin carcinogen 9,10-dimethyl-1,2-benzanthracene (initiator) prior to the first application of *o*-, *m*- or *p*-cresol (promoters). In each case, *o*-, *m*- or *p*-cresol treatment produced an increased number of skin papillomas per mouse and a higher percentage of treated mice with at least one papilloma. Controls (exposed to benzene solvent) did not develop papillomas (Boutwell and Bosch 1959). However, no chronic toxicity/carcinogenicity studies were identified where each of the individual isomers were administered alone, i.e., without co-exposure from another substance.

The U.S. EPA classification system for carcinogenicity has been revised since 1991 (US EPA 2005), and, as stated by the ATSDR (2008), cresols would likely fall into the category for which there is “inadequate information to assess carcinogenic potential,” based on this new classification system. Since then, the U.S. NTP (2008) conducted two carcinogenicity studies using a 60/40 *meta*-/*para*-cresol mixture, one on mice and the other on rats. The mixture was applied to the diet of female mice at doses of 0, 1000, 3000 or 10 000 ppm (equivalent to average doses of 0, 100, 300 or 1040 mg cresols/kg bw/d) for up to 105 weeks. There was a significant increase in squamous cell papillomas of the forestomach at 1040 mg/kg bw/d, whereas non-cancer effects included an increase in hyperplasia of lung bronchioles (dose-related) and follicular degeneration in the thyroid (not dose-related) at 100, 300 and 1040 mg/kg bw/d (all treatment doses), decreased body-weight gain, and an increased incidence of hyperplasia of respiratory epithelium in the nose at the mid- and high-doses and increased incidence of eosinophilic foci in the liver at 1040 mg/kg bw/d. In rats, the mixture was applied to the diet of males at doses of 0, 1500, 5000 or 15 000 ppm (equivalent to average doses of 0, 70, 230 or 720 mg cresols/kg bw/d) for 105 weeks. There was an increased incidence of renal tubule adenoma at 720 mg/kg bw/d. This increase was qualified by the study authors as marginal and not statistically significant, but as exceeding the range of historical controls (Sanders et al 2009). Non-cancer effects included dose-related increases in nasal goblet cell hyperplasia and nasal respiratory epithelium hyperplasia at all treatment doses, an increased incidence of nasal squamous metaplasia and decreased body-weight gain at the mid- and high-doses, and increased incidences of nasal inflammation, eosinophilic foci in the liver, and transitional

epithelium hyperplasia of the pelvis in the kidney at 720 mg/kg bw/d. Although the two-year time-weighted average low dose was 70 mg cresols/kg bw/d, the ATSDR (2008) noted that the mean dose received by the low-dose rats in the first 13 weeks of the two-year study was actually 123 mg/kg bw/d, and that the hyperplasia of the nose in the low-dose group was observed at incidences very similar to those reported in a 13-week rat study where males received 123 mg/kg bw/d using the same 60/40 *m*-/*p*-cresol mixture and dosing regime. The actual lowest-observed-adverse-effect level (LOAEL) for toxicity ("17/50 with minimal hyperplasia of the nasal respiratory epithelium, 3/50 in controls") in the two-year study was 123 mg/kg bw/d. This is because 123 mg/kg bw/d was "the mean dose during the first 13 weeks when the nose lesions probably developed" (ATSDR 2008).

The authors of the U.S. NTP (2008) report summarized the above studies in a separate journal article (Sanders et al. 2009), noting the possibility that the non-cancer lesions were "... due to inhalation exposure of the cresol, specifically *p*-cresol, volatilizing from the feed during consumption, and not from systemic exposure following oral absorption."

In the two-year mouse feeding study with the *m*-/*p*-cresol mixture, a non-cancer oral LOAEL of 100 mg/kg bw/d was determined based on increased incidences of bronchiole hyperplasia of the lung and follicular degeneration of the thyroid gland in female mice (NTP 2008). Based on these effects, the ATSDR (2008) derived a chronic-duration oral minimal risk level (MRL)[3] of 0.1 mg/kg/d for cresols. The MRL was derived using the LOAEL of 100 mg/kg/d from the mouse study divided by an uncertainty factor of 1000.

With regards to carcinogenicity, the U.S. NTP (2008) concluded that there was "equivocal evidence of carcinogenic activity" of 60:40 *m-/p*-cresol in male rats based on the marginal increase in incidence of renal tubule adenoma, and that there was "some evidence of carcinogenic activity" of 60:40 *m-/p*-cresol in female mice based on the statistically significant increased incidence of forestomach squamous cell papillomas (i.e., studies are interpreted as showing a chemical-related increased incidence of neoplasm, in which the strength of the response is less than that required for clear evidence, as stated in U.S. NTP [2008]). As noted by Sanders et al. (2009), the only significant increased incidence of a neoplastic lesion observed in these studies was that of squamous cell papillomas in the forestomach of mice exposed to 10 000 ppm. A definitive association with

[3] The ATSDR derives MRLs for acute, intermediate and chronic duration exposures in its toxicological profiles of chemicals. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (non-carcinogenic) over a specified duration of exposure. The ATSDR is a U.S. advisory body, not a regulatory body.

irritation at the site of contact could not be made, because of limited evidence of injury in the gastric mucosa at the time of necropsy. However, regenerative changes (apparently due to irritation) were observed in the esophagus and forestomach of some exposed animals in the sub-chronic studies (NTP 1992b). Sanders concluded that it is plausible that the papillomas could have been associated with regenerative changes that were resolved over time. Sanders notes that no other neoplasms associated with cresols exposure were observed in this or any other tissue in female mice (Sanders et al. 2009).

Adams et al. (2008) argued that the forestomach tumours observed in the NTP studies are not relevant to humans. The rodent forestomach stores food, is constantly exposed to acidic gastric juice, and its mucosa is partially composed of a keratinizing squamous epithelial layer, whereas the human esophagus does not store food, is not in constant contact with strong acidic gastric juice, and its mucosa is composed of a non-keratinizing squamous epithelium. Due to these differences and the postulation that lesions observed at the site of contact are due to an irritant effect of high concentrations of cresols from gavage dosing, Adams et al. (2008) did not consider the incidence of forestomach papillomas observed in the mouse study as being relevant to humans. No direct observations of forestomach irritation in experimental animals were identified (regenerative changes may have occurred due to irritation); data from human case reports of acute exposure to cresols (12–50% or “concentrated” mixtures) showed evidence of effects on the alimentary tract. In these cases, the concentration of mixed cresols was not reported, but effects included diffuse erosions in the gastrointestinal system, including mouth and throat burns, erosion or corrosive injuries in the esophagus and stomach, lung edema, and effects on other tissues and organ systems (blood, skin, liver, renal and central nervous systems), including death (Minami et al. 1990; Hayakawa 2002; Monma-Ohtaki et al. 2002; Kinoshita et al. 2006). It appears that mixed cresols may have more of a corrosive than irritating effect on the human alimentary tract.

The hypothesis that the mice forestomach tumours may not be relevant to humans is plausible, but is based on limited evidence. A benchmark dose (BMD) based on an increased incidence of forestomach squamous cell papillomas in female mice was derived. Although a significant increase in incidence was observed only at the top dose, the BMD analysis was considered to be valid based on (a) an adequate number of dose groups (4), (b) no issues with mortality affecting incidence rate, and (c) the potential for the dose selection to have masked a dose-response relationship (i.e., if another dose had been selected between 306 and 1042 mg/kg bw/d, the incidence of forestomach squamous cell papillomas may have shown a clear dose-response relationship). All available models for dichotomous data adequately fit the data, so the two models that resulted in the lowest BMDs and lower 95% confidence interval limit, based on a 10% excess risk of the benchmark response ($BMDL_{10}$), were chosen. These were the Multistage-Cancer and Quantal-Linear models, which resulted in a BMD and $BMDL_{10}$ of 584 and 376 mg/kg bw/d, respectively (see Appendix F).

One very limited study in humans was identified. In a cross-sectional study of seven workers occupationally exposed to unknown concentrations of cresol vapours for 1.5–3 years, frequent headaches, nausea and vomiting were observed. Four of the workers had high blood pressure, impaired renal function, abnormal blood calcium levels and marked tremors (DECOS 1998). Due to the very small sample size, lack of details on the composition and concentrations of the cresol vapours, and study design, little can be concluded from this study, other than noting that some of the target systems (central nervous system [CNS] and blood) were similar to those observed in experimental animals given repeated exposures of *o*-cresol (Uzhdavini et al. 1972).

11.2.2 Genotoxicity

There are a number of *in vitro* genotoxicity studies for the individual isomers and cresol mixtures. When tested separately, each of the three isomers was negative in mutagenicity studies using *Salmonella typhimurium* and mouse lymphoma cells (Jagannath and Brusik 1981; Pepper et al. 1981; Pool and Lin 1982; Haworth et al. 1983; Cifone 1988a; Kubo et al. 2002). *o*-cresol was positive in a chromosome aberration test in Chinese hamster ovary (CHO) cells but equivocal in indicator tests (sister chromatid exchange [SCE] in CHO and human fibroblast cells) (Galloway and Brusick 1981; Pepper et al. 1981; Cheng and Kligerman 1984; Murli 1988; RTECS 2009a), equivocal overall in DNA damage and repair assays using rat and mouse cells and human lymphocytes (Pepper et al. 1981; Li et al. 2005), and negative for cell transformation in mouse cells (Brusick 1988a). *m*-cresol was equivocal in chromosome aberration tests in CHO and Syrian hamster embryo (SHE) cells as well as in indicator tests (SCE in SHE and human fibroblast cells) (Cheng and Kligerman 1984; Murli 1988; GENE-TOX 1998b; Hikiba et al. 2005; Miyachi and Tsutsui 2005), equivocal in DNA damage and repair assays using rat and SHE cells (Cifone 1988b; Hamaguchi and Tsutsui 2000), and negative for cell transformation in mouse cells (Brusick 1988b). *p*-cresol was positive in a chromosome aberration test in CHO cells and negative in an indicator test (SCE in human fibroblast cells) (Cheng and Kligerman 1984; Murli 1988 [presumably the same study as Hazleton Labs 1988c]), equivocal in DNA damage and repair assays using human cells (lung fibroblast and promyelocytic leukaemia cells) (Crowley and Margard 1978; Gaikwad and Bodell 2001), and equivocal for cell transformation in mouse cells (incomplete data on activation status in both studies) (Crowley and Margard 1978; Brusick 1988b).

A 1:1:1 mixture of *o*-, *m*- and *p*-cresol was negative in an *S. typhimurium* mutagenicity study, but positive in a mouse lymphoma cell mutagenicity study, a DNA damage and repair assay in rat hepatocytes, and an indicator test (SCE in CHO cells), and positive for cell transformation in mouse cells (Galloway and Brusick 1980; Myhr and Brusick 1980; Pepper et al. 1980). A 60/40% mixture of *m*- and *p*-cresol was negative in an *S. typhimurium* mutagenicity study (NTP 1992b).

There were limited data on *in vivo* genotoxicity. *o*-cresol was negative for germ cell mutagenicity in a dominant lethal assay in the mouse and in a sex-linked recessive lethal (SLRL) test in *Drosophila melanogaster* (Ivett 1989a; Sernav 1989), equivocal for clastogenicity and aneugenicity in micronucleus tests in the mouse (positive in bone marrow via intraperitoneal [i.p.] injection but negative in peripheral blood erythrocytes via oral exposure) (NTP 1992b; Li et al. 2005), and negative in an indicator test (bone marrow, lung and liver cells in an SCE assay in the mouse via i.p. injection) (Cheng and Kligerman 1984). *m*-cresol was negative for clastogenicity in the bone marrow in mice exposed orally, and negative in an indicator test (bone marrow, lung and liver cells in an SCE assay in the mouse via i.p. injection) (Cheng and Kligerman 1984; Hazleton Labs 1988b; Ivett 1989c). *p*-cresol was negative for germ cell mutagenicity in a dominant lethal assay in the mouse and in an SLRL test in *D. melanogaster*, and negative in an indicator test (bone marrow, lung and liver cells in an SCE assay in the mouse via i.p. injection) (Cheng and Kligerman 1984; Hazleton Labs 1989a, 1989b; Ivett 1989b). A 60/40% mixture of *m*- and *p*-cresol was negative for clastogenicity and aneugenicity in peripheral blood erythrocytes of mice exposed orally (NTP 1992b).

No *in vivo* data were identified for the mixture of all three isomers, and no *in vivo* mutagenicity data were identified for *m*-cresol. For clastogenicity and aneugenicity, no data were identified for mice (or other species) exposed to mixtures of the cresols via i.p. injection. As shown above, mice exposed orally showed negative results for all isomers and the *m*-/*p*-cresol mixture, and mice exposed via i.p. injection showed mostly negative results for the individual isomers (one positive result for *o*-cresol). In view of the mostly equivocal results in the *in vitro* tests in mammalian cells and the lack of definitive *in vivo* genotoxicity studies for mixtures of the cresols, the genotoxic potential of the isomers and mixtures cannot be clearly defined.[4]

[4] The genotoxicity database for the cresols is similar to phenol, as shown in Environment Canada and Health Canada (2000): “Although phenol is primarily negative in bacterial tests for mutagenicity, it induces gene mutations and structural chromosomal aberrations in mammalian cells *in vitro*. While results of available studies are mixed, in investigations of optimum design, phenol has induced micronuclei in the bone marrow of mice exposed *in vivo*. On the basis of available data, therefore, it is considered to be a weak *in vivo* clastogen.” Given this weak response, there is no benefit in reading across from phenol to cresols. Additionally, differences in toxicokinetics between phenol and cresols suggests a read-across methodology is not practical (see “Absorption, Distribution, Metabolism, and Excretion”).

11.2.3 Developmental Toxicity

Oral developmental toxicity studies using the individual isomers were identified. No developmental toxicity studies were identified for mixtures of the isomers.

Pregnant rabbits were orally gavaged with *o*-cresol at doses of 0, 50 or 100 mg/kg bw/d on gestation days 6–18. At 50 and 100 mg/kg bw/d, dams showed signs of mild respiratory distress, ocular discharge and hypoactivity, while at 100 mg/kg bw/d, fetuses showed increased incidences of skeletal variations and subepidermal hematoma (Tyl 1988c). Developmental effects (increased incidence of skeletal variations) were observed at 450 mg/kg bw/d in the presence of unspecified maternal toxicity in pregnant rats dosed with *o*-cresol at doses of 0, 30, 175 or 450 mg/kg bw/d on gestation days 6-15 (Tyl 1988a, 1988b).

Pregnant rabbits were orally gavaged with *m*-cresol at doses of 0, 5, 50 or 100 mg/kg bw/d on gestation days 6–18. At 50 and 100 mg/kg bw/d, dams showed signs of laboured breathing, ocular discharge and audible respiration, but no adverse effects were observed in fetuses at the highest dose tested (BRRC 1988b; Tyl 1988c). In another standard developmental toxicity study in pregnant rats orally gavaged with *m*-cresol on gestation days 6–15, no adverse effects were observed in dams or fetuses at the highest dose tested, 450 mg/kg bw/d (BRRC 1988a; Tyl 1988a, 1988b). However, in a study in which neonate rats were gavaged on post-natal days 4–21 with 0, 30, 100 or 300 mg/kg bw/d, a developmental LOAEL of 100 mg/kg bw/d was determined based on tremors (under contact stimulus)[5] at 100 and 300 mg/kg bw/d (ATSDR 2008). At 300 mg/kg bw/d, decreased weight gain, deep respiration, and hypersensitivity on handling were observed (Koizumi et al. 2003). The authors of the study, Koizumi et al. (2003), state that the LOAEL was 300 mg/kg bw/d (and the no-observed-adverse-effect level [NOAEL] = 30 mg/kg bw/d), although they acknowledge that there were dose-related tremors in a small number of males at 100 and 300

[5] It is listed as a developmental LOAEL in Table 3 of ATSDR (2008), but with the following comment: “Tremors observed in newborn rats but not in 5-week old exposed for 28 days.” The ATSDR (2008) states the following in its text: “Studies in animals suggest that fetotoxicity occurs only with doses of cresols that are also toxic to the mother and further standard developmental toxicity studies do not appear necessary at this time. A study showed that newborn rats (exposed daily on postnatal days 4–21) were more sensitive to the neurological effects of bolus doses of cresols than young rats (exposed daily for 28 days). This may be due to age-related differences in toxicokinetics.”

mg/kg bw/d, and thus the LOAEL is determined to be 100 mg/kg bw/d in this assessment.

For *p*-cresol, pregnant rabbits were orally gavaged with the test substance at doses of 0, 5, 50 or 100 mg/kg bw/d on gestation days 6–18. At 50 and 100 mg/kg bw/d, there was a dose-related increase in mortality, laboured breathing, ocular discharge, audible respiration, cyanosis and hypoactivity in the dams, but no adverse effects were observed in fetuses at the highest dose tested (BRRC 1988b; Tyl 1988c). In another standard developmental toxicity study, pregnant rats were orally gavaged with *p*-cresol at doses of 0, 30, 175 or 450 mg/kg bw/d on gestation days 6–15. Both maternal toxicity (mortality, ataxia, tremors, laboured breathing and audible respiration) and developmental toxicity (decreased body weight and increased incidence of skeletal variations in fetuses) were observed at the highest dose tested (BRRC 1988b; Tyl 1988c).

As shown above, maternal toxicity was observed at lower or equivalent doses in rats and rabbits, when compared to developmental toxicity, in studies on the individual isomers. The lowest LOAEL for maternal toxicity was 50 mg/kg bw/d for *o*-, *m*- and *p*-cresol, and the lowest LOAEL for developmental toxicity was 100 mg/kg bw/d for *o*- and *m*-cresol, but 450 mg/kg bw/d for *p*-cresol. For *m*-cresol, the effect level was classified as possibly a "developmental LOAEL" by the ATSDR (2008), even though it was based on a study in neonate rats orally dosed on post-natal days 4–21, and the tremors observed at the LOAEL were suggestive of effects on the CNS; in a standard developmental toxicity study, adverse effects in rat fetuses were not observed at doses up to 450 mg/kg bw/d with *m*-cresol. However, the lowest developmental LOAEL for *o*-cresol was 100 mg/kg bw/d based on effects observed in rabbit fetuses.

11.2.4 Reproductive Toxicity

Oral reproduction studies using the individual isomers and an *m*-/*p*-cresol mixture were identified.

Mice were exposed to 0 or 660 mg/kg bw/d of *o*-cresol in the diet for 15 weeks during a continuous breeding protocol (NTP 1992a); mink were exposed to 0, 5–10, 25–40 or 105–190-mg/kg bw/d of the same isomer in the diet for six months during a one-generation reproduction study (Hornshaw et al. 1986); and rats were orally gavaged with doses of 0, 30, 175 or 450 mg/kg bw/d in a two-generation reproduction study (BRRC 1989a; Tyl and Neeper-Bradley 1989a, 1989b). No reproductive effects were reported in any of these studies. However, overt CNS effects (ataxia and hypoactivity) were observed at 175 mg/kg bw/d in the F1 adults and at 450 mg/kg bw/d in the F0 and F1 generations.

Rats were orally gavaged with doses of 0, 30, 175 or 450 mg/kg bw/d of *m*-cresol in a two-generation reproduction study. Although no reproductive effects were observed, decreased body weights in F1 adults were reported to occur at doses

of 30 mg/kg bw/d and higher.[6] At 175 and 450 mg/kg bw/d, there was an increased incidence of perioral wetness (suggestive of salivation) in the F1 generation (BRRC 1989c; Neeper-Bradley and Tyl 1989b; Tyl and Neeper-Bradley 1989c).

Rats were orally gavaged with doses of 0, 30, 175 or 450 mg/kg bw/d of *p*-cresol in a two-generation reproduction study. Although no reproductive effects were observed, mortality, decreased body-weight gain in survivors, and mild perioral wetness (suggestive of salivation) were reported in animals treated with doses of 175 and 450 mg/kg bw/d in the F1 generation, and at the dose of 450 mg/kg bw/d in the F0 generation (BRRC 1989b; Neeper-Bradley and Tyl 1989a; Tyl and Neeper-Bradley 1989b).

Mice were exposed to 0, 375, 1390 or 1682 mg/kg bw/d of an *m*- and *p*-cresol mixture (60/40%) in the diet for 15 weeks during a continuous breeding protocol. A reproductive toxicity LOAEL of 1390 mg/kg bw/d was determined based on decreased male reproductive organ weights (prostate, seminal vesicle, testes) in the F1 generation, and at 1682 mg/kg bw/d there was an increase in cumulative days to litter (by almost three days, to the fifth litter) in the F0 generation, and decreased epididymal and seminal vesicle weights in F0 males. Although there were no effects on sperm parameters or reproductive organ histology, the decreased reproductive organ weights are considered to be adverse because they occurred in the F1 generation after exposure had ceased before birth of the litters. A developmental LOAEL of 1682 mg/kg bw/d was also determined, based on a lower number of live pups/litter in the F1 generation. A systemic LOAEL of 1390 mg/kg bw/d was determined, based on decreased body-weight gain in females in the F0 and F1 generations, as well as decreased body weights in males in the F1 generation (Izard et al. 1992; NTP 1992c; RTI 1992; Heindel et al. 1997). No reproductive toxicity studies were identified for the mixture of all three isomers.

Note that the systemic LOAELs determined in rats for *o*- and *p*-cresol were based mainly on CNS effects and/or mortality, whereas the systemic LOAEL for *m*-cresol was based on decreased body weights (however, CNS effects were observed at the next-highest dose for *m*-cresol). No CNS effects were observed in the mouse study using the *m*-/*p*-cresol mixture at higher doses than those conducted with the isomers in rats. However, in this study, the mice were exposed via the diet, whereas in the rat studies the animals were exposed via

[6] This unpublished study is cited in the CIR Expert Panel (2006), ATSDR (2008) and JECFA (2011). The ATSDR (2008) states that body-weight gain was decreased at 30 mg/kg bw/d and higher, but the CIR Expert Panel (2006) and JECFA (2011) both indicate that body weight was decreased.

oral gavage. The mouse study conducted with *o*-cresol up to 660 mg/kg bw/d via the diet also did not show any CNS effects.

11.2.5 Sub-chronic Toxicity

Oral and inhalation studies using *o*-cresol and cresol mixtures were identified, but only oral studies using *m*- or *p*-cresol were identified.

For *o*-cresol, four oral sub-chronic studies in rats or mice, and one sub-chronic inhalation study in mice and other species, were identified.

In two oral studies, rats were gavaged with *o*-cresol at doses of 0, 50, 175, [450][7] or 600 mg/kg bw/d for 13 weeks, and two oral studies in which rats were fed *o*-cresol in the diet at doses of 0, 126−129, 247−256, 510−513, 1017−1021 or 2024−2028 mg/kg bw/d or mice were fed *o*-cresol in the diet at 0, 199−237, 400−469, 794−935, 1490−1723 or 2723−3205 mg/kg bw/d for 13 weeks. In one of the gavage studies in rats, a LOAEL of 50 mg/kg bw/d (lowest dose tested) was determined based on CNS effects (hypoactivity, rapid laboured respiration, excessive salivation, and tremors). At 450 mg/kg bw/d, convulsions occurred. Neurobehavioural tests, conducted six times over the 13 weeks, showed only sporadic differences that were not dose-related (TRL 1986; US EPA 1987). In the other gavage study in rats, a LOAEL of 175 mg/kg bw/d was determined based on CNS effects (at this dose, two animals showed tremors on study day 1 and one of these animals became comatose). At 600 mg/kg bw/d, 9 males and 19 females died, coma and convulsions were observed, and there was a decreased weight gain in survivors (US EPA 1986, 1988a). In the 13-week feeding studies with *o*-cresol, a LOAEL of 1020 mg/kg bw/d, based on bone marrow hypocellularity in rats and a LOAEL of 1723 mg/kg bw/d, based on decreased final body weights in female mice (also observed were forestomach epithelial hyperplasia in males at 2723 mg/kg bw/d, and a lengthened oestrous cycle in females at 3205 mg/kg bw/d) were determined (NTP 1992b). No evidence of CNS effects were observed in the feeding studies.

Mice exposed by inhalation to 9 mg/m^3 *o*-cresol for 4 months were reported to show morphological changes in the respiratory tract (including the lungs), accelerated loss of a conditioned defensive reflex, leukocytosis, decreased myeloid-erythroid ratio in the bone marrow, and evidence of liver toxicity (an increased susceptibility to hexanol narcosis) (Uzhdavini et al. 1972). Rats, guinea pigs and rabbits exposed by inhalation to the same concentration for 4 months resulted in the brain, liver, and kidney/ureter/bladder being identified as “toxicity

[7] One of the two studies used an extra dose level of 450 mg/kg bw/d.

targets" (it is not clear if these three species were part of the same or different studies) (Bandman et al. 1994).

For *m*-cresol, two 13-week oral gavage studies in rats were identified; in both cases, the rats were dosed at 0, 50, 150 or 450 mg/kg bw/d. In one of the studies, a LOAEL of 50 mg/kg bw/d was determined based on CNS effects (hypoactivity, rapid laboured respiration, and excessive salivation). The highest dose (450 mg/kg bw/d) produced significant neurological effects such as increased salivation, urination, tremors, lacrimation, palpebral closure, and rapid respiration; animals also showed abnormal patterns in the neurobehavioral tests conducted six times over the 13 weeks (tests were conducted at all doses) (TRL 1986; US EPA 1987). In the other study, a LOAEL of 150 mg/kg bw/d was determined based on decreased body-weight gain in male rats. CNS effects (lethargy, tremor, hunched posture, dyspnoea) were observed at 450 mg/kg bw/d (US EPA 1986, 1988c; Microbiological Associates 1988a).

For *p*-cresol, two 13-week oral gavage studies in rats and one 20-week oral feeding study in hamsters were identified. In one of the rat gavage studies, a LOAEL of 50 mg/kg bw/d was determined, based on CNS effects (hypoactivity, rapid laboured respiration, excessive salivation, and tremors). The highest dose (600 mg/kg bw/d) resulted in convulsions. Neurobehavioural tests, conducted six times over the 13 weeks, showed only sporadic differences that were not dose-related (TRL 1986). In the other gavage study, a LOAEL of 175 mg/kg bw/d was determined based on decreased body-weight gain in males and mild haematological effects (6–8% decreases in red blood cell count and haemoglobin) in females. At the highest dose (600 mg/kg bw/d), effects observed were deaths in 3 of 30 animals, lethargy, salivation, tremors, convulsions, decreased body-weight gain, increased relative liver (males) and kidney weights, liver inflammation, and epithelial metaplasia of the trachea (Microbiological Associates 1988b; US EPA 1988b). In hamsters fed a diet containing 0 or 1415 mg/kg bw/d of *p*-cresol for 20 weeks, an increased incidence of forestomach hyperplasia was observed at 1415 mg/kg bw/d (Hirose et al. 1986).

Two 13-week feeding studies using a cresol mixture, one in rats and the other in mice, and one 4-month inhalation study in rats, were identified. Rats were exposed to doses of 0, 123–131, 241–254, 486–509, 991–1024 or 2014–2050 mg/kg bw/d of an *m*- and *p*-cresol mixture (60/40%) in the diet for 13 weeks. The LOAEL was 123 mg/kg bw/d based on a dose-related increase in hyperplasia of the nasal respiratory epithelium in males. At 254 mg/kg bw/d and higher, there was also a dose-related increase in hyperplasia of the nasal respiratory epithelium in females. Although other parameters were affected at higher doses, no clinical signs of CNS effects were reported (NTP 1992b). Mice were exposed to doses of 0, 96–116, 194–239, 402–472, 776–923 or 1513–1693 mg/kg bw/d of an *m*- and *p*-cresol mixture (60/40%) in the diet for 13 weeks. The LOAEL was 776 mg/kg bw/d based on a dose-related increase in minimal hyperplasia of the

nasal epithelium in males. No other toxicological effects were observed (NTP 1992b).

In the sub-chronic inhalation study, rats were exposed to 0, 1.45 or 5 mg/m^3 of an *m*-/*p*-cresol mixture (66/33% + 1% *o*-cresol) "… for 4 months, 4 times daily, five times a week." Effects observed at 5 mg/m^3 (LOEC) were irritation of the lungs, increased relative kidney weights along with histopathological changes, increased liver fat, and, in females, decreased relative uterus weight and changes in the estrus cycle. Limited information was available on potential structural dystrophic and functional changes in the CNS, lungs and heart myocardium at this concentration (Uzhdavini et al. 1976).

The ATSDR noted that the nasal epithelium appears to be a sensitive target for cresols, and nasal lesions could be due to direct contact with the epithelium; however, the ATSDR (2008) stated that "… until it can be demonstrated with some certainty that the nasal lesions are not caused by a systemic effect of cresol and in the interest of protecting humans potentially exposed under similar conditions, the MRL was based on the increased incidence of the nasal lesions in rats." Thus, the ATSDR (2008) derived an intermediate-duration MRL of 0.1 mg/kg bw/d for oral exposure, using benchmark modelling. A benchmark response of 10% was selected for the benchmark analysis of nasal lesion incidence data in rats in the 13-week rat study, and corresponding benchmark dose and $BMDL_{10}$ values were determined by the ATSDR (2008). Although MRLs are not determined in Canada, the critical effect level (LOAEL = 123 mg/kg bw/d) determined for this same 13-week rat study was also based on the nasal lesion incidence data.

11.2.6 Short-term Toxicity

Oral and inhalation studies using *o*- and *p*-cresol were identified, whereas only oral studies using *m*-cresol or cresol mixtures were identified. In the oral gavage studies with the individual isomers, lowest oral LOAELs were based on CNS effects, whereas, for the oral feeding study conducted with an *m*-/*p*-cresol mixture, the lowest oral LOAEL was based on nasal toxicity (no repeated dose studies were identified in which cresol mixtures were administered via gavage). In the inhalation studies, the lowest LOAEC for *o*-cresol was based on respiratory tract and blood effects, and the LOAEC for *p*-cresol mixture was based on several organs identified as toxicity targets.

For *o*-cresol, five oral studies in rats, mice, mink and Ferrets, and four inhalation studies in rats, mice and guinea pigs, were identified.

In one oral study in which rats were gavaged with *o*-cresol at doses of 0, 50 or 600 mg/kg bw/d for two weeks, a LOAEL of 50 mg/kg bw/d was determined based on CNS effects (hypoactivity and rapid laboured respiration). At 600 mg/kg bw/d, convulsions occurred (TRL 1986). In four oral studies in which rats, mice,

mink and Ferrets were fed *o*-cresol for four weeks, with doses ranging from 35–5000 mg/kg bw/d depending on the species, LOAELs of 200 and 400 mg/kg bw/d (and NOAELs of 125 and 290 mg/kg bw/d) were determined in mink and Ferrets, respectively, based on a decreased red blood cell count (Hornshaw et al. 1986). In rats and mice, effects were observed at higher doses in these studies: uterine atrophy in mice at 1670 and 5000 mg/kg bw/d, and decreased body-weight gain in rats at 2510 mg/kg bw/d (NTP 1992b).

Rats exposed via inhalation to 9 mg/m^3 of *o*-cresol for ≥ 1 month showed haematopoietic effects, respiratory tract irritation and sclerosis of the lungs, whereas guinea pigs exposed to the same concentration and duration showed no effects (Uzhdavini et al. 1972). In another study, rats were exposed to 10 mg/m^3 of *o*-cresol for 40 days, and the brain, liver and kidney/ureter/bladder were identified as "toxicity targets" (no further information was provided) (Bandman et al. 1994). Mice exposed to an average concentration of 50 mg/m^3 for one month showed clinical and histopathological signs of respiratory irritation followed by hypoactivity lasting until the end of exposure, and degeneration of heart muscle, liver, kidney and nervous tissue of the CNS (Uzhdavini et al. 1972; Bandman et al. 1994).

For *m*-cresol, five oral studies in rats and mice were identified; two were gavage studies in rats, two were feeding studies in rats, and one was a feeding study in mice. In a two-week gavage study in rats, a LOAEL of 50 mg/kg bw/d was determined based on CNS effects (hypoactivity and rapid laboured respiration). At 450 mg/kg bw/d, convulsions occurred (TRL 1986). In another study, rats were gavaged with *m*-cresol at doses of 0, 300 or 1000 mg/kg bw/d for 28 days, and CNS effects (salivation, tremors) and decreased body-weight gain were observed at 1000 mg/kg bw/d (Koizumi et al. 2003). The feeding studies in rats and mice were all 28 days in duration. Effects observed were uterine atrophy and decreased body-weight gain in females at the highest dose (2310 mg/kg bw/d) tested in rats, and CNS effects (lethargy and laboured respiration) in female mice at 2080 and 4940 mg/kg bw/d (NTP 1992b).

For *p*-cresol, three oral studies in rats and mice and one inhalation study in rats were identified. In a two-week gavage study in rats, a LOAEL of 50 mg/kg bw/d was determined based on CNS effects (hypoactivity and rapid laboured respiration). At 600 mg/kg bw/d, convulsions occurred (TRL 1986). Rats and mice were fed *p*-cresol in the diet for 28 days. Effects observed were nasal toxicity in mice (respiratory epithelial hyperplasia) at doses of 60–1590 mg/kg bw/d, and in rats (respiratory epithelial hyperplasia and atrophy of the olfactory epithelium) at doses of 256–2180 mg/kg bw/d. In mice dosed at 1410–1590 mg/kg bw/d (the highest of five dose levels, including controls), there were overt signs of toxicity in both sexes (hunched posture, lethargy, hypothermia and laboured breathing), and decreased body-weight gain in males; and one male died. In rats dosed at 2060–2180 mg/kg bw/d (the highest of six dose levels, including controls), body-weight gain was decreased in both sexes, and, in

females, bone marrow hypocellularity and uterine atrophy were observed (NTP 1992b). In an inhalation study, rats were exposed to 10 mg/m^3 of *p*-cresol for 40 days, and the brain, liver and kidney/ureter/bladder were identified as "toxicity targets" (no further information was provided) (Bandman et al. 1994).

Two four-week feeding studies (one in rats and the other in mice) using cresol mixtures were identified. Rats were exposed to doses of 0, 26–27, 90–95, 261–268, 877–886 or 2570–2600 mg/kg bw/d of an *m*-/*p*-cresol mixture (60/40%) in the diet for 28 days. The LOAEL was 95 mg/kg bw/d based on a dose-related increase in hyperplasia of the nasal respiratory epithelium in females (dose-related increase in males at 261 mg/kg bw/d and higher). Although other effects were observed at higher doses, no clinical signs of CNS effects were reported (NTP 1992b). Mice were exposed to doses of 0, 50−65, 161−200, 471−604, 1490−1880 or 4530−4730 mg/kg bw/d of an *m*-/*p*-cresol mixture (60/40%) in the diet for 28 days. The LOAEL was 604 mg/kg bw/d, based on hyperplasia of the nasal epithelium in female mice. At 1490 mg/kg bw/d and higher, decreased body-weight gain and nasal and bronchial effects were observed in males. At the top dose (4530−4730 mg/kg bw/d), signs of CNS effects (hunched posture, hypothermia, lethargy), alopecia and bone marrow hypocellularity occurred in both sexes; and, in females, body-weight gain was decreased and atrophy of the ovaries and uterus was observed (NTP 1992b). In contrast to the feeding study with the mixture, CNS effects were observed at doses ranging from 1450−1590 mg/kg bw/d of *p*-cresol, and 2080−4940 mg/kg bw/d of *m*-cresol in four-week mouse dietary studies.

11.2.7 Acute Toxicity

There is a sufficient database of acute oral, dermal and inhalation studies for the individual isomers, but limited acute studies for cresol mixtures. For all three isomers, acute oral effects observed prior to death in rats were hypoactivity, tremors, convulsions, salivation and dyspnoea (EI Du Pont 1969), and for *m*-/*p*-cresol the effects observed prior to death were convulsions, adynamia (loss of normal or vital powers) and complete prostration (Uzhdavini et al. 1976). Acute dermal effects for all three isomers in rabbits included nervous system toxicity (somnolence and tetany; lacrimation, salivation, hypersensitivity, convulsions and hypoactivity; and the treated skin showed severe erythema and burns) followed by death (Biofax 1969b; Vernot et al. 1977), and for *m*-/*p*-cresol the effects observed in rats were convulsions, adynamia (loss of normal or vital powers), complete prostration, haematurea and skin lesions at the application site, followed by death (Uzhdavini et al. 1976). For all three individual isomers and an undefined cresol mixture, an acute dermal LOAEL of 147 mg/kg bw was determined, based on skin corrosion in rabbits exposed via four-hours covered contact of the test material (Vernot et al. 1977). Acute inhalation effects for all three isomers in rats or mice prior to death included irritation of mucous membranes and nervous system toxicity (tremors and clonic convulsions, neuromuscular excitation, and convulsions) (Uzhdavini et al. 1972; Pereima

1975). There were several case reports of humans ingesting or being dermally exposed to cresol mixtures, with reported toxic effects on the gastrointestinal system (including mouth and throat burns, vomiting and abdominal pain, and gastrointestinal bleeding); the skin (burns, discolouration), blood (including septic shock), liver, brain and renal system, often followed by acute respiratory failure, facial pain and paralysis; semi-unconsciousness, unconsciousness or coma; and death occurred in some cases (Isaacs 1922; Klinger and Norton 1945; Cason 1959; Labram and Gervais 1968; Chan et al. 1971; Jouglard et al. 1971; Green 1975; Bruce et al. 1976; Cote et al. 1984; Yashiki et al. 1990; Lin and Yang 1992; Hashimoto et al. 1998; Wu et al. 1998; Liu et al. 1999; Kamijo et al. 2003; Seak et al. 2010;).

Skin irritation studies in rabbits and/or guinea pigs using the individual isomers or the mixed isomers resulted in corrosivity or severe reactions after 4- or 24-hr covered contact (Mellon Institute 1949; Biofax 1969a; Ferro Corporation 1974; Younger Laboratories 1974; Vernot et al. 1977; Dow Chemical Company 1978; RIFM 1980a), and all three isomers showed severe eye irritation in rabbits (Mellon Institute 1949; Biofax 1969a; EI Du Pont 1983). No eye irritation studies were identified for mixtures of the isomers. Corrosive damage to the skin was reported in humans dermally exposed to cresols (Evers et al. 1994; OECD 2005), and skin depigmentation has been reported on “local exposure to cresols” (Deichmann and Keplinger 1981; Sax and Lewis 1989; NTP 1992b, which was citing NIOSH 1978). In a respiratory study, 10 volunteers subjected to a “brief” exposure to 6 mg/m^3 *o*-cresol complained of mucosal irritation symptoms, including dryness, nasal constriction, and throat irritation (Uzhdavini et al. 1972).

Sensitization studies in mice, guinea pigs and humans were identified. No skin sensitization was observed in mice when each of the three isomers was tested in a local lymph node assay (Yamano et al. 2007), and mostly negative results were observed in guinea pigs challenged with different concentrations of the individual isomers or the *m*-/*p*-cresol mixture (Uzhdavini et al. 1976; Sharp 1978; Bruze 1986; RIFM 2001). Human volunteers subjected to patch tests using 0.87% *o*-cresol or 4% *o*- or *p*-cresol did not show reactions (Kligman 1972; RIFM 1980b; Bruze and Zimerson 2002). However, some patients who had previously shown positive reactions to other substances (phenol formaldehyde resin or methylol phenols), or to textile dyes, or who already showed hand dermatitis, showed positive reactions when tested with various concentrations of *o*-, *m*- or *p*-cresol (Seidenari et al. 1991; Bruze and Zimerson 1997, 2002).

There are European Union Classification, Labelling and Packaging (CLP) regulations for all three isomers or cresol mixtures: toxic in contact with skin (Acute Tox. 3: H311), toxic if swallowed (Acute Tox. 3: H301), and causes severe

skin burns and eye damage (Skin Corr. 1B: H314) (ECHA C&L Inventory database 2012).[8]

11.2.8 Toxicokinetics

The oral or dermal absorption of cresols has not been quantified in humans (ATSDR 2008). Limited gavage studies in rabbits using all three isomers (Bray et al. 1950), and using a mixture of *p*- and *m*-cresol in rats (Morinaga et al. 2004), suggest gastrointestinal absorption of over 65%. The deaths and severe toxicity reported in laboratory animals exposed by inhalation of *o*-cresol provide indirect evidence of an extensive absorption via the lungs (ATSDR 2008).

Cresols are much more toxic when administered by oral gavage than when given in the diet. The difference is most likely related to differences in pharmacokinetics between the two modes of administration. Studies in rats dosed by oral gavage with a single dose of *m*- and *p*-cresol mixture indicate that cresols can distribute rapidly into many organs and tissues. Oral studies in rats and rabbits indicate that cresols undergo conjugation with sulphate and glucuronic acid, and also form oxidative metabolites in the liver. The conjugates are excreted in the urine (ATSDR 2008). Rats preferentially metabolize *m*-cresol to a sulphate conjugate, whereas the *p*-cresol is preferentially converted to a glucuronide (Morinaga et al. 2004). The metabolism of cresols seems to be similar in humans and rats, in the sense that both species excrete sulphate and glucuronide conjugation products in the urine (ATSDR 2008).

For comparison, the toxicokinetics of phenol show some similarities to, but also some differences from, those of the cresols. As shown in Environment Canada and Health Canada (2000), “The metabolism of phenol occurs primarily by direct conjugation with glucuronic acid and sulphate in the intestine and liver, and to a lesser extent in other tissues. A small percentage of the absorbed dose of phenol is metabolized by cytochrome P450 enzymes to hydroquinone, which is then also

[8] The Classification codes in parentheses are based on the Global Harmonized System (GHS) for classification introduced and enacted in December 2008 under the REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL ON CLASSIFICATION, LABELLING AND PACKAGING OF SUBSTANCES AND MIXTURES, AMENDING AND REPEALING DIRECTIVES 67/548/EEC AND 1999/45/EC, AND AMENDING REGULATION (EC) No 1907/2006. The ECHA C&L Inventory database (2012) has a “*” entry under “Specific Concentration Limits, M-factors,” which means that “The classification as obtained from Annex VII shall then substitute the minimum classification indicated in the Annex if it differs from it.” In this case, the classifications for cresols when present at ≥ 1% but < 5% in a mixture or formulation were taken from Annex VII, which helped to translate the previous codes shown in Annex VI, table 3.2 of the CLP Regulations available at http://ec.europa.eu/enterprise/sectors/chemicals/documents/classification/.

subsequently conjugated with sulphate and glucuronic acid. The urinary metabolites of phenol that have been identified in mammals, including humans, are phenyl glucuronide, phenyl sulphate and the corresponding conjugates of hydroquinone — 4-hydroxyphenyl glucuronide and 4-hydroxyphenyl sulphate." For cresols, some major urinary metabolites identified in mammals were ether glucuronide, ethereal sulphate, *p*-hydroxybenzoic acid (IPCS 1995), and *p*-cresylsulfate and *p*-cresylglucuronide (see next two paragraphs). Cytochrome P-450 enzymes metabolize phenol to hydroquinone, which is the putative toxic metabolite of phenol (Environment Canada, Health Canada 2000), whereas, for cresols, formation of the quinone methide intermediate was mediated by P-450 cytochromes in liver microsomes and slices (Thompson et al. 1995; Yan et al. 2005).

Distribution and excretion was determined in male rats dosed intravenously with 9.7 mg/kg bw of *p*-cresol. Urinary excretion of *p*-cresol was 23 ± 10% of the administered dose, and the excretion half-life was 1.5 hr. Approximately 85% of the dose was recovered in urine 4 hr after injection, of which 64% was identified as p-cresylglucuronide and 21% as *p*-cresol. The mean volume of distribution in serum was 2.9 ± 1.4 l/kg bw (Lesaffer et al. 2001, 2003).

No information was identified on how cresols are transported in blood, but it is reasonable to assume that they may be bound to albumin, the most important binding protein for many acidic and basic drugs (ATSDR 2008). In a study of healthy subjects and patients with chronic renal failure, no free *p*-cresol could be detected in the blood of healthy subjects; 100% was protein-bound (De Smet et al. 1998).

No distribution information was identified for *o*- or *m*-cresol.

p-cresol is a normal body constituent, generated from protein breakdown; mean concentrations of 8.6 µmol/L (0.93 mg/L) in serum have been reported in healthy subjects (De Smet et al. 1998). It arises from conversion by intestinal bacteria of the amino acids tyrosine and phenylalanine to 4-hydroxyphenylacetic acid, which is then further decarboxylated to *p*-cresol (De Smet et al. 1997; Vanholder et al. 1999). However, *p*-cresol does not appear to be the main constituent of this conversion pathway from tyrosine; rather, its conjugates are the main end products, as shown by Vanholder et al (2011).

The ATSDR (2008) stated that "Little information is available regarding the mechanism(s) of [systemic] toxicity of cresols." In *in vitro* studies using rat liver cells or mouse spleen cells, *p*-cresol showed effects that suggested its mechanism of action is different from that of the *o*- or *m*-isomers (Thompson et al. 1994, 1995, 1996; Yamano et al. 2007). However, the relevance of these findings to *in vivo* studies is unknown, because the individual cresol isomers showed little or no liver or spleen toxicity in repeated dose oral studies in rats and mice. *p*-cresol appeared to be more toxic than the other isomers in feeding

studies with experimental animals, and lower dermal LD_{50} or inhalation LC_{50} values were observed for *p*-cresol in acute studies when compared to *o*- and *m*-cresol.[9] However, oral repeated-dose studies and acute dermal studies resulted in determining the same dermal LOAEL (147 mg/kg bw) for each of the three isomers, oral LOAELs (50 mg/kg bw/d) were the same for all three isomers based on CNS effects, and a lower systemic oral LOAEL (30 mg/kg bw/d based on decreased body weights) was also determined for *m*-cresol. This suggests that, *in vivo*, all three isomers may have equivalent toxic potential.

11.2.9 Confidence in the Toxicity Database

Confidence in the toxicity database for *ortho*-, *meta*-, *para*- and the mixed cresols is considered moderate to high, because empirical data were identified for all the standard toxicity endpoints via oral exposure. There were limited short-term inhalation data. Repeated-dose inhalation studies, especially the longer-term inhalation studies (> short-term) were lacking for some of the individual isomers (*m*- and *p*-cresol) and the cresol mixture, and inhalation reproductive and developmental toxicity studies were lacking for the individual isomers and mixture. Although repeated-dose and reproductive/developmental toxicity studies via dermal exposure were lacking, the severe irritation caused by / corrosive nature of the isomers and mixture would not warrant a need to expand the toxicity database for this route of exposure. Information on exposure to cresols in humans was based mostly on case reports of acute exposures, with very sparse information on repeated exposures or experimentally designed studies.

The *in vivo* genotoxicity database was limited for a mixture of cresols (only one mouse micronucleus test using *m*-/*p*-cresol was identified), and also limited for determining mutagenicity potential of the individual isomers (two dominant lethal assays conducted in mice with *o*- or *p*-cresol were identified).

11.3 Characterization of Risk to Human Health

Carcinogenicity is a potential critical effect for cresols, although tumours occurred only at high oral doses in experimental animals. A BMD analysis was conducted on the statistically significant increased incidence of squamous cell papillomas in the forestomach of mice treated with a mixture of *m*- and *p*-cresols, and a lowest BMD and $BMDL_{10}$ of 584 and 376 mg/kg bw/d, respectively, were calculated based on the best fitting models (Multistage-Cancer and Quantal-Linear models).

[9] See Supporting Document (Health Canada 2015).

In terms of non-cancer effects, CNS effects were observed throughout acute and repeated-dose toxicity studies. Acute oral, dermal and inhalation studies in experimental animals and case reports of humans ingesting or being dermally exposed to cresols all resulted in observations of CNS effects.

The predominant sources of exposure to cresols for the general population are expected to be orally via ingestion of food. A minor source is through inhalation of air from environmental media in the vicinity of pulp and paper mills.

A number of repeated-dose studies in experimental animals exposed orally or by inhalation to individual isomers or a cresol mixture were available. The lowest oral LOAEL determined was 50 mg/kg bw/d for each of *o*-, *m*- and *p*-cresol, based on CNS effects in rats after they were gavaged with *o*-, *m*- or *p*-cresol for periods of two or 13 weeks. This is considered to be conservative, because CNS effects were observed at much higher doses in dietary (oral feeding) studies. In both an oral reproduction study using *m*-cresol (Neeper-Bradley and Tyl 1989b) and a study in which neonate rats were gavaged on post-natal days 4–21 with *m*-cresol (Koizumi et al 2003), no CNS effects were observed at 30 mg/kg bw/d (nor were any reproductive or developmental effects observed at that dose), and the dose of 30 mg/kg bw/d is determined to be a NOAEL for CNS effects.

