Screening Assessