Screening Assessment for the Challenge

Phosphonic acid, [[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-, monoethyl ester, calcium salt (2:1)

Chemical Abstracts Service Registry Number
65140-91-2

Environment Canada
Health Canada

September 2011

Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment on Phosphonic acid, [[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-, monoethyl ester, calcium salt (2:1), hereinafter referred to as PADMEC, Chemical Abstracts Service Registry Number[1] 65140-91-2. This substance was identified as a high priority for screening assessment and included in the Challenge initiative under the Chemicals Management Plan because it was found to meet the ecological categorization criteria for persistence, bioaccumulation potential and inherent toxicity to non-human organisms, and was believed to be in commerce in Canada.

The substance PADMEC was not considered to be a high priority for assessment of potential risks to human health, based upon application of the simple exposure and hazard tools developed for categorization of substances on the Domestic Substances List.

PADMEC is an organic substance that is used as an antioxidant/stabilizer in plastics, synthetic fibres, elastomers, adhesives, waxes, oils and fats, to protect against thermo-oxidative degradation. The substance is not naturally produced in the environment. Between 1000 and 100 000 kg of PADMEC were imported into Canada in 2005, and even though none was reportedly in commerce in Canada in 2006, one company has indicated to the Government of Canada that they are considering importing PADMEC in the future. This information indicates that releases of this substance into the Canadian environment could be expected.

Based on expected usage patterns and certain assumptions, most of the substance would end up in waste disposal sites. A small proportion would be released to water through wastewater (0.8%) and a smaller proportion to soil through landfills and land application of biosolids. No releases to air would be expected. The anionic form of PADMEC that exists at ambient pH range is very soluble in water, is not volatile and is expected to adsorb strongly to mineral surfaces. Therefore, PADMEC would likely be found mainly in water and sediments.

PADMEC is expected to degrade slowly in the environmental media where it may be released. It is considered persistent in water and soil. New experimental and modelled data relating to its partitioning between octanol and water suggest that it has a low potential to accumulate in the lipid tissues of organisms. The substance has been determined to meet the persistence criteria but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations*. In addition, new experimental toxicity data suggest that PADMEC has low toxicity to aquatic organisms.

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For this screening assessment, a very conservative exposure scenario was prepared in which the upper end of the range for quantities of PADMEC imported into Canada in 2005 (100 000 kg) was assumed to be used at a single industrial site, with discharge into the aquatic environment. Comparison of the PEC and PNEC indicates a low potential for harm to aquatic organisms from this substance.

Empirical health effects data were not identified for PADMEC. Based on health effects data for an analogue, a high hazard potential has not been identified for PADMEC. As PADMEC is not currently imported or manufactured in Canada at levels above the reporting threshold, the likelihood of exposure to the general population in Canada is considered to be low. Accordingly, risk to the general population is considered to be low.

Based on the information available, it is concluded that PADMEC is 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 human life and health, 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, therefore, concluded that PADMEC does not meet any of the criteria set out in section 64 of the CEPA 1999. PADMEC meets criteria for persistence in water and soil but not the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations*.

This substance will be considered for inclusion in the Domestic Substances List inventory update initiative. In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment.

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or to human health.

Based on the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherent toxicity to aquatic organisms (iT), and were believed to be in commerce in Canada; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE) and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006a), that challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk assessment, and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as high priorities.

The substance phosphonic acid, [[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-, monoethyl ester, calcium salt (2:1) (PADMEC) had been identified as a high priority for assessment of ecological risk as it had been found to be persistent, bioaccumulative and inherently toxic to aquatic organisms and was believed to be in commerce in Canada. The Challenge for this substance was published in the *Canada Gazette* on January 31, 2009 (Canada 2009a, 2009b). A substance profile was released at the same time. The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. As a result of the Challenge, submissions of information pertaining to the properties, bioaccumulation potential, persistence, hazard and uses of the substance were received.

Although PADMEC was determined to be a high priority for assessment with respect to the environment, it did not meet the criteria for GPE or IPE and high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

Screening assessments focus on information critical to determining whether a substance meets the criteria as set out in section 64 of CEPA 1999. Screening assessments examine

scientific information and develop conclusions by incorporating a weight-of-evidence approach and precaution[2].

This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, stakeholder research reports and from recent literature searches, up to July 2010 for the ecological and human health sections of the document. Key studies were critically evaluated; modelling results may have been used to reach conclusions.

When available and relevant, information presented in hazard 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.

This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. The ecological portion of this assessment has undergone external written peer review/consultation. 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 Canada. Approaches used in the screening assessments under the Challenge have been reviewed by an independent Challenge Advisory Panel.

The critical information and considerations upon which the assessment is based are summarized below.

[2] 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 to 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 1999 on the substances in the Chemicals Management Plan (CMP) Challenge Batches 1-12 is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the Controlled Products Regulations, which is part of regulatory framework for the Workplace Hazardous Materials Information System [WHMIS] for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA 1999 does not preclude actions being taken under other sections of CEPA or other Acts.

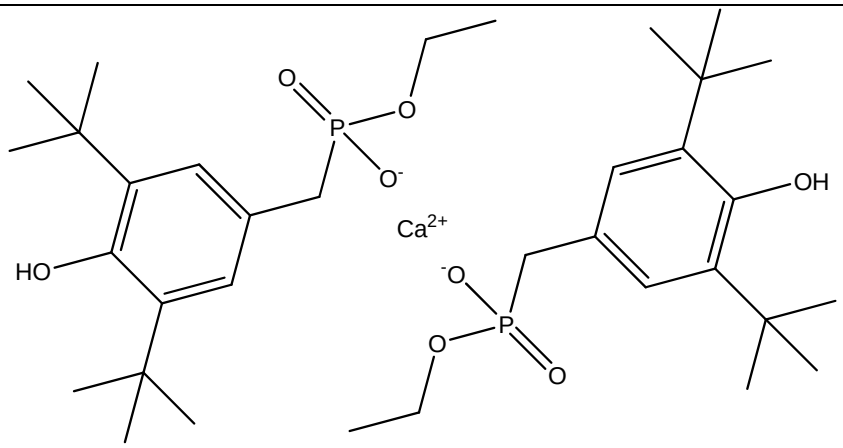
Substance Identity

Substance name

For the purposes of this document, this substance will be referred to as PADMEC, derived from the DSL name.

Table 1. Substance identity for PADMEC

Chemical Abstracts Service Registry Number (CAS RN)	**65140-91-2**
DSL name	**phosphonic acid, [[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-, monoethyl ester, calcium salt (2:1)**
National Chemical Inventories (NCI) names[1]	*phosphonic acid, [[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-, monoethyl ester, calcium salt (2:1)* (TSCA, DSL, AICS, PICCS, ASIA-PAC) *calcium diethyl bis[[[3,5-bis(1,1-dimethylethyl-4-hydroxyphenyl]methyl]phosphonate]* (EINECS) *calcium bis[ethyl (3,5-di-tert-butyl-4-hydroxybenzylphosphonate)]* (ENCS) *[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]phosphonic acid monoethyl ester calcium salt (2:1)* (ECL) *phosphonic acid, [[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl-monoethylester,calcium salt (2:1)* (PICCS)
Other names	*calcium (3,5-di-tert-butyl-4-hydroxybenzyl monoethyl phosphonate); calcium bis(ethyl 3,5-di-tert-butyl-4-hydroxybenzylphosphonate); calcium bis[ethyl (3,5-di-tert-butyl-4-hydroxyphenyl)methanephosphonate]; ethyl 3,5-di-tert-butyl-4-hydroxybenzylphosphonate, calcium salt; IR 1425WL; Irganox 1425; Irganox 1425WL; Irganox I 1425; phosphonic acid, P-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-, monoethyl ester, calcium salt (2:1)*
Chemical group (DSL Stream)	Discrete organics
Major chemical class or use	Phenols
Major chemical sub-class	Phosphonate esters
Chemical formula	$C_{34}H_{56}O_8P_2Ca$

Chemical structure	
SMILES[2]	c1(c(C(C)(C)C)cc(cc1C(C)(C)C)CP(=O)([O])OCC)O[Ca]c1(c(C(C)(C)C)cc(cc1C(C)(C)C)CP(=O)([O-])OCC)O
Molecular mass	694.85 g/mol

[1] National Chemical Inventories (NCI). 2009: AICS (Australian Inventory of Chemical Substances); ASIA-PAC (Asia-Pacific Substances Lists); ECL (Korean Existing Chemicals List); EINECS (European Inventory of Existing Commercial Chemical Substances); ELINCS (European List of Notified Chemical Substances); ENCS (Japanese Existing and New Chemical Substances); PICCS (Philippine Inventory of Chemicals and Chemical Substances); and TSCA (Toxic Substances Control Act Chemical Substance Inventory).

[2] Simplified Molecular Input Line Entry System

Physical and Chemical Properties

Table 2 contains experimental and modelled physical and chemical properties of PADMEC that are relevant to its environmental fate. The studies for log D (log of the distribution coefficient between octanol and water for ionic species; see footnote 1 of Table 2) and water solubility were critically reviewed for validity. These reviews (Robust Study Summaries) are found in Appendix I.

The counterions of PADMEC are expected to become ionized (negatively charged) at environmentally relevant pH values (6 to 9), based on very low first pKa value of 2.38 and high second pKa value of 12.5 (see Table 2). PADMEC is also a salt, and as such, an equilibrium will exist in water between the salt and the dissociated form. Physical and chemical properties for both the non-dissociated and dissociated forms of PADMEC are included in Table 2 below, and are similar for both forms.

Models based on quantitative structure-activity relationships (QSAR) were used to generate data for the physical and chemical properties of PADMEC. These models are mainly based on fragment addition methods, i.e. they rely on the structure of a chemical. Ionizing substances and salts such as PADMEC are difficult to model as most models, such as EPIWIN (2008) and CPOPs (2008), only accept SMILES (see Table 1, footnote

2) for neutral (uncharged) molecules, and do not account for the electrostatic interactions that result from charged species. The model ACD/PhysChem Suite (2009) used to estimate certain properties such as log D and water solubility does account for the ionized form at various pH values (see Table 2). However, this model does not accept salts, so PADMEC was modelled in ACD/PhysChem Suite (2009) as a dissociated molecule as shown in Figure 1 and explained below. The fact that electrostatic interactions are not accounted for in the models increases the uncertainty related to these predicted properties.

Because models such as EpiSuite (2008) and CPOPs (2008) do not accept salts or ionized species, the neutral form of one half of the structure of PADMEC was input into the models to represent the dissociated form (Figure 1) (SMILES in Appendix II). To model the non-dissociated structure, bonding between the calcium ion and the oxygens of the phosphonic acid groups was required (see SMILES in Appendix I). This also results in a neutral species.

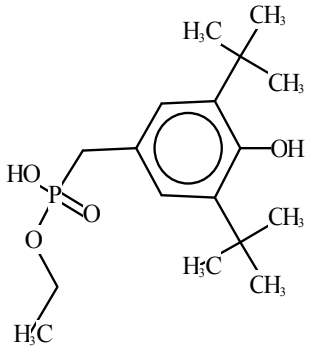


Figure 1. Dissociated, neutral structure of PADMEC used for modelling

The experimental physical-chemical property values in Table 2 take into account the forms of PADMEC that were present in solution during the experiments, that is both the dissociated and non-dissociated forms, although the proportion of each that was present is unknown. Because of the high solubility of PADMEC, it is expected that both the non-dissociated and dissociated forms will exist at an equilibrium in solution.

Table 2. Physical Chemical properties of PADMEC (non-dissociated and dissociated forms)

Form of PADMEC	Type	Value	Temperature (°C)	Reference
Melting point (ºC)				
Non-dissociated	Modelled	90.3	-	MPBPWIN 2008
Dissociated	Modelled	86.4	-	MPBPWIN 2008
Both	Experimental	>260		Study Submission (2010a)
Boiling point (ºC)				
Non-dissociated	Modelled	480	-	MPBPWIN 2008
Dissociated	Modelled	440	-	MPBPWIN 2008
		408	-	ACD/ PhysChem Suite (2009)
Density(kg/m^3)				
Both	Experimental	1.2 x 10^3 (1.2 g/cm^3)	NA	Study Submission (2010a)
Vapour pressure (Pa)				
Non-dissociated	Modelled	6.03 x 10^{-10}	25	MPBPWIN 2008
Dissociated	Modelled	3.25 x 10^{-9}	25	MPBPWIN 2008
Both	Experimental	<0.01	20	Study Submission (2010a)
Henry's Law constant (Pa·m^3/mol)				
Non-dissociated	Calculated[1]	3.40 x 10^{-10}	25	HENRY 2008
Dissociated	Modelled	2.94 x 10^{-8}	25	HENRY 2008
Log D (Distribution coefficient)[2] (dimensionless)				
Non-dissociated	Calculated[3]	1.46 (pH=7.0)	25	-
Dissociated	Modelled	0.15 (pH=6.0) -0.031 (pH=7.0)* -0.054 (pH=8.0)	25	ACD/ PhysChem Suite (2009)
	Calculated[4]	-0.57 (pH=7.0)	25	-
Both	Experimental (K_{ow} study)	0.83 (pH 5.5)[5]	NA	Study Submission (2010b)
Log K_{oc} (Organic carbon-water partition coefficient) (dimensionless)				
Non-dissociated	Modelled[6]	1.84	25	KOCWIN 2008
Dissociated		0.85		
Water solubility (mg/L)				
Non-dissociated	Modelled	1230	25	WSKOWWIN 2008

Form of PADMEC	Type	Value	Temperature (°C)	Reference
Dissociated	Modelled	8222	25	WSKOWWIN 2008
		743 1000 1000	pH = 5.5 pH = 7.0 pH = 8.0	ACD/ PhysChem Suite (2009)
Both	Experimental	2400	20	Study Submission (2010c)
pK_a(Acid dissociation constant) (dimensionless)				
Dissociated	Modelled[7]	2.38 (pK_a 1) 12.5 (pK_a 2)	25	ACD/ PhysChem Suite (2009)

NA = not available
*indicates selected value for modelling
[1] Calculated by HENRY (2008) based on modelled vapour pressure and modelled water solubility of 1230 mg/L.
[2] Log D is the log of the distribution coefficient which takes into account the presence of the ionic species; represents a net amount of the neutral and ionic forms expected to partition into the lipid phase at a given pH.
[3] Based on estimated log K_{OW} (neutral form) of 6.08 (KOWWIN 2008), as well as the estimated pKa of 2.38 (log D = log Kow + pKa – pH).
[4] Based on estimated log K_{OW} (neutral form) of 4.03 (KOWWIN 2008), as well as the estimated pKa of 2.38.
[5] This value is not considered to be reliable since the substance was ionized at the pH of the study.
[6] Based on estimated log D at pH 7 (1.46 for non-dissociated form, -0.031 for dissociated form) and thus takes into account influence of the more soluble ionic forms of the substance but does not account for acid-base pairing or electrostatic interactions with solid substrates.
[7] It was not possible to model the pKa of the non-dissociated form (model does not accept salts).

Sources

PADMEC is not a naturally occurring substance.

Information was collected through surveys conducted for the years 2005 and 2006 under *Canada Gazette* notices issued pursuant to section 71 of CEPA 1999 (Canada 2006b, Canada 2009b). These notices requested data on the Canadian manufacture, import and use of PADMEC.

No companies reported manufacturing, importing or using PADMEC in 2006 (Environment Canada 2009), either above or below the reporting threshold of 100 kg/year. However, in 2009, one company identified themselves as a stakeholder who may import PADMEC into Canada in the future. As of February 2011, this company was still not importing, manufacturing or using this substance in Canada (personal communication of company representative with Ecological Assessment Division, Environment Canada, unreferenced). This company supplied the Government of Canada with empirical physical/chemical property, persistence, bioaccumulation and ecotoxicity studies, which have been summarized in this report. This same company has asked that its identity, as well as its usage pattern data for this substance remain confidential.

In 2005, fewer than four companies reported importing PADMEC in the 1001-100 000 kg/year range, with the usage pattern being confidential (Environment Canada 2007a), and one company reported importing PADMEC in a quantity below 100 kg/year

(Environment Canada 2007a). PADMEC is not used in Canada as a formulant or as an active ingredient in pest control products (Health Canada 2007, 2010).

PADMEC is listed as a Low Production Volume (LPV) chemical in Europe (ESIS 2010). PADMEC is not currently reported (2009 reporting year) under the U.S. Toxics Release Inventory Program (US EPA 2010a). This chemical was reported under the U.S. Toxic Substances Control Act Inventory Update Rule for the following reporting periods: 1986, 1990, 1994, 1998, 2002 and 2006 (US EPA 2010b, US EPA 2006a). In 2006, less than 500 000 pounds (227 000 kg) of this substance was produced in or imported into the U.S. (US EPA 2006a). In 1990, 1994 1998 and 2002, 10 000 to 500 000 pounds (4540 to 227 000 kg) of this substance was produced in or imported into the U.S. (US EPA 2010b).

PADMEC was used in Sweden in 2008 at a volume of 27 tonnes, and was not used in 2007 (0 tonnes) (SPIN 2010). It has also been used in Finland (see Uses section below), though quantity information was not available (SPIN 2010).

Uses

PADMEC use was not reported in Canada in 2006 (see Sources section). The company that submitted information on PADMEC to the Government of Canada (as described in Sources section), has asked that its use pattern data remain confidential. Similarly, the use of PADMEC reported for 2005 is confidential. However, this information was taken into consideration in this assessment. PADMEC is not used in Canada as an active ingredient or as a formulant in pesticide products (PMRA 2007, PMRA 2010).

In Canada, PADMEC is not listed in the *Food and Drug Regulations* as an approved food additive; however, Health Canada has not objected to its use in some plastic food packaging materials (2010 personal communication from Food Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced). PADMEC is not currently listed on the Cosmetic Ingredient Hotlist (Health Canada 2009) and no products containing PADMEC were notified on the Cosmetics Notification System (CNS) database (CNS 2010).

Internationally, PADMEC is used as a high molecular weight antioxidant. It is a stabilizer for organic substrates such as plastics, synthetic fibres, elastomers, adhesives, waxes, oils and fats, to protect against thermo-oxidative degradation (Cradlechem 2003). PADMEC can be used as a stabilizer in polyolefins, particularly polypropylene fibres, as well as in polyesters, crosslinked elastomers, specialty adhesives and tackifier resins (Cradlechem 2010). PADMEC is also used as an esterification catalyst for the preparation of rosin esters (Cradlechem 2010).

PADMEC is included on the US FDA List of Indirect Food Additives Used in Food Contact Substances, as part of the category: antioxidants and stabilizers (US FDA 2010a). PADMEC is approved for use in polypropylene, polyethylene and olefin copolymers and polyethylene phthalate polymers at maximum levels of 0.2-0.3% by weight, and in

adhesives, cement used to seal cans and in resins and polymers used in paperboard at levels not exceeding 0.5% by weight) (US FDA 2010a).

It is used in Finland in the manufacture of rubber and plastic products as a stabilizer (SPIN 2010). Usage volumes were not reported due to confidentiality (SPIN 2010).

Releases to the Environment

A method has been developed by Environment Canada to estimate a substance's losses during different stages of its life cycle, including its fate within a finished product or article (Environment Canada 2008). This method consists of a life cycle analysis and a spreadsheet tool (Mass Flow Tool or MFT) that integrates information on the manufacturing, importation and use data available for the substance. Starting with an identified mass of the substance, each life cycle stage is subsequently evaluated for quantities lost and/or generated. Relevant factors are considered, uncertainties recognized and conservative (i.e. protective of the environment) assumptions may be made during each stage, depending on information available. In this case, most of the assumptions were based on the OECD Emission Scenario Document on Plastics Additives (OECD 2009). This document contains release factors for losses during industrial processes such as compounding and conversion, and losses during the service life of the product. This document states that the release factors are meant to represent reasonable worst-case losses "…so that the estimates should be towards the high end of possible values".

The estimated losses represent the complete mass balance of the substance over its life cycle and include releases to wastewater and other receiving compartments (land, air), chemical transformation, transfer to recycling activities and transfer to waste disposal sites (landfill, incineration). However, unless specific information on the rate or potential for release of the substance from landfills and incinerators is available, the method does not quantitatively account for releases to the environment from disposal. Ultimately, the estimated losses provide a first tier in the exposure analysis of a substance and help to estimate environmental releases and focus exposure characterization in the assessment.

In general, releases of a substance to the environment depend upon various losses from its manufacture, industrial use, and/or consumer/commercial use. These losses can be grouped into seven types: (1) discharge to wastewater; (2) emission to air; (3) loss to land; (4) chemical transformation; (5) disposal to landfill; (6) loss to incineration; and (7) disposal through recycling (i.e., recycling is deemed a loss and not considered further). They are estimated using regulatory survey data, industry data and data published by different organizations. The discharge to wastewater refers to raw wastewater prior to treatment, whether it is on-site industrial wastewater treatment or off-site wastewater treatment. In a similar manner, the loss via chemical transformation refers to changes in a substance's identity that may occur within the manufacture, industrial use, and consumer/commercial use stages, but excludes those during waste management operations such as incineration and wastewater treatment. The loss to land includes unintentional transfer or leakage to soil or paved/unpaved surfaces during the substance's

use and service life (e.g., from the use of agricultural machinery or automobiles). The loss to land, however, does not include transfers subsequent to a substance's use and service life (e.g., land application of biosolids and atmospheric deposition).

The losses estimated for PADMEC over its lifecycle, based on its use in plastics (and based on loss assumptions from OECD (2009), as explained above) are presented in Table 3 (Environment Canada 2010).

Table 3. Estimated Losses of PADMEC during Its Lifecycle

Type of Loss	Proportion (%)	Pertinent Lifecycle Stages
Wastewater	0.8	Industrial use, and consumer/commercial use
Air emission	0	Industrial use, and consumer/commercial use
Land	0[1]	Industrial use, and consumer/commercial use
Chemical transformation	0[1]	NA
Landfill	96.2	Industrial use, and consumer/commercial use
Incineration	3	Industrial use, and consumer/commercial use
Recycling	0[1]	NA

[1]No emission factor was found, so releases were assumed to be zero

PADMEC is estimated to be released to wastewater at 0.8 % of the total quantity imported (used) as a result of industrial and consumer/commercial uses, based on its use as an antioxidant/stabilizer in plastics. This loss occurs mostly during its industrial use, which would be a point-source release (non-dispersive). Assumptions made during this step include losses during raw material handling, compounding operations, and losses during the product service life. The majority of PADMEC is estimated to be lost through waste disposal (i.e., incineration 3% (of which 100% is assumed to be chemically transformed), and landfill 96.2%).

Releases to wastewater during the consumer/commercial use of items containing PADMEC are estimated to account for one quarter of the total releases of PADMEC to wastewater. These losses would occur gradually over time and be widely dispersed in the environment, rather than point-source releases.

The above loss estimates indicate that PADMEC has a potential for release to the environment. In general, wastewater is likely a common source for releases of this substance to water and a potential source to soil through the subsequent waste management of sludge. Landfills have the potential to leach substances into groundwater or there may be releases of substances to the atmosphere. Due to its negligible volatility, releases of PADMEC to the atmosphere would not be significant. Also, as PADMEC is expected to adsorb strongly to mineral surfaces (see Environmental Fate section), leaching from landfill sites or from soil is not expected to be significant.

Environmental Fate

Based on its high water solubility and very low log D and log K_{OC} (Table 2) and potential, releases to wastewater (see Table 3), it would be expected that PADMEC be found mainly in water. However, phosphonates are known to adsorb very strongly to almost all mineral surfaces due to electrostatic interactions, (Nowack 2003). Therefore, most of the PADMEC released to water is expected to end up in sediments. The relatively low acid dissociation constant (pK_a) of 2.38 for the PADMEC phosphonate group indicates that, at environmentally relevant pH values (pH 6-9), the majority of PADMEC found in water will be in dissociated, ionized form.

If PADMEC is used in plastics or for any other use that generates solid wastes, it will end up in landfill sites through waste disposal (Table 3). PADMEC would tend to remain in the landfill sites, due to the high adsorption of phosphonates to mineral surfaces, and their low biodegradation potential (Nowack 2003).

PADMEC does not volatilize to air from soil or water as indicated by its negligible volatility and Henry's Law constant. This substance is not expected to be released directly to air or to soil (see Table 3). The assumptions of no degradation in water and soil for this substance are supported by the assessment of its persistence in these media, as presented below.

Persistence and Bioaccumulation Potential

Environmental Persistence

Empirical ready biodegradation data shown in Table 4a indicate that 1% and 26 % of PADMEC is degraded (depending on the concentration tested) over 28 days in a ready-biodegradation test. The robust study summary for this study is included in Appendix I. It should be noted that there is some uncertainty about the identity of the substance used in this study: the test substance was identified only by its trade name and the purity was not reported. Also, the study authors used an emulsifier to achieve a better distribution in the medium due to the reported poor solubility of the test substance. However, data shown in Table 2 of this screening assessment report indicates that PADMEC is highly soluble in water. It is likely that the test substance was electrostatically adsorbing to the mineral medium used in the test system, due to its negative charge at ambient pH range.

Table 4a. Empirical data for biodegradation of PADMEC

Method	Degradation value	Degradation endpoint	Test Duration	Reference
OECD Method 301B	1% (21 mg/L)[1] 26% (11 mg/L)[1]	%$ThCO_2$	28 days	Study Submission 2010d

[1] - % biodegradation at given concentration of test substance

The above test data is consistent with data for other phosphonates, which show little to no biodegradation in test and natural systems (Nowack 2003).

Given the uncertainty associated with the empirical data shown in Table 4a, a QSAR-based weight-of-evidence approach (Environment Canada 2007b) was applied using the degradation models shown in Table 4b below. Given the ecological importance of the aquatic compartment, the fact that most of the available models apply to this compartment and the fact that PADMEC is expected to be released to the aquatic compartment (see Table 3), degradation in the aquatic compartment was primarily examined. Table 4b summarizes the results of available QSAR models for degradation in water.

It should be noted that the BIOWIN (2008) model, which is based on structural fragments, does not include the phosphonate group in its training set; the structural fragments that that are represented include: aromatic alcohol and carbon with 4 single bonds and no hydrogens.

Table 4b. Modelled data for degradation of PADMEC[1] in water

Fate Process	Model and model basis	Model Result and Prediction	Extrapolated Half-life (days)
WATER			
Hydrolysis	HYDROWIN 2008[2]	NA; structure out of model domain	NA
Primary biodegradation			
Biodegradation (aerobic)	BIOWIN 2008[2] Sub-model 4: Expert Survey (qualitative results)	3.1[3] "biodegrades fast"	≤ 182
Ultimate biodegradation			
Biodegradation (aerobic)	BIOWIN 2008[2] Sub-model 3: Expert Survey (qualitative results)	2.1[3] "biodegrades slowly"	≥ 182
Biodegradation (aerobic)	BIOWIN 2008[2] Sub-model 5: MITI linear probability	-0.05[4] "biodegrades very slowly"	≥ 182
Biodegradation (aerobic)	BIOWIN 2008[2] Sub-model 6: MITI non-linear probability	0.007[4] "biodegrades very slowly"	≥ 182
Biodegradation (aerobic)	TOPKAT 2004 Probability	Structure outside of model domain	NA
Biodegradation (aerobic)	CATABOL (2004-2008) % BOD (biological oxygen demand)	0.014 "biodegrades very slowly"	≥ 182

NA = not applicable
[1] The dissociated form of PADMEC was used for modelling (see Figure 1)
[2] EPIsuite (2008)
[3] Output is a numerical score from 0 to 5
[4] Output is a probability score.

Both the experimental (Table 4a) and modelled (Table 4b) ultimate biodegradation results suggest that PADMEC will not biodegrade quickly in the environment. PADMEC also contains structural features that suggest that it is likely to be persistent: two tert-butyl groups on each phenolic ring, highly branched structures that provide stability, as well as the C-P bond which also has high stability (Nowack 2003).

Using an extrapolation ratio of 1:1: 4 for a water: soil: sediment biodegradation half-life (Boethling et al. 1995), the ultimate biodegradation half-life for PADMEC in soil is also >182 days and in sediment is >365 days, indicating that PADMEC is expected to be persistent in soil and sediment.

Based on the empirical and modelled data (see Tables 4a and 4b), PADMEC meets the persistence criteria in water and soil (half-lives ≥ 182 days) and in sediment (half-life ≥ 365 days) as set out in the *Persistence and Biaccumulation Regulations* (Canada 2000). This substance is not expected to be found in air.

Potential for Bioaccumulation

New experimental and modelled log D values for PADMEC that take into consideration its ionic character suggest that it has low potential to bioaccumulate in biota (see Table 2).

Table 5a presents empirical bioconcentration factor (BCF) values from one study conducted with fish. The robust study summary is included in Appendix I. Based on a plot showing concentration of PADMEC in fish tissue over time, the steady-state for bioconcentration seems to be reached after 6 weeks. Therefore, the BCF values at 6 weeks are reported in Table 5a. The mean BCF is 30.5 L/kg.

Table 5a. Empirical data for bioconcentration of PADMEC

Test organism	Test duration	BCF value wet weight (L/kg)	Reference
Fish (Carp)	6 weeks[1]	10.3, 20.6 (exposure concentration of 2.5 ppm) 38.8, 52.3 (exposure concentration of 0.27 ppm)	Study Submission 2010e

[1] BCF values at steady-state (6 weeks) are reported here

Because only one experimental BCF study for PADMEC was available, a predictive approach was applied using available bioaccumulation factor (BAF) and BCF models as shown in Table 5b below.

According to the *Persistence and Bioaccumulation Regulations* (Canada 2000) a substance is bioaccumulative if its BCF or BAF is $\geq$ 5000. Measures of BAF are the preferred metric for assessing bioaccumulation potential of substances. This is because BCF may not adequately account for the bioaccumulation potential of substances via the diet, which predominates for substances with log K_{OW} > ~4.0 (Arnot and Gobas 2003). Kinetic mass-balance modelling is in principle considered to be the most reliable method for predicting the bioaccumulation potential, because it allows for metabolism correction (Arnot et al. 2008). However, since the ionized form of PADMEC, which predominates at environmentally relevant pH values, has a very low log D (<1), it is not expected to be taken up via the diet (gill uptake will predominate), and therefore the BAF and BCF for PADMEC are expected to be essentially the same.

It was not possible to model BCF and BAF values for PADMEC using the two Arnot-Gobas mass-balance based sub-models within the BCFBAF Program of EPI Suite (2008), which take into account metabolism, because ionizing substances are outside of the domain of these sub-models. Therefore, only the regression-based BCF result from BCFBAF (2008) is shown in Table 5b. The log D of -0.031 at pH 7 (see Table 2) was input into the BCF models whose results are shown in Table 5b. The BCFBAF (2008) program automatically assigns a log BCF of 0.50 (BCF = 3.16) to ionic compounds with log K_{OW} less than 5.0.

Table 5b: Modelled data for bioaccumulation in fish of PADMEC

PADMEC structures modelled	Model and model basis	Endpoint	Value wet weight (L/kg)	Reference
Both dissociated and non-dissociated	BCF, maximum	BCF	3.16	BCFBAF 2008
Both dissociated and non-dissociated	BCF, maximum	BCF	10.1	Dimitrov et al. 2005

The Dimitrov et al. (2005) model prediction is valid, as the structures of PADMEC (both dissociated and non-dissociated) were within the parameter domain, and scored 71 and 73% within the structural domain of this model, respectively, indicating the model training set contained substances with moderate similarity to PADMEC.

The available empirical data and modelled values (Tables 5a,b) indicate that PADMEC is expected to have low bioaccumulation potential. Therefore, PADMEC does not meet the bioaccumulation criterion (BAF $\geq$ 5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential to Cause Ecological Harm

Ecological Effects Assessment

A - In the Aquatic Compartment

Experimental toxicity data for PADMEC are summarized in Table 6 and described below, and a discussion of available modelled data is also given below. The experimental and modelled data indicate that PADMEC has low acute toxicity to aquatic organisms.

Table 6. Empirical toxicity data for PADMEC

Test organism	Type of test	Endpoint	Value (mg/L)[1]	Reference
Aerobic waste water bacteria	Acute 3 hours	IC_{20}[2] IC_{50}[2]	>100 >100	Study submission 2010f
Algae *(Scenedesmus subspicatus)*	Acute & Chronic (72 hours)	EC_{50}[3] NOEC[4]	>100 100	Study submission 2010g

Water flea (Daphnia magna)	Acute (24 hours)	EC_{50}[3] LOEC[5] NOEC	510 320 180	Study submission 2010h
Zebra fish (*Brachydanio rerio)*	Acute (96 hours)	LC_{50}[6] LOEC[5] (survival) LOEC[5] (sublethal effects)	>100 100 18	Study submission 2010i

[1] All values are based on nominal concentrations (concentrations were not measured).
[2] IC_X – The inhibiting concentration for a specified percent effect. A point estimate of the concentration of a test substance that causes X % reduction in a quantitative biological measurement such as growth rate.
[3] EC_X – The concentration of a substance that is estimated to cause some effect on X % of the test organisms.
[4] 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.
[5] LOEC – The Low Observed Effect Concentration is the lowest concentration in a toxicity test that caused a statistically significant effect in comparison to the controls.
[6] LC_X – The concentration of a substance that is estimated to be lethal to X % of the test organisms.

In all of the above toxicity studies (see Table 6), with the exception of the algae study, the test substance (as identified by its trade name) was described as practically insoluble or poorly soluble. Given the high measured and modelled solubility of this substance (see Table 2), this may be cause to question the reliability of these studies. The algae study did not provide a description of the test substance's solubility, but stated that "The test substance was homogeneously distributed in the test vessels at all test times and test concentrations." In the daphnia study an emulsifier was used (alkylphenol-polyglycol-ether) as a solubility aid. The bacteria study stated that "The substance was not dissolved but distributed in the test medium." In the zebra fish study, it was noted that "Initially, a slight deposit was observed in all test concentrations. After 48 h exposure the test substance appeared homogeneously distributed in all test concentrations." A robust study summary for the zebra fish study is included in Appendix I, as this study was used for derivation of the predicted no effect concentration (PNEC) (see below).

The purity of the test substance was not described in the above studies, except for the algae study, in which the substance was identified by its trade name and was indicated to be >95% pure (impurities not identified). Concentrations of the test substance in the test replicates were not measured in any of the above studies. All of the studies summarized in Table 6 are considered to be of low reliability, due to reasons including the above-described issues relating to the substance identity, solubility and lack of measured concentrations.

In the zebra fish study, the nominal concentrations tested were 10, 18, 32, 58 and 100 mg/L (concentrations were not measured). Mortalities were only observed at the 100 mg/L concentration. There were two mortalities out of a group of 10 fish at this concentration after 24 hours and the number of mortalities did not increase after 48, 72 or 96 hours. Therefore, the LOEC for survival is 100 mg/L (nominal). However, there was no dose-response relationship, and therefore, it is questionable whether the observed mortalities were caused by the test substance. Sublethal effects were also observed during the study: A slight effect on swimming behaviour was noted at the 18 and 32

mg/L concentrations, with moderate and severe effects noted at 58 and 100 mg/L, at 48, 72 and 96 hours. Also, severe effects on equilibrium were noted at the 58 and 100 mg/L concentrations and moderate to severe effects on respiratory function were noted at 100 mg/L. Based on these sublethal effects, which showed increasing severity of effects with concentration, the LOEC is 18 mg/L for effects on swimming behaviour.

A range of aquatic toxicity values were obtained from the QSAR models ECOSAR (2008) and CPOPs (2008). PADMEC was outside of the model domain of TOPKAT (2004). The training sets of AIEPS (2003-2007) and the OECD QSAR Application Toolbox (v. 1.1.02) (OECD 2008) were also not considered to be adequate for PADMEC, and so the results from these models are not further discussed.

Both the log K_{ow} and molecular weight of PADMEC are within the applicability domains of ECOSAR (2008). PADMEC was modelled in ECOSAR (2008) as a phenol and as a neutral organic, however, these training sets are not adequate for PADMEC, as they do not contain substances with log K_{ow} values < 1, and they do not contain substances that are chemically similar to PADMEC such as salts of phosphonate esters.

In CPOPs (2008), PADMEC was modelled as a "reactive, unspecified", which is a group that encompasses all substances which CPOPs estimates will have higher toxicity than baseline narcotics. CPOPs (2008) does not contain a more specific structure-activity relationship (SAR) appropriate for this substance (e.g., such as the phenols group in ECOSAR (2008)). The toxicity estimate is based on PADMEC's toxicity being higher than that of a baseline narcotic with similar K_{OW}. The CPOPs (2008) results for both daphnid and fish acute values indicate that the toxicity of PADMEC is lower than 7000 mg/L. This modelled toxicity value indicates that PADMEC is likely to have low acute toxicity to aquatic organisms (acute LC/EC_{50}s > 10 mg/L), which is consistent with the empirical data shown in Table 6.

A conservative predicted no-effect concentration (PNEC) for aquatic organisms was derived from the lowest empirical aquatic toxicity value available – the 96 hour LOEC for Zebra fish (*Brachydanio rerio*) of 18 mg/L, based on sublethal effects (swimming behaviour) (Table 6). This value was selected as the critical toxicity value, and divided by an assessment factor of 100 to account for interspecies and intraspecies variability in sensitivity, to estimate a long-term no-effects concentration from a short-term study, and to account for uncertainties and limitations of the toxicity data set, to give a PNEC value of 0.18 mg/L. Given the expected high persistence of PADMEC in the environment (see Persistence and Bioaccumulation section), chronic exposure would be expected to occur.

B - In Other Environmental Compartments

No ecological effects studies were found for this substance in media other than water.

Ecological Exposure Assessment

No data concerning concentrations of PADMEC in water in Canada have been identified; therefore, environmental concentrations were estimated from available information, including estimated substance quantities, release rates, and size of receiving water bodies.

A – Industrial Release

Aquatic exposure to PADMEC is expected if the substance is released from industrial use to a wastewater treatment plant and the treatment plant discharges its effluent to a receiving water body. The concentration of the substance in the receiving water near the discharge point of the wastewater treatment plant is used as the predicted environmental concentration (PEC) in evaluating the aquatic risk of the substance. It can be calculated using the equation

$$C_{water-ind} = \frac{1000 \times Q \times L \times (1 - R)}{N \times F \times D}$$

where

$C_{water-ind}$:	aquatic concentration resulting from industrial releases, mg/L
Q:	total substance quantity used annually at an industrial site, kg/yr
L:	loss to wastewater, fraction
R:	wastewater treatment plant removal rate, fraction
N:	number of annual release days, d/yr
F:	wastewater treatment plant effluent flow, m^3/d
D:	receiving water dilution factor, dimensionless

A highly conservative industrial release scenario was used to estimate the aquatic concentration of the substance. This scenario is hypothetical and is made conservative (i.e., protective of the environment) by assuming that 100 000 kg of PADMEC, which is the top end of the 1000-100 000 kg range of the substance reported to be used by Canadian industry in 2005 (Environment Canada 2007a) (see Sources section), is used by one single industrial facility at a small, hypothetical site and the loss to a local wastewater treatment plant (WWTP) is 0.65% of the total quantity, resulting from raw material handling and compounding operations. Such a small site is selected to have a WWTP effluent flow at the 10^{th} percentile (3 456 m^3/d) of the WWTP discharge rates across Canada. The scenario also assumes that the release occurs 250 days per year, typical for small and medium-sized facilities, and the receiving water dilution factor is at its minimum value of one (no dilution). The use quantity of 100 000 kg is highly conservative considering that no PADMEC was reported to be in commerce in Canada in 2006 (Environment Canada 2009).

This scenario assumes the WWTP removal rate of PADMEC is 50%, which is considered to be conservative, as phosphonates adsorb very strongly onto almost all mineral surfaces, due to ionic interactions (Nowack 2003). The elimination of phosphonates during wastewater treatment was found to be very high, even with high concentrations of phosphonates present (Nowack 2003). However, the studies cited in Nowack (2003) did not investigate PADMEC specifically.

Based on the above assumptions, this very conservative scenario yields an aquatic concentration of PADMEC of 0.38 mg/L.

B – Consumer Product Release

A release scenario based on uses of manufactured products containing PADMEC was not performed, as these releases would be expected to be widely dispersed compared to concentrated point-source releases produced by industrial operations. PADMEC is used as an antioxidant and thermal stabilizer in a variety of products, including in food contact applications (see Uses section). Releases of PADMEC to the environment (wastewater)

from consumer/commercial uses would be expected to account for approximately 25% of total releases to wastewater, and would be dispersed over wide areas, as described in the Releases to the Environment section.

Characterization of Ecological Risk

The approach taken in this ecological screening assessment was to examine relevant information and develop conclusions based on a weight-of-evidence approach and using precaution, as required under CEPA 1999. Lines of evidence considered include results from a conservative risk quotient calculation, as well as information on persistence, bioaccumulation, toxicity, sources and fate of the substance.

PADMEC is expected to be persistent in water and soil, and is expected to have a low bioaccumulation potential, because of the low log D of the ionized form of this substance, which will predominate in water at ambient pH. Once released into the environment, it will be found mainly in water and sediments. Based on limited toxicity data, it has also been demonstrated to have low potential for toxicity to aquatic organisms.

A risk quotient analysis, integrating conservative estimates of exposure with toxicity information, was performed for the aquatic medium to determine whether there would be potential for ecological harm in Canada. The very conservative industrial generic exposure scenario presented above yielded a predicted environmental concentration (PEC) of 0.38 mg/L for aquatic ecosystems. A predicted no-effect concentration (PNEC) of 0.18 mg/L for aquatic organisms was derived from the empirical toxicity value for Zebra fish, after applying an assessment factor (see Ecological Effects Assessment section). The resulting risk quotient (PEC/PNEC) is 2.1. Recognizing the very conservative assumptions used in the exposure scenario, comparison of the PEC and PNEC indicates a low potential for harm to aquatic organisms from industrial discharge of PADMEC into water.

Uncertainties in Evaluation of Ecological Risk

Uncertainties in this risk assessment exist due to a lack of data on some physical and chemical properties of PADMEC, including its acid dissociation constant, Henry's Law constant and solids-water partition coefficient, and also the low quality of some of the available empirical data. Modelled data were used to fill critical data gaps for physical/chemical properties, biodegradation, bioaccumulation and exposure. The structure of PADMEC is not well represented in many QSAR and bioaccumulation models, and is ionized as well, which increases the uncertainty associated with the modelled results. The bioaccumulation modelling is conservative, as metabolism is not taken into account, which could reduce the bioaccumulation potential of the substance. The results of the empirical bioaccumulation testing are also consistent with what would be expected for PADMEC given its physical-chemical properties and structure.

Uncertainties are also present due to the lack of information on environmental concentrations of PADMEC in Canada. However, the current lack of manufacturing and importation into Canada suggests low releases into the Canadian environment. Uncertainties are also associated with the fraction of the substance released during use. These uncertainties were addressed by making conservative assumptions when estimating releases.

The experimental concentrations associated with toxicity to aquatic organisms have an additional source of uncertainty in that the studies only reported nominal, not measured concentrations in solution, and most also reported the test substance being poorly soluble, despite a high measured and modelled solubility. Despite this, the available empirical data indicate that PADMEC is not highly hazardous to aquatic organisms. Modelled toxicity results also pointed to a low hazard to aquatic organisms, however, the structure of PADMEC was not well represented in the model training sets, which increases the uncertainty associated with these results.

Given the use of this substance in other countries, such as in the US in indirect food contact applications (US FDAa 2010, see Uses Section), it is possible that PADMEC is entering the Canadian market as a component of manufactured items and/or consumer products. Available information is currently not sufficient to derive a quantitative estimate that would help determine the importance of this source. However, it is anticipated that the proportions of PADMEC released to the various environmental media would not differ from those estimated here (see Releases to the Environment section).

Potential to Cause Harm to Human Health

Exposure Assessment

Empirical data on concentrations of PADMEC in environmental media in Canada were not identified. Concentrations in environmental media were not estimated but are expected to be low since overall use of PADMEC in Canada was reported as being below the threshold of 100 kg per year in 2006 (Environment Canada 2009), and the likelihood of release to the environment is minimal. Therefore, the likelihood of exposure of the general population in Canada to this substance is considered to be low.

PADMEC may be present in low quantity in food packaging as a result of its function as an antioxidant in plastics. No empirical data monitoring levels of PADMEC in food packaging or in food have been identified. Exposure via food packaging is expected to be low based on its low overall use.

Empirical data on concentrations of PADMEC in consumer products were not identified.

Health Effects Assessment

A summary of the available information on health effects of PADMEC is provided in Appendix III.

No classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity or in-depth reviews of the health effects of PADMEC were identified. However, Health Canada has issued several letters of no objection for specific uses of PADMEC as a component of various food packaging materials (2010 personal communication from Food Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced), similar to limits established by the US Food and Drug Administration (US FDA 2010a) and the European Commission (EUROPA 2008).

No mutagenic potential was observed in Ames assays tested with PADMEC in the presence or absence of metabolic activation (S9).[3] No activity was observed in an in vivo nucleus anomaly test in Chinese hamsters orally administered PADMEC for 2 consecutive days. In the only identified repeated-dose toxicity study, an oral lowest-observable-effect level (LOEL) of 6000 ppm (equivalent to 300 mg/kg-bw per day; based on Health Canada 1994) was identified based on a slight decrease in body weight gain and reduced grooming activity in both sexes of rats and elevated serum alkaline phosphatase levels in male rats administered PADMEC in diets at 0, 700, 2000 or 6000 ppm (equivalent to 0, 35, 100 and 300 mg/kg-bw per day respectively; based on Health Canada 1994) for 13 weeks. PADMEC was not an irritant to eyes. For skin, only mild irritation was observed on the abraded skin, which may have been due to the abrasion process. No empirical reproductive and developmental toxicity studies were identified. PADMEC showed no estrogenic potential based in an in vitro yeast two-hybrid assay (Ogawa et al. 2006). Predictive (Q)SAR models (TOPKAT 2004; CASETOX 2008; DEREK 2008; Model Applier 2008; Toxtree 2009) on PADMEC generated negative results for carcinogenicity and genotoxicity and predominately negative results for reproductive and developmental toxicity (Appendix IV).

Structurally similar substances were examined to further inform the assessment of potential health effects associated with exposure to PADMEC (Appendix V).

Phosphonic acid, [[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-, diethyl ester (CAS# 976-56-7) was considered an appropriate analogue based on its structural similarity with PADMEC, as demonstrated by a Tanimoto association coefficient of 72% between PADMEC and this substance (SciFinder; CAS 2010). PADMEC is regulated and approved by the US FDA to be used as a food contact substance (US FDA 2010b,c). However, no empirical data were identified.

[3] Toxicity studies not referenced were obtained from Food Packaging Materials and Incidental Additives Section of Health Canada. References to these data cannot be identified due to confidentiality (July 2010 personal communication from Food Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

Another analogue identified for PADMEC is Phenol, 4,4',4''-[(2,4,6-trimethyl-1,3,5-benzenetriyl)tris(methylene)]tris[2,6-bis(1,1-dimethylethyl)- (CAS# 1709-70-2), which is also commercially known as Irganox 1330, Ethanox 330 or Ionox 330. This analogue has a similar use pattern as PADMEC, a 61% structural similarity in SciFinder when compared to PADMEC (CAS 2010) and is associated with available empirical data. Additionally, it was determined that it has physico-chemical properties (i.e. molecular weight, physical state, vapour pressure) which fell within range of those associated with PADMEC.

Toxicity studies identified for Irganox 1330 are summarized in Appendix VI. Negative results were observed in *in vitro* genotoxicity studies in Ames tests (Ciba-Geigy 1992b; Akita University 1984). No treatment-related tumours were observed in several chronic 2-year toxicity studies conducted in rats, mice and dogs (Shell Research 1968a,b, 1969). In terms of repeated-dose toxicity, a subchronic lowest LOEL was determined to be 31600 ppm (equivalent to 1600 mg/kg-bw per day; based on Health Canada 1994) based on reduced body weights in female rats when male and female rats were orally administered Irganox 1330 in diets at 0 to 31600 ppm for 90 days (Stevenson et al. 1965). The long-term lowest LOEL was 10000 ppm (equivalent to 500 mg/kg-bw per day; based on Health Canada 1994) based on decreased body weights and organ weights in female rats when male and female rats were orally administered Irganox 1330 in diets at 0 to 10000 ppm for 2 years (Shell Research 1968a). No reproductive or developmental toxicity was observed in a three generation study conducted in rats (Shell Research 1970).

The confidence in the toxicity database for PADMEC is considered to be low as very limited empirical data were identified. However, the use of modelling and data from an analogue substance helped to increase confidence in the hazard assessment for PADMEC.

Characterization of Risk to Human Health

Limited empirical data identified for PADMEC, (Q)SAR modeling and empirical data from an analogue did not indicate a high hazard potential. There is no evidence of mutagenicity, carcinogenicity, reproductive or developmental toxicity for PADMEC or its analogue. In terms of repeated-dose toxicity, the major effect was reduced body weight in rats for PADMEC and its analogue Irganox 1330. The critical LOEL was 300 mg/kg-bw per day based on a slight decrease in body weight gain and reduced grooming activity in both sexes of rats and elevated serum alkaline phosphatase levels in male rats in a 13-week oral PADMEC study.

There was no report of industrial activity in 2006 for PADMEC above the reporting threshold of 100 kg per year (Environment Canada 2009) and the likelihood of exposure of the general population to PADMEC from environmental media, food or consumer products is expected to be low. Accordingly, risk to the general population is considered to be low.

Uncertainties in Evaluation of Risk to Human Health

Only oral toxicity studies were identified for PADMEC. Inhalation and dermal toxicity studies and long term oral toxicity data were not identified. An analogue substance was used to determine consistency of effects due to treatment with PADMEC and extrapolate long term oral toxicity for PADMEC. However, inhalation and dermal toxicity data were also lacking for the analogue. There is uncertainty when extrapolating from an analogue with regards to the hazard potential for PADMEC.

The lack of Canadian data for PADMEC in environmental media, food and consumer products is a source of uncertainty in determining exposure of the general population of Canada. However, concern associated with this uncertainty is low considering the low reported industrial activity and expected minimal presence of PADMEC in the environment.

Conclusion

Based on the information available, it is concluded that PADMEC is 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. Additionally, PADMEC meets the criteria for persistence but does not meet the criteria for bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Based on the information available, it is concluded that PADMEC is 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 human life or health.

Therefore, it is concluded that PADMEC does not meet any of the criteria under section 64 of CEPA 1999.

This substance will be considered for inclusion in the Domestic Substances List inventory update initiative. In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment.

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Appendix I - Robust Study Summaries

1. Water Solubility

Reference (Study ID): 11165-65140912-001 (study reference is confidential)

Test Substance

Identity: Substance identified only by its trade name.

Remarks: No details provided on purity of the test substance.

Method

Method: Adapted from EEC directive 84/449 A.6 (Flask method)
GLP: Yes [ ] No[x] not specified
Year: *(study performed)* 1992

Test Conditions: *(Detail and discuss any significant protocol deviations.)*

Test solution: 5.0378 g of test substance in 500 mL Millipore water SQS HPLC quality
Saturation temperature: 30 °C
Saturation time: 24 h
Equilibration temperature: 20 °C

Equilibration time: 24 h
Analytical method: photometric determination at 276 nm

Only the study summary was provided, so several of the mandatory test report items (as specified in OECD Guideline 105) were not included in the report including: Preliminary test data, the individual analytical determinations and the average for different flasks which were in agreement, the pH of each sample, evidence of any chemical instability of the substance.

Results/Conclusions

Value (mg/L) at temperature (^{o}C): 2.4 g/L
pH value and concentration at temperature (^{o}C): not provided

Remarks:

Reliability: Low reliability

Remarks: Documentation insufficient for assessment

2. Partition Coefficient (log D)

Reference: 11165-65140912-002 (study is confidential)

Test Substance:
Identity: Substance identified only by its trade name.
Remarks: Purity of test substance not discussed

Method: Shake-flask; not a standard method
GLP: Yes [ ] No[X]
Year: 1989

Test Conditions: *(Detail and discuss any significant protocol deviations.)*
-The test flasks were only shaken for 1 hour before being centrifuged at 2700 g to separate the phases (According to OECD 107, the test flasks should be shaken for 24 hours.)
- The test methods are not fully described (the concentrations of test substance that were tested, how many concentrations were tested, whether duplicates were used, etc.)

Results
Log D: -0.08 at pH 5.5
Temperature (^{o}C): 25 °C
Remarks: The test substance will be ionized at the pH of the test, since the estimated pKa of this substance is 2.4 (ACD/ PhysChem Suite 2009). This adds uncertainty to the partition coefficient obtained, according to OECD 107 which states "Measurements should be made on ionizable substances only in their non-ionized form (free acid or free base) produced by the use of an appropriate buffer with a pH of at least one unit below (free acid) or above (free base) the pK." "Dissociation or association of the dissolved molecules results in deviations from the partition law."

The ACD/ PhysChem Suite (2009) model estimated the partition coefficient, log D = 3.44 for the neutral form. At a pH of 5.5, it predicts the log D = 0.41.

Conclusions
Remarks: see above

Reliability
Not acceptable.

This is based mainly on the test being conducted on the ionized species of the substance. However, important criteria of the standard OECD method have also not been met, such as the shaking time, and replicates/duplicates.

3. Aerobic Biodegradation

Reference: 11165-65140912-003

Test Substance
Identity: Substance identified only by its trade name.
Remarks: Purity of test substance not described.

Method
Method/guideline followed: OECD 301B (1981), Modified Sturm Test
Type *(test type)*: Aerobic [X] Anaerobic [ ]
Year: *(study performed):* 1989
Contact time *(units):* 28 days
Inoculum: Bacteria collected from activated sludge of STP in Switzerland and prepared "…according to the method described in the guideline".

Test Conditions: (*Detail and discuss any significant protocol deviations, whether there was bacterial inhibition, and detail differences from the guideline followed including the following as appropriate:*

- *Inoculum (concentration and source):*
- *Concentration of test chemical, vehicle used, pre-acclimation conditions:*
- *Temperature of incubation(°C):* 22 ± 2 °C
- *Dosing procedure:*
- *Sampling frequency:*
- *Appropriate controls and blank system used:* Reference substance: Aniline (20 mg/L) containing 0.5 mL nonylphenol 10EO5PO solution.
- *Analytical method used to measure biodegradation:* The CO2 formed was adsorbed with NaOH and determined on a carbon analyzer.
- *Method of calculating measured concentrations (i.e., arithmetic mean, geometric mean, etc.):* No concentrations of test substance were measured (nominal only).
- *Other:*
    - The emulsifier nonylphenol 10EO5PO was added to the test solution "…due to the poor solubility of the test substance…" 0.5 mL 10EO5PO was added to 20 mg/L reference substance.
    - The volume of the test solution was reduced from 3.0 L to 1.5 L.

Results

- Degradation % after time (28 days): 26% of $ThCO_2$ evolved (11.1 mg/L test substance); 1% $ThCO_2$ (20.5 mg/L test substance).
- Breakdown products: Yes [ ] No [X].

Remarks: *(Describe additional information that may be needed to adequately assess data for reliability and use, e.g. lag time, observed inhibition, excessive biodegradation, excessive standard deviation, kinetics,, number of micro-organisms present, time required for 10% degradation and total degradation at the end of the test, e.g. 10 day window.)*

Conclusions

Remarks: Authors concluded that the test substance is not biodegradable.

Reliability

Low reliability. Identity of the test substance is not confirmed and the purity is not provided. The test substance is described as poorly soluble, when the measured solubility is 2400 mg/L. Concentrations of the test substance were not measured.

4. Bioaccumulation

The relevant Test Guideline for this endpoint is **OECD Test Guideline 305: 'Bioconcentration: Flow-through Fish Test'**.

Reference: 11165-65140912-004, (Summary document, Confidential study) – full report in Japanese only; some of the data tables in the report were understandable.
NA = data not available (only the summary report is in English)

Test Substance
Identity, Chemical Name and CAS #: Test substance is identified by its chemical formula and trade name.
Test Substance Remarks: Purity of test substance appears to be 98% (based on interpretation of report in Japanese).

Method: MITI method
Species Name: Carp
Exposure Period: Uptake phase: 56 days, period in clean water (depuration phase): ?
Concentration: Concentration in test medium at which the test was performed (water, soil, sediment, pore water).
Elimination: There is some data on the "recovery ratio" – given in %
GLP: No
Year: 1980
Deviations: NA
Method of analysis: HPLC, limit of detection ? and limit of quantification ?
Reference substance: Yes/No (If yes, specify) NA
Method of analysis for reference substance:

Test Conditions
Test Solution: (Describe preparation of solution of test substance.) NA
Test system/performance: NA
If an experimental study was performed, describe the test system and test performance: e.g. static/semistatic/flow-through test, details of apparatus/equipment,
Composition of test media (e.g. ingredients, solubilisers): NA
Exposure conditions (including illumination/photoperiod),
standard deviations) for species tested (including holding/feeding, adaptation) NA
Number of test organisms, loading: NA
Number of replicates: 2 replicates per concentration tested
Details of controls: NA
Duration of uptake and depuration phase: Uptake: 8 weeks, Depuration: ?
Test substance concentrations: 3.0 ppm (2.49 ppm – measured), 0.3 ppm (0.27 ppm, measured)

Frequency of test media quality measurements (e.g. DOC/TOC, pH, temperature): pH, DO and one other element measured at 0, 3 and 7 days and every 7 days thereafter. pH ranged between 7.0 and 7.3; DO ranged between 6.4 and 7.2.
Details on sampling and analysis of test species and test media samples (e.g. sampling schedule, sample preparation and analytical method): NA

Results
Mortality/behaviour: Mortality and/or observed abnormal behaviour of test organisms under each exposure regime, in controls and with reference substance: NA
Lipid content of the test organisms: mean value: 7.9 ± 2.1%
Concentrations of test material during test: Concentration of test material (with standard deviation and range) for all sampling times in test organisms (total), in specific tissues thereof (e.g. lipid) and in the surrounding medium; concentration values for controls and reference compound: NA

Bioconcentration factor (BCF): Calculate the steady-state BCFs and/or the kinetic BCFk (expressed in relation to the whole body, the total lipid content or specified tissues of the test organisms). Peak BCFs reached after 6 weeks at 0.27 ppm exposure: 52.3, 38.8 (units not given, but assumed L/kg). At 2.49 ppm exposure: 10.3, 20.6. After 8 weeks: 0.27 ppm: 32.3, 36.9. 2.49 ppm: 14.5, 10.7.
Uptake and depuration rate constants: Give values (including 95 % confidence limits and standard deviations) for the uptake and depuration (loss) rate constants (all expressed in relation to the whole body, the total lipid content or specific tissues of the test organisms); give relevant details on computation/data analysis: NA
Depuration time: Give depuration time required for clearance of 50 % (DT50) and 90 % (DT90) of residues : NA
Metabolites If identified (use of radiolabelled test material), any accumulated metabolites (accounting for > 10 % of residues) should be described: NA
Other Observations: Report anything unusual observations about the test, any deviations from the procedures and any other relevant information affecting results: NA

Conclusions

Remarks: Note the study author's conclusions and whether the submitter agrees: NA

Reliability:

Based on the information available in the English study summary: Not acceptable. Too much missing information.

5. Acute Toxicity

No	Item	Weight	Yes/No	Specify
1	Test for acute toxicity of {Trade Name]to Zebra-Fish (Brachydanio rerio). 1988. Reference: 11165-65140912-005			
2	Substance identity: CAS RN	n/a	N	
3	Substance identity: chemical name(s)	n/a	N	
4	Chemical composition of the substance	2	N	
5	Chemical purity	1	N	
6	Persistence/stability of test substance in aquatic solution reported?	1	N	
	Method			
7	Reference	1	Y	OECD-Guideline No. 203
8	OECD, EU, national, or other standard method?	3	Y	
9	Justification of the method/protocol if not a standard method was used	2		
10	GLP (Good Laboratory Practice)	3	N	
	Test organism			
11	Organism identity: name	n/a	Y	*Zebra fish (Brachydanio rerio)*
12	Latin or both Latin & common names reported?	1	Y	
13	Life cycle age / stage of test organism	1	Y	
14	Length and/or weight	1	Y	Length: 22 - 26 mm; Weight: 0.1 - 0.15 g
15	Sex	1	N	
16	Number of organisms per replicate	1	Y	10