Inhalation studies conducted with cresols were limited. The lowest dose associated with adverse effects was observed in a study conducted with mice exposed to *o*-cresol at 9 mg/m^3 for four months. This LOAEC of 9 mg/m^3 was also based on morphological changes in the respiratory tract (including the lungs), effects in the blood and bone marrow, and evidence of liver toxicity in mice (Uzhdavini et al. 1972).[10] Studies of similar or shorter duration at cresol concentrations lower than 9 mg/m^3 in rats and humans showed effects, but they were not considered to be adverse.

The primary source of exposure to cresols for the general population is expected to be via the diet. Based on available data, it is expected that exposure to cresols

[10] The LOAEC of 9 mg/m^3 converted to an intake estimate in mice is 12 mg/kg bw/d for *o*-cresol (as per Health Canada 1994). In the 13-week rat feeding study using *m*-/*p*-cresol, the ATSDR (2008) determined $BMDL_{10}$s of 13.9 and 30.8 mg/kg bw/d based on nasal epithelial hyperplasia in male and female rats, respectively. These $BMDL_{10}$s are 1.2–2.6 times higher than the four-month air intake estimate in the mouse for *o*-cresol. Histopathological changes in the respiratory tract were a common effect observed in both sub-chronic and long-term mouse and rat studies (mice exposed to *o*-cresol via inhalation for four months and to *m*-/*p*-cresol via the diet for two years; rats exposed to *m*-/*p*-cresol in the diet for 13 weeks and two years).

from the diet represents up to 98% of the total intake for all age groups in Canada. Daily intakes of 2.9 (for adults 60+ years) to 22.3 (for non-formula-fed infants of 0–6 months) µg/kg bw in the general population are expected from foods and beverages. However, the risk characterization for cresols focusses on the incremental exposure from anthropogenic sources. Concentrations of cresols in ambient air may be higher in the vicinity of pulp and paper mills. For such mills, comparison of the lowest LOAEC (9.0 mg/m^3 for *o*-cresol) with the upper-bounding concentration of 2.49 µg/m^3 cresols in air (estimated at 600 m from the mill) results in an MOE of approximately 3600. Based on conservative parameters used in modelling concentrations from pulp and paper mills, the above MOE is considered adequate, taking into consideration the limitations in the health effects and exposure databases.

Comparison of the lowest LOAEC (9.0 mg/m^3 for *o*-cresol) to the highest concentration of cresols selected for indoor air (i.e., 1.76 µg/m^3), which could include anthropogenic sources, results in a margin of exposure (MOE) of approximately 5100 for inhalation exposure. This margin is considered adequate to address uncertainties in the health effects and exposure databases.

Upper-bounding estimates of daily intake from inhalation exposure varies between 0.5 (for ≥ 60 yr-old inhaling ambient and indoor air away from point sources; see Appendix 8a) to 1.5 ug/kg bw/d (for 0.4–5 yr-old inhaling ambient air near a point source; see Appendix 8b). These levels are at least 16 700-fold lower than the oral short-term NOAEL of 30 mg/kg bw/d noted above, and several orders of magnitude lower than the $BMDL_{10}$ of 376 mg/kg based on increased incidence of squamous cell papillomas in the forestomach of mice treated with a mixture of *m*- and *p*-cresols.

Table 8-1: Margins of exposure for various exposure scenarios

Exposure scenario	**Exposure route and duration**	**Upper-bounding estimate of exposure**	**Cresol isomer(s): critical effect level**	**Cresol isomer(s): critical effects and duration of study**	**Margins of exposure**
General population	Inhalation – long-term	1.76 µg/m^3 (indoor air)	***o*-cresol:** LOAEC = 9 mg/m^3	***o*-cresol:** Morphological changes in the respiratory tract (including the lungs), effects in the blood and bone marrow, and evidence of liver toxicity	**Approximately 5100**

Exposure scenario	Exposure route and duration	Upper-bounding estimate of exposure	Cresol isomer(s): critical effect level	Cresol isomer(s): critical effects and duration of study	Margins of exposure
				in a 4-month mouse inhalation study	
General population	Inhalation – long-term, point source	2.49 µg/m^3 (pulp and paper mills)	***o*-cresol:** LOAEC = 9 mg/m^3	***o*-cresol:** Morphological changes in the respiratory tract (including the lungs), effects in the blood and bone marrow, and evidence of liver toxicity in a 4-month mouse inhalation study	**Approximately 3600**

Based on the adequacy of margins between upper-bounding estimates of exposure and critical effect levels observed in animal studies with one or more of these compounds, a concern for human health was not identified, and it is proposed to conclude that *o*-, *m*- and *p*-cresol and mixed cresols do not meet the criteria under paragraph 64(*c*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

11.4 Uncertainties in Evaluation of Risk to Human Health

Potential differences in the effects of individual isomers and mixtures of isomers on different species were not further explored, because this is beyond the scope of a Screening Assessment. There was moderate to high confidence in the hazard database, but inhalation studies for short-term exposures were limited, and lacking for longer-term exposures and reproductive/developmental endpoints. The mode of action of carcinogenicity has not been fully elucidated for the isomers or mixtures, and the genotoxic potential of the isomers and mixtures cannot be clearly defined.

Based on an adequate exposure database, which included Canadian data for cresols in most media, confidence in the environmental exposure estimates for

the cresols is moderate. Due to limitations in the methodology used for measuring concentrations, exposure estimates for mixed cresols were either based on the *m*-/*p*-cresol mixture or summing estimates of this mixture with that of *o*-cresol, and sometimes summing the values for each of the individual isomers. Also, given that maximum values or upper-bounding values from the monitoring literature or from the use of modelling (i.e., SCREEN3) were employed, it is likely that exposure estimates are conservative.

12. Conclusion

Considering all available lines of evidence presented in this Screening Assessment, there is low risk of harm to organisms or the broader integrity of the environment from these substances. It is concluded that *o*-, *m*- and *p*-cresol and mixed cresols do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have immediate or long-term harmful effects on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends.

Based on the adequacy of the margins between the upper-bounding estimates of exposure via environmental media for *o*-, *m*- and *p*-cresol and mixed cresols, and critical effect levels associated with one or more of these substances, it is concluded that *o*-, *m*- and *p*-cresol and mixed cresols do not meet the criteria under paragraph 64(*c*) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is concluded that *o*-, *m*- and *p*-cresol and mixed cresols do not meet any of the criteria set out in section 64 of CEPA.

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Appendix A. Cresols dispersion modelling for a pulp and paper mill

Table A-1: Select inputs of SCREEN3

Parameter	Value	Notes
Emission rate (g/s)	0.33	Based on release quantities of 10.4 tonnes/year (Environment Canada 2013b) occurring over 365 days (at 24 hours per day)
Stack[1] height (m)	27.4	Email from Forest Products and Fisheries Act Division to Environment Canada; unreferenced
Stack[1] diameter (m)	0.1	Email from Forest Products and Fisheries Act Division to Environment Canada; unreferenced
Stack[1] gas exit velocity (m/s)	1.4	Email from Forest Products and Fisheries Act Division to Environment Canada; unreferenced
Stack[1] gas exit temperature (K)	373	Email from Forest Products and Fisheries Act Division to Environment Canada; unreferenced
Ambient air temperature (K)	293	Default
Receptor height above ground (m)	1.74	Assumed to represent height of small arboreal terrestrial organisms
Urban/rural option	Urban	Default, facility is situated in an urban setting
Building downwash option	Selected	Default, provides a more conservative scenario (SCREEN3 1995)
Building height (m)	0	Vent height given already included building height
Minimum horizontal dimension (m)	20	Default, represents typical low-rise industrial facility (Law et al. 2004)
Maximum horizontal dimension (m)	100	Default, represents typical low-rise industrial facility (Law et al. 2004)
Simple terrain	Selected	Default, provides a more conservative scenario than using complex terrain (SCREEN3 1995)
Full meteorological conditions	Selected	Default, identifies worst case conditions (SCREEN3 1995)
Terrain height (m)	0	Default, corresponds to one half of the stack height

[1] Stack characteristics are meant to be representative of ventilation system in chemical kraft mills, on the roof of a typical facility. In a typical facility, many vents can emit to the air from various point sources, but only one vent has been assumed in that scenario (limitation of the model).

Table A-2: Ambient concentrations of *o*-cresol in the vicinity of a pulp and paper mill

Distance (m)	1-hour concentration (ug/m^3)	Chronic (1-yr) concentration (ug/m^3)
100	**76.17**	7.62[a]
200	57.96	5.80
400	34.41	3.44
600	24.88	**2.49**[b]
800	17.94	1.79
1000	13.56	1.36
2000	5.471	0.55
3000	3.25	0.33
4000	2.273	0.23
5000	1.735	0.17

[a] Selected for ecological considerations.
[b] Selected for human health considerations

Appendix B. Upper-bounding estimates of daily intake (µg/kg bw/d) of cresols by various age groups within the general population of Canada

Route of Exposure	0–6 mo[a] Breast-milk-fed[b]	0–6 mo Formula-fed[c]	0–6 mo Not formula-fed[c]	0.5–4 yr[d]	5–11 yr[e]	12–19 yr[f]	20–59 yr[g]	≥60yr[h]
Ambient Air[i]	4.31 E-02	4.31 E-02	4.31 E-02	9.23 E-02	7.19 E-02	4.09 E-02	3.51 E-02	3.05 E-02
Indoor Air[j]	4.31 E-01	4.31 E-01	4.31 E-01	9.24 E-01	7.20 E-01	4.10 E-01	3.52 E-01	3.06 E-01
Drinking Water[k]	NA	5.33 E-02	1.33 E-02	6.45 E-03	6.45 E-03	3.37 E-03	2.82 E-03	2.78 E-03
Food and Beverages[l]	NA	NA	2.23 E+01	1.42 E+01	8.53 E+00	4.96 E+00	3.60 E+00	2.93 E+00
Soil[m]	9.00 E-10	9.00 E-10	9.00 E-10	1.45 E-09	4.72 E-10	1.14 E-10	9.52 E-11	9.38 E-11
Total Intake	4.74 E-01	5.28 E-01	2.28 E+01	1.52 E+01	9.33 E+00	5.41 E+00	3.99 E+00	3.27 E+00

Abbreviations: NA, not applicable; mo, months; yr, years.