17	Organism loading rate	1	Y	0.09 g/L
18	Food type and feeding periods during the acclimation period	1	Y	No food 24 h prior to exposure
Test design / conditions				
19	Test type (acute or chronic)	n/a	Y	Acute
20	Experiment type (laboratory or field)	n/a	Y	Laboratory
21	Exposure pathways (food, water, both)	n/a	Y	Water
22	Exposure duration	n/a	Y	96 h
23	Negative or positive controls (specify)	1	Y	Negative
24	Number of replicates (including controls)	1	Y	6 Concentrations, incl. controls
25	Nominal concentrations reported?	1	Y	5 nominal concentrations, 10 - 100 mg/L
26	Measured concentrations reported?	3	N	
27	Food type and feeding periods during the long-term tests	1	Y	No food during acute test
28	Were concentrations measured periodically (especially in the chronic test)?	1	N	
29	Were the exposure media conditions relevant to the particular chemical reported? (e.g., for the metal toxicity - pH, DOC/TOC, water hardness, temperature)	3	Y	
30	Photoperiod and light intensity	1	Y	
31	Stock and test solution preparation	1	N	
32	Was solubilizer/emulsifier used, if the chemical was poorly soluble or unstable?	1	N	Test substance was characterized as "practically Insoluble".
33	If solubilizer/emulsifier was used, was its concentration reported?	1		
34	If solubilizer/emulsifier was used, was its ecotoxicity reported?	1		
35	Monitoring intervals (including observations and water quality parameters) reported?	1	Y	
36	Statistical methods used	1	N	
Information relevant to the data quality				

37	Was the endpoint directly caused by the chemical's toxicity, not by organism's health (e.g. when mortality in the control >10%) or physical effects (e.g. 'shading effect')?	n/a	Y	
38	Was the test organism relevant to the Canadian environment?	3	Y	
39	Were the test conditions (pH, temperature, DO, etc.) typical for the test organism?	1	Y	
40	Does system type and design (static, semi-static, flow-through; sealed or open; etc.) correspond to the substance's properties and organism's nature/habits?	2	Y	
41	Was pH of the test water within the range typical for the Canadian environment (6 to 9)?	1	Y	8.0 - 8.4
42	Was temperature of the test water within the range typical for the Canadian environment (5 to 27°C)?	1	Y	22 °C
43	Was toxicity value below the chemical's water solubility?	3	Y	
Results				
44	Toxicity values (specify endpoint and value)	n/a	n/a	96-h LC50 >100 mg/L
45	Other endpoints reported - e.g. BCF/BAF, LOEC/NOEC (specify)?	n/a		96-h LC0 = 58 mg/L
46	Other adverse effects (e.g. carcinogenicity, mutagenicity) reported?	n/a		Slight effect on swimming behaviour at 18 mg/L at 48 h & longer; severe loss of equilibrium at 58 mg/L at 72 & 96 h; severe repiratory function effects at 100 mg/L at 72 & 96 h.
47	***Score*: ... %**			***66.7***
48	***EC Reliability code*:**			***3***
49	***Reliability category (high, satisfactory, low)*:**			***Low***
50	***Comments***			

Appendix II – PBT Model Inputs Summary Table

	Phys-Chem/Fate	**Phys-Chem/Fate**	**PBT Profiling**	**Biodegradation/Ecotoxicity**
Model Input Parameters	ACD/ PhysChem Suite (2009)	EPISuite (2008) (all models, including: KOWWIN, KOCWIN, BCFBAF BIOWIN and ECOSAR)	Canadian-POPs (CPOPs) 2008 (including: Catabol, Dimitrov, OASIS Toxicity Model)	TOPKAT (2004), AIEPS (2003-2007), OECD (2008)
SMILES code, dissociated form	c1(c(C(C)(C)C)cc(cc1C(C)(C)C)CP(=O)(O)OCC)O			
SMILES code, non-dissociated form		CCOP(O[Ca]OP(=O)(OCC)Cc2cc(C(C)(C)C)c(O)c(C(C)(C)C)c2)(=O)Cc1cc(C(C)(C)C)c(O)c(C(C)(C)C)c1		
Molecular weight (g/mol), dissociated/ non-dissociated		328.39/ 694.85		
Melting point (ºC)		270		
Boiling point (ºC)				
Data temperature (ºC)				
Density (kg/m^3)				
Vapour pressure (Pa)				
Henry's Law constant ($Pa \cdot m^3/mol$)				
Log K_{aw} (Air-water partition coefficient; dimensionless)				
Log Kow (Octanol-water partition coefficient; dimensionless)		-0.031	-0.031	
Log K_{oc} (Organic carbon-water partition coefficient – L/kg)				
Water solubility (mg/L)				

Appendix III: Summary of health effects information for PADMEC[1]

Endpoint	Lowest effect levels[1]/results
Experimental animals and *in vitro*	
Acute toxicity	**Oral LD_{50}** (rat) > 2000 mg/kg-bw (Ash M and Ash I 2004). **Oral LD_{50}** (rat) > 6000 mg/kg-bw No inhalation or dermal studies were identified
Short-term repeated-dose toxicity	No studies were identified.
Subchronic toxicity	**Oral LOEL:** 6000 ppm (equivalent to 300 mg/kg-bw per day; based on Health Canada 1994) was identified based on a slight decrease in body weight gain and reduced grooming activity in both sexes and elevated serum alkaline phosphatase levels in males in Sprague Dawley rats (20-25 per sex per group) administered PADMEC in diets at 0, 700, 2000 or 6000 ppm (equivalent to 0, 35, 100 and 300 mg/kg-bw per day respectively; based on Health Canada 1994) for 13 weeks followed by a recovery period of 4 weeks in control and 6000 ppm treated groups (5 per sex per group). During week 8, a number of rats developed Sialodacryoadentitis, a viral disease common to this strain, and exhibited a marginal loss of appetite. All infected rats showed complete recovery by week 10 with no residual effects. Reduced grooming activity was observed in both males and females at 6000 ppm with no recovery after post-exposure. A slight transient decrease in body weight gain was observed during week 6 at 6000 ppm. Elevated serum alkaline phosphatase levels were observed in males at 6000 ppm during week 4 and 12. No treatment-related effects on mortality, food consumption, ophthalmology and hearing, urinalysis, haematology, organ weights, gross pathology and histopathology were observed. No inhalation or dermal studies were identified.
Chronic toxicity/ carcinogenicity	No studies were identified.
Developmental toxicity	No studies were identified.
Reproductive toxicity	No studies were identified.
Endocrine disruption *in vitro*	**Estrogenic activity:** **Negative:** *In vitro* yeast two-hybrid assay based on the ligand-dependent interaction of the estrogen receptor (ER) α and the coactivator TIF2. Estrogenic activity was detected as the β-galactosidase activity in the presence or absence of metabolic activation S9 (Ogawa et al. 2006).
Genotoxicity and related endpoints: *in vivo*	**Nucleus anomaly test:** **Negative:** Chinese hamsters (3 per sex per treated and 6 per sex per control groups) orally administered 0, 1250, 2500 or 5000 mg/kg-bw per day PADMEC for 2 consecutive days. Four treated animals died during the course of the experiment (1 male of each dose group and 1 female at 2500 mg/kg-bw).

[1] Toxicity studies not referenced were obtained from Food Packaging Materials and Incidental Additives Section of Health Canada. References to these data cannot be identified due to confidentiality (July 2010 personal communication from Food Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

Endpoint	**Lowest effect levels[1]/results**
Genotoxicity and related endpoints: *in vitro*	**Mutagenicity:** **Negative:** Ames test**,** *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA1538; *Escherichia coli* Wp2 uvr A in the presence or absence of metabolic activation (S9).
Sensitization	No studies were identified.
Irritation	**Skin irritation:** Very mild irritation (slight erythema, no edema) on abraded skin when tested in rabbits.
	Eye irritation: No irritation was observed in rabbits.
Humans studies	
	No studies were identified.

[1] Toxicity studies not referenced were obtained from Food Packaging Materials and Incidental Additives Section of Health Canada. References to these data cannot be identified due to confidentiality (July 2010 personal communication from Food Directorate, Health Canada to Existing Substances Risk Assessment Bureau, Health Canada; unreferenced).

Appendix IV: (Q)SAR Predictions for PADMEC

(Q)SAR PREDICTIONS ON CARCINOGENICITY

Model/ Species	Mice		Rat		Rat	Mice	Rodent	Mammal
	Male	Female	Male	Female				
MA	N	N	N	N	N	N	N	-
CT	ND	ND	ND	ND	-	-	ND	-
TK	ND	ND	ND	ND	-	-	-	-
Derek	-	-	-	-	-	-	-	ND

(Q)SAR PREDICTIONS ON GENOTOXICITY

Model/Endpoint	chrom. ab.	chrom. ab. other rodent	chrom. ab. Rat	micronucleus mouse	micronucleus rodent	UDS	UDS human lymphocytes	UDS rat hepatocytes	*Drosophila*	*Drosophila* HT	*Drosophila* SLRL	*S. cerevisiae*	Yeast	hgprt	mam. mutation	mam. mutation DL	mouse lymphoma mut	*E. coli*	*E. coli* w	microbial	*Salmonella*	BB cancer alert
MA	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	-	N	N	N	N	-
CT	ND	-	-	ND	-	ND	-	-	ND	-	-	-	-	-	-	-	ND	-	-	-	ND	-
TK	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	ND	-
TT	-	-	-	-	N	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	N

Model/Endpoint	Chromosome damage	Genotoxicity	Mutagenicity
DEREK	NR	NR	NR

MA – Model Applier (2008); CT – CASETOX (2008); TK – TOPKAT (2004); TT – Toxtree (2009); DEREK (2008); BB – Benigni-Bossa rulebase for mutagenicity and carcinogenicity (Toxtree model); chrom.ab. – chromosomal aberration; mam. – mammalian; UDS – unscheduled DNA synthesis; mut. – mutation; N – negative; P – positive; ND – not in domain (model indicates query chemical to be outside of it's applicability domain); NR – no result; (-) - no model available in (Q)SAR suite.