[a] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0 L of water per day (formula-fed) (intake from water is synonymous with intake from food or 0.2 L/d [not formula-fed]), and to ingest 30 mg of soil per day (Health Canada 1998).

[b] No measured data were identified on the concentration of cresols in breast milk and formula.

[c] Exclusively for formula-fed infants, intake from water is synonymous with intake from food. The concentration of cresols in water used to reconstitute formula was based on drinking water data. There were no data quantifying cresols in formula. Approximately 50% of non-formula-fed infants are introduced to solid foods by 4 months of age, and 90% by 6 months of age (NHW 1990).

[d] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.2 L of water per day, and to ingest 100 mg of soil per day (Health Canada 1998).

[e] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 0.4 L of water per day, and to ingest 65 mg of soil per day (Health Canada 1998).

[f] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 0.4 L of water per day, and to ingest 30 mg of soil per day (Health Canada 1998).

[g] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 0.4 L of water per day, and to ingest 30 mg of soil per day (Health Canada 1998).

[h] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 0.4 L of water per day, and to ingest 30 mg of soil per day (Health Canada 1998).

[i] The sum of the method detection limits of cresols isomers from ambient air sampling (1.23 µg/m^3) was used to calculate the upper-bounding limit of exposure based on 75 ambient air samples collected from 75 homes in the Ottawa Residential Home Study Canada (Health Canada 2003). This represents a 3-hour period for time spent outdoors.

[j] The sum of the 95th percentiles of cresol isomers from indoor air sampling (1.76 µg/m^3) was used to calculate the upper-bounding limit of exposure based on 75 ambient air samples collected from 75 homes in the Ottawa Residential Home Study Canada (Health Canada 2003).

Where cresols were not detected, values were replaced with the detection limit as a non-detect substitution method. This represents a 21-hour period for time spent indoors.

[k] The detection limit of 0.5 µg/L from the City of Montreal drinking water surveillance report for the year 2000 for all three individual cresol isomers was used to calculate the intake from drinking water (Bernier et al. 2000).

[l] Canadian monitoring data for concentrations of cresols in food were identified and were used to estimate dietary intake. Dietary intake estimates from food are based on concentrations in foods that are selected to represent the 12 food groups addressed in calculating intake (Health Canada 1998):

Dairy products: 200 µg/kg in “cheese/butter” (ETL 1991, 1992)
Fats: 200 µg/kg in “cheese/butter” (ETL 1991, 1992)
Fruits: Not detected in Canadian studies (ETL 1991, 1992, 1995)
Vegetables: Not detected in Canadian studies (ETL 1991, 1992, 1995)
Cereal products: 74 µg/kg in “cereal products” (ETL 1991)
Meat and poultry: 420 µg/kg in“canned meats” (ETL 1992)
Fish: Not detected in Canadian studies (ETL 1991, 1992, 1995)
Eggs: Not detected in Canadian studies (ETL 1991, 1992, 1995)
Foods primarily sugar: Not detected in Canadian studies (ETL 1991, 1992, 1995)
Mixed dishes and soups: 340 µg/kg in “canned soup: meat” (ETL 1991)
Nuts and seeds: Not analyzed in Canadian studies (ETL 1991, 1992, 1995)
Soft drinks, alcohol, coffee, tea: 21.25 µg/kg (adjusted from 0.017 ug/mL by applying a density factor of 0.8 g/mL for alcohol) in “beer/wine” (ETL 1991)

Amounts of foods consumed on a daily basis by each age group are described by Health Canada (1998). Daily food intakes were obtained from the 1970–1972 Nutrition Canada Survey.

[m] A soil environmental concentration (i.e., the PEC) of 0.00023 mg/kg dw was estimated for land application of biosolids on an agricultural field, as detailed further in the Ecological Exposure Assessment section.

Appendix C. Upper-bounding estimates of daily intake (µg/kg bw/d) of cresols in air by the general population of Canada near a pulp and paper mill facility

Route of Exposure [a]	0–6 mo Breast-milk-fed	0–6 mo Formula-fed	0–6 mo Not formula-fed	0.5–4 yr	5–11 yr	12–19 yr	20–59 yr	≥60 yr
Ambient Air	8.72 E-02	8.72 E-02	8.72 E-02	1.87 E-01	1.46 E-01	8.28 E-02	7.11 E-02	6.18 E-02
Indoor Air	6.10 E-01	6.10 E-01	6.10 E-01	1.31 E+00	1.02 E+00	5.80 E-01	4.98 E-01	4.33 E-01

Note: See Appendix B for information on receptor characteristics and exposure factors.
Abbreviations: mo, months; yr, years.
[a] The cresols exposure concentration of 2.49 µg/m^3, derived using SCREEN3, was estimated to determine ambient and indoor air exposure intakes for residents within the vicinity of a pulp and paper mill.

Appendix D. Monitoring of cresols related to intensive livestock operations in North America and elsewhere

Table D-1: Cattle facilities

Ref.	Sampling location	Sampling period	Heads	Dist. from source	*o*-cresol (µg/m^3)	*m*-cresol (µg/m^3)	*p*-cresol (µg/m^3)
Borhan et al. 2012 (Dairy)	Central Texas, U.S.(Free-stall operation)	Aug. 2009 and Jan. 2010	460	At the facility	-	-	128
Borhan et al. 2012	Central Texas, U.S.	Aug. 2009 and Jan. 2010	460	Manure lane bedding	-	-	62
Borhan et al. 2012	Central Texas, U.S.	Aug. 2009 and Jan. 2010	460	Bedding area	-	-	-
Borhan et al. 2012	Central Texas, U.S.	Aug. 2009 and Jan. 2010	460	Loafing pen	-	-	230
Borhan et al. 2012	Central Texas, U.S.	Aug. 2009 and Jan. 2010	460	Lagoon -1°	-	-	327
Borhan et al. 2012	Central Texas, U.S.	Aug. 2009 and Jan. 2010	460	Lagoon -2°	-	-	168
Borhan et al. 2012	Central Texas, U.S.	Aug. 2009 and Jan. 2010	460	Settling basin	-	-	66
Borhan et al. 2012	Central Texas, U.S.	Aug. 2009 and Jan. 2010	460	Silage	-	-	318
Borhan et al. 2012	Central Texas, U.S.	Aug. 2009 and Jan. 2010	460	Walkway	-	-	84
Cai et al. 2010[a] (Dairy)	Wisconsin and Indiana, U.S.	Winter and summer[b]	NS	Animal buildings (enclosed barns)	-	-	(3.09–6.31)[c]
Parker 2008 (Dairy)	Lab wind-tunnel analysis[d]	2004; 2006	300	Above WW lagoon	-	-	179; 17.75

Ref.	Sampling location	Sampling period	Heads	Dist. from source	*o*-cresol (µg/m^3)	*m*-cresol (µg/m^3)	*p*-cresol (µg/m^3)
Parker 2008 (Dairy)	Lab wind-tunnel analysis[d]	2004; 2006	300	Above WW treatment lagoon	-	-	405.2; 37.43
Buser et al. 2007	Texas Panhandle, U.S.	NS		Feedlot property line	-	-	0.30
Buser et al. 2007	Texas Panhandle, U.S.	NS		13 km	-	-	"high"
Koziel et al. 2006	Texas, U.S.	March 2004	55 000	16 km	-	-	detect[e]
Wright et al. 2005	Texas, U.S.		50 000	20 m from feedlot	-	-	detect
Wright et al. 2005	Texas, U.S.		50 000	2000 m from feedlot	-	-	detect
McGinn et al. 2003	Lethbridge, AB, Canada	Mar. 23 to Sept. 24, 1999	6000	3 to 200 m from feedlot	0.004	0.002	0.003
McGinn et al. 2003	Lethbridge, AB, Canada	Mar. 23 to Sept. 24, 1999	12 000	3 to 200 m from feedlot	0.029	0.014	0.039
McGinn et al. 2003	Lethbridge, AB, Canada	Mar. 23 to Sept. 24, 1999	25 000 NS	3 to 200 m from feedlot	0.003	0.014	0.020
McGinn et al. 2003	Lethbridge, AB, Canada	Mar. 23 to Sept. 24, 1999	NS	Background[f]	-	-	0.002

[a] Add-on study to the National Air Emission Monitoring Study (NAEMS).
[b] Winter (Dec.-Jan.) and summer (Jul.-Aug.).
[c] Values in parentheses = range.
[d] Concentrations in the wind tunnel at a wind velocity of 1.3 m/min.
[e] "Detected" = Only analytical instrumentation response data provided.
[f] Conc. in air (wind) not going over feedlot.

Table D-2: Swine facilities

Ref.	Sampling location	Sampling period	Heads	Dist. from source	*o*-cresol µg/m^3	*m*-cresol µg/m^3	*p*-cresol µg/m^3
Akdeniz et al. 2013	Minnesota, U.S. (Farrow-	Jul., Sept. and Nov.	NS	Facility (ambient)	< 0.44	-	8.5 (8.2–8.9) [a]

Ref.	Sampling location	Sampling period	Heads	Dist. from source	*o*-cresol µg/m^3	*m*-cresol µg/m^3	*p*-cresol µg/m^3
	to-feeder barns; enclosed barns)	2011					
Akdeniz et al. 2013	Minnesota, U.S.	Jul., Sept. and Nov. 2011	300	Office space	3.4 (3.2–3.5)	-	9.7 (9.5–10.8) [a]
Akdeniz et al. 2013	Minnesota, U.S.	Jul., Sept. and Nov. 2011	300	Gestation room	23.0 (15.5–31.5)	-	57.6 (50.4–65.4) [a]
Akdeniz et al. 2013	Minnesota, U.S.	Jul., Sept. and Nov. 2011	16	Farrowing room	35.3 (22.8–48.9)	-	85.0 (75.8–96.8) [a]
Akdeniz et al. 2013	Minnesota, U.S.	Jul., Sept. and Nov. 2011	450	Nursery room	17.9 (11.6–25.5)	-	42.6 (37.5–48.5) [a]
Cai et al. 2010[b]	Indiana, Iowa, U.S. (Finishing barn and gestation/farrowing barns)	Winter season[c]	NS	In swine gestation room	-	-	69
Feilberg et al. 2010[d]	Mid-Jutland, Denmark	May and June 2009	-Each pen contained 16 pigs	~1 m above the exhaust duct entrance	-	-	17.2 (4.9–30.1)
Koziel et al. 2006	Iowa, U.S. (Finishing barns)	Nov. 2004	4000	-"near plot" at the exhaust fan of 4 deep pit swine barns	-	-	detect[e]
Koziel et al. 2006	Iowa, U.S. (Finishing barns)	Nov. 2004	4000	294 m	-	-	detect

Ref.	Sampling location	Sampling period	Heads	Dist. from source	*o*-cresol µg/m^3	*m*-cresol µg/m^3	*p*-cresol µg/m^3
Blunden et al. 2005	Zebulon, NC —Barham Farm (Farrow-to-wean barns)	Apr. 2002	4000	- In front of barn	-	-	0.56
Blunden et al. 2005	Zebulon, NC —Barham Farm (Farrow-to-wean barns)	Nov 2002	4000	Upwind	-	-	6.18
Blunden et al. 2005	Raleigh, NC — Grinnells Lab	Apr. 2002	NS	In front of barn	-	-	0.10
Blunden et al. 2005	Raleigh, NC — Grinnells Lab	Nov. 2002	NS	Upwind	-	-	ND
Blunden et al. 2005	~Richlands, NC —Howard Farm	June 2002	NS	In front of barn	-	-	8.67
Blunden et al. 2005	~Richlands, NC —Howard Farm	Dec. 2002	NS	Upwind	-	-	30.02
Blunden et al. 2005	Greenville, NC —Stokes Farm	Sept. 2002	NS	In front of barn	-	-	22.67
Blunden et al. 2005	Greenville, NC —Stokes Farm	Jan. 2003	NS	Upwind	-	-	ND
Blunden et al. 2005	~Kingston, NC — Moore	Oct. 2002	NS	In front of barn	-	-	ND

Ref.	Sampling location	Sampling period	Heads	Dist. from source	*o*-cresol µg/m^3	*m*-cresol µg/m^3	*p*-cresol µg/m^3
	Bro.Farm						
Blunden et al. 2005	~Kingston, NC — Moore Bro.Farm	Feb. 2003	NS	Upwind	-	-	7.28
Wright et al. 2005	Texas, U.S. **(**Ventilated finish barn)	.	5000	0.5 m	-	-	detect
Wright et al. 2005	Texas, U.S. **(**Ventilated finish barn)	.	5000	250 m	-	-	detect
Zahn et al. 1997	Iowa, N. Carolina; Oklahoma, U.S.	July 1996	3550	0 m from slurry storage basin	-	-	4230
Zahn et al. 1997	Iowa, N. Carolina; Oklahoma, U.S.	July 1996	3550	25 m from slurry storage basin	-	-	880
Zahn et al. 1997	Iowa, N. Carolina; Oklahoma, U.S.	July 1996	3550	100 m from slurry storage basin	-	-	460

[a] Values in parentheses = range.
[b] Add-on study to the National Air Emission Monitoring Study (NAEMS).
[c] Winter (Dec-.Jan).
[d] Experimental farm; *m*-cresol was measured and used as a surrogate for *p*-cresol.
[e] "Detect" = only analytical instrumentation response data provided.

Appendix E. Concentrations of cresols (CAS RN 1319-77-3) (µg/kg) in food and beverages grown or purchased in Canadian cities

Table E-1: Dairy products

Food Group/Item	Calgary, AB (ETL 1991)	Windsor, ON (ETL 1992)	Ville-Mercier, QC (ETL 1995)
Milk products	ND	ND	NA
Cheese/butter	0.2	0.2	ND
Dairy/Ice cream	NA	NA	ND

Table E-2: Meat & poultry

Food Group/Item	Calgary, AB (ETL 1991)	Windsor, ON (ETL 1992)	Ville-Mercier, QC (ETL 1995)
Fresh beef; Beef/veal	ND	ND	ND
Fresh Pork/Pork	ND	ND	ND
Pork (bacon/sausage); Pork cured	ND	0.17	ND
Lamb-chops	ND	ND	ND
Poultry	ND	ND	ND
Eggs	ND	ND	ND
Organ meat	0.27	1.4	ND
Uncanned meats	ND	0.055	NA
Canned meats	ND	0.42	ND
Luncheon uncanned	NA	NA	ND

Table E-3: Fish

Food Group/Item	Calgary, AB (ETL 1991)	Windsor, ON (ETL 1992)	Ville-Mercier, QC (ETL 1995)
Fresh fish Cod	ND	ND	NA
Freshwater fish	ND	ND	ND
Canned fish oil	ND	ND	ND
Shellfish	ND	ND	ND
Marine fish	NA	NA	ND

Table E-4: Mixed dishes & soups

Food Group/Item	Calgary, AB (ETL 1991)	Windsor, ON (ETL 1992)	Ville-Mercier, QC (ETL 1995)
Canned soup: meat	0.34 µg/mL	ND	ND
Canned soup: pea,	ND	ND	ND

Food Group/Item	Calgary, AB (ETL 1991)	Windsor, ON (ETL 1992)	Ville-Mercier, QC (ETL 1995)
tomato			
Dehydrated soups	ND	0.014	ND

Table E-5: Cereal products

Food Group/Item	Calgary, AB (ETL 1991)	Windsor, ON (ETL 1992)	Ville-Mercier, QC (ETL 1995)
Bread	ND	0.031	ND
Flour Products; Flour/cakes	0.074	0.021	ND
Cereals	ND	ND	ND
Fruit pies	ND	ND	ND
Pasta	ND	0.01	ND

Table E-6: Vegetables

Food Group/Item	Calgary, AB (ETL 1991)	Windsor, ON (ETL 1992)	Ville-Mercier, QC (ETL 1995)
Root vegetables; Potatoes/vegetables	ND	ND	ND
Vine vegetables	ND	ND	NA
Rice/vegetables	NA	NA	ND

Table E-7: Fruits & fruit products

Food Group/Item	Calgary, AB (ETL 1991)	Windsor, ON (ETL 1992)	Ville-Mercier, QC (ETL 1995)
Fruits	ND	ND	ND
Fruit juices; Canned fruit	ND	ND	ND

Table E-8: Fats

Food Group/Item	Calgary, AB (ETL 1991)	Windsor, ON (ETL 1992)	Ville-Mercier, QC (ETL 1995)
Cooking oils; Oil/fats	ND	ND	ND
Peanut butter	ND	ND	ND
Cheese/butter	0.2	0.2	NA

Table E-9: Foods, primarily sugar

Food Group/Item	Calgary, AB (ETL 1991)	Windsor, ON (ETL 1992)	Ville-Mercier, QC (ETL 1995)
Sugar/jams; Sugar/candy	ND	ND	ND

Table E-10: Drinks and alcohol

Food Group/Item	Calgary, AB (ETL 1991)	Windsor, ON (ETL 1992)	Ville-Mercier, QC (ETL 1995)
Coffee/tea	ND	0.005 µg/mL	ND
Soft drinks	0.0085 µg/mL	ND	ND
Wine/beer; Alcohol	0.017 µg/mL	ND	ND
Tap water; Water	ND	ND	ND

Note: Concentrations in µg/kg unless otherwise specified.
Abbreviations: ND, not detected (below detection limit); NA, not applicable/not tested

Appendix F. Goodness of fit statistics for benchmark dose models fitted to the 2-year mouse squamous cell papilloma data for *m*-/*p*-cresol

Model	Chi^2	*p*-value for Chi-square	AIC	Scaled Residuals -Dose 0 mg/kg bw/d	Scaled Residuals -Dose 100 mg/kg bw/d	Scaled Residuals -Dose 306 mg/kg bw/d	Scaled Residuals -Dose 1042 mg/kg bw/d	Accept ?	BMD mg/kg bw/d	BMDL mg/kg bw/d
Quantal-Linear	1.37	0.713	73.28	0.00	0.113	-1.034	0.537	Yes	584	376
Multi-stage: Cancer	1.37	0.713	73.28	0.00	0.113	-1.034	0.537	Yes	584	376
Multi-stage (2-poly)	0.92	0.633	74.47	0.00	0.733	-0.608	0.097	Yes	650	402
Probit	0.82	0.665	74.66	-0.582	0.679	-0.127	-0.006	Yes	782	636
Logistic	0.79	0.674	74.71	-0.626	0.630	-0.039	-0.012	Yes	820	683
Weibull	1.15	0.562	74.72	0.00	0.779	-0.722	0.158	Yes	615	393
Gamma	1.17	0.556	74.77	0.00	0.758	-0.751	0.184	Yes	608	392
Log-Logistic	1.22	0.542	74.79	0.00	0.802	-0.741	0.178	Yes	606	381
Log-Probit	1.03	0.311	76.99	-0.694	0.737	-0.055	0.008	Yes	724	510