(Q)SAR PREDICTIONS ON DEVELOPMENTAL TOXICITY

Model Applier

Endpoint/ Species	mice	rabbit	rat	rodent
Retardation	N	N	N	N
Weight decrease	N	N	ND	N
Fetal death	N	N	N	N
Post impl. loss	N	N	N	N
Pre impl. loss	N	N	N	N
Structural	N	ND	N	N
Visceral	N	-	N	N

Multicase Casetox

Endpoint/Species	Hamster	Mammal	Miscellaneous
Teratogenicity	-	P	ND
Developmental	ND	-	-

(Q)SAR PREDICTIONS ON REPRODUCTIVE TOXICITY

Model Applier

Model/ endpoint	Female			Male		
Species	mice	rat	rodent	Mice	Rat	rodent
repro	ND	ND	N	ND	P	N
sperm	-	-	-	N	N	N

Multicase Casetox

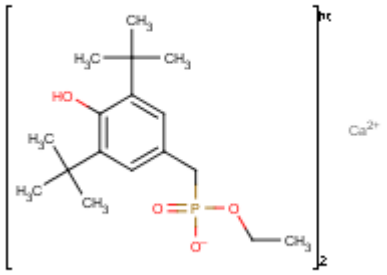
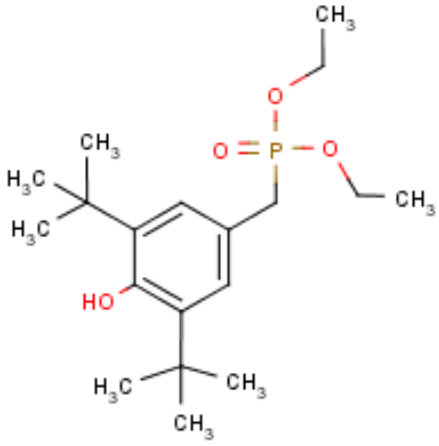
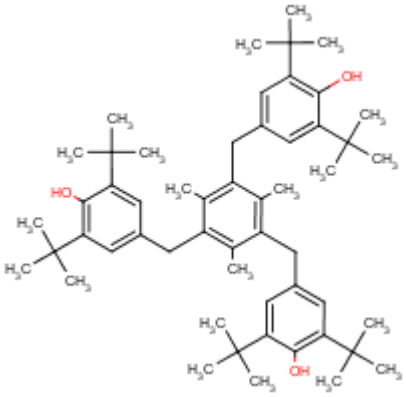
mice	rat	rabbit	human
ND	ND	ND	ND

DEREK

Mammal
NR

N – negative; P – positive; ; NR – no result; ND – not in domain (model indicates query chemical to be outside of it's applicability domain); (-) - no model available in (Q)SAR suite;
impl.—implantation.

Appendix V: Structures for PADMEC and analogue substances

Name/ CAS RN	Structure
PADMEC **CAS RN #65140-91-2** **MW: 694.85** **Physical state: solid** **Vapour pressure: 6.03x10^{-10} Pa (modelled, EPIWIN 2008), <0.01 Pa (experimental, Study Submission 2010a)**	
Phosphonic acid, [[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-, diethyl ester **CAS RN # 976-56-7** **MW: 356.44** **Physical state: solid** **Vapour pressure: 1.51x10^{-7} Torr (2.01x10^{-5} Pa) (modelled, CAS 2010)**	
Phenol, 4,4',4''-[(2,4,6-trimethyl-1,3,5-benzenetriyl)tris(methylene)]tris[2,6-bis(1,1-dimethylethyl)- **Commercially known as Irganox 1330/Ethanox 330/ Ionox 330** **CAS RN # 1709-70-2** **MW: 775.22** **Physical state: solid** **Vapour pressure: 1.3x10^{-12} Pa (experimental, US EPA 2006b), 5.02x10^{-22} Torr (6.69x10^{-20} Pa) (modelled, CAS 2010)**	

Appendix VI: Summary of health effects information for Irganox 1330 (CAS RN #1709-70-2) – analogue for PADMEC

Endpoint	Lowest effect levels[i]/results

Endpoint	Lowest effect levels[i]/results
Experimental animals and *in vitro*	
Acute toxicity	**Oral LD_{50} (rat)** > 5000 mg/kg-bw (Stevenson et al. 1965). **Dermal LD_{50} (rat)** > 2000 mg/kg-bw (Ciba-Geigy 1992a). No inhalation studies were identified.
Short-term repeated-dose toxicity	No studies were identified.
Subchronic toxicity	**Lowest oral LOEL** = 31600 ppm (equivalent to 1600 mg/kg-bw per day; based on Health Canada 1994) based on significantly decreased body weights in female Carworth E/N rats (10 per sex per group) orally fed Irganox 1330 in diets at 0, 316, 1000, 3160, 10000 or 31600 ppm (equivalent to 0, 16, 50, 160, 500 and 1600 mg/kg-bw per day respectively; based on Health Canada 1994) for 90 days. No treatment related effects were observed in food intake, food utilization, haematology, clinical chemistry, organ weights, pathology and urine analysis (Stevenson et al. 1965). Albino rats (10-12 per sex per group) were orally fed Irganox 1330 in diets at 0 or 5000 ppm (equivalent to 0 or 250 mg/kg-bw per day; based on Health Canada 1994) for 90 days. No treatment related effects on organ weights and histopathology were observed. Pneumonitis of the lung, pericholangitis of the liver and nephritis of the kidney were observed in some control and treated animals. No effects on body weight gains, food consumption, water consumption, mortalities, haematological and clinical chemistry and urine studies were observed (Lifestream laboratories 1966a). Beagle dogs (3-4 per sex per group) orally fed Irganox 1330 in diets at 0 or 5000 ppm (equivalent to 0 or 150 mg/kg-bw per day; based on Health Canada 1994) for 90 days. No significant abnormalities of absolute and relative organ weights and no significant histopathological changes related to treatment were observed. No effects on body weight, food consumption, mortality, behavioural reactions, haematology, clinical blood chemistry and urine analysis were observed (Lifestream laboratories 1966b). No dermal or inhalation studies were identified.
Chronic toxicity/ carcinogenicity	**Lowest oral LOEL** = 10000 ppm (equivalent to 500 mg/kg-bw per day; based on Health Canada 1994) based on decrease in body weights and organ weights in female Carworth Farm E strain rats (a total of 40 per sex per treated and 60 per sex per control groups) orally fed Irganox 1330 in diets at 0, 400, 2000 or 10000 ppm (equivalent to 0, 20, 100 and 500 mg/kg-bw per day respectively; based on Health Canada 1994) for 2 years. Five per sex per group were sacrificed after 26, 52 and 78 weeks of feeding. For interim sacrifice, decreased body weights and no effect on absolute and relative organ weights were observed in males at 10000 ppm after 52 weeks. For animals treated for 2 years, females at 10000 ppm exhibited reduced body weights, food intakes, absolute liver and kidney weights and relative liver weights. No effects on general health, behaviour and mortality were observed. No adverse effects were observed related to food consumption, behavioural reactions, urine analysis, gross pathologic studies and histopathologic studies. No significant differences in haematology and clinical studies were observed. No gross or microscopic lesions attributable to treatment were observed. The authors suggested that the effects on body and organ weights observed in females at 10000 ppm were probably related to low initial body weights (Shell Research 1968a). Carworth Farm E strain rats (30 per sex per treated and 40 per sex per control groups) were orally fed Irganox 1330 (purity 98%) in diets at 0, 1000 or 5000 ppm (equivalent

Endpoint	Lowest effect levels[i]/results
	to 0, 50 and 250 mg/kg-bw per day respectively; based on Health Canada 1994) for 2 years. A decrease in body weight was observed in males at 5000 ppm during week 78. During the final 6 months of treatment, a trend of decrease body weight was observed in all treated and control males that the authors stated 'this loss appeared to be an effect of age rather than of treatment". No effects on behaviour, general health, food intake, pathology and tumour incidences were observed. Renal lesions (nephrosis) were observed in virtually all rats at the end of the study. The most common tumours were thyroid adenoma and basophil adenoma of the anterior adenoma observed in both control and treated animals (Shell Research 1969). Carworth Farm No. 1 strain mice (36 per sex per treated and 36 per sex per control groups) were orally fed Irganox 1330 (purity 98%) in diets at 0, 1000 or 5000 ppm (equivalent to 0, 130 and 650 mg/kg-bw per day respectively; based on Health Canada 1994) for 2 years. During the last 3 months of treatment, a decrease in body weight was observed in all treated and control groups that the authors stated 'this loss appeared to be an effect of age rather than of treatment". No treatment related histopathological lesions or tumours were observed. No differences in the tumour incidence between treated and control animals were observed (Shell Research 1969). Histopathological data was not presented in US EPA 2006b. Beagle dogs (4-5 per sex per group) were orally fed Irganox 1330 (purity 98%) in diets at 0, 2000 or 10000 ppm (equivalent to 0, 60 and 300 mg/kg-bw per day respectively; based on Health Canada 1994) for 2 years. No treatment related effects on general health, behaviour, body weights, absolute and relative organ weights, haematology and clinical chemistry were observed. No gross or microscopic changes were observed. Pathological findings indicated lesions associated with ascarid infestation in livers of treated and control animals. Renal and pulmonary diseases were observed in most treated and control animals (Shell Research 1968b). No dermal or inhalation studies were identified.
Reproductive / Developmental toxicity	**Rat oral NOEL:** 5000 ppm (equivalent to 250 mg/kg-bw per day; based on Health Canada 1994) in Carworth Farm E strain rats (20 per sex per group) orally fed Irganox 1330 (98% purity) in diets at 0 or 5000 ppm for three generations (specific duration of treatment not specified in US EPA 2006b). No effects on general health, behaviour, mortality compared to controls were observed. No effects on reproduction, number of pregnancies, litters and young born from weaning to maturity in all three generations compared to controls were observed. No lesions, gross or histological changes were observed. US EPA (2006b) noted "details missing from the submission of 3-generation study include the sexes of the pups, weights of the pups at days 0 and 4, weights of reproductive organs, data on spermatogenesis, data on the teratogenic effects observed in the F3 generation, histopathological examination data, and statistical analyses" (Shell Research 1970). No dermal or inhalation studies were identified.
Genotoxicity and related endpoints: *in vivo*	No studies were identified.

Endpoint	**Lowest effect levels[i]/results**
Genotoxicity and related endpoints: *in vitro*	**Mutagenicity:** **Negative:** Ames test**,** *Salmonella typhimurium* TA98, TA100, TA1535 and TA1537; *Escherichia coli* WP2 uvA in the presence or absence of metabolic activation S9 with dose ranged from 625-5000 µg/plate (Ciba-Geigy 1992b). **Negatvie:** Ames test**,** histidine-auxotrophic mutants of *Salmonella typhimurium* TA97, TA98, TA100; *Escherichia coli* WP2/pKM101 in the presence or absence of metabolic activation S9 with dose ranged from 50-2000 µg/plate (Akita University 1984).
Sensitization	No studies were identified in US EPA 2006b.
Irritation	**Skin irritation:** No studies were identified.
	Eye irritation: No studies were identified.
Humans studies	
	No studies were identified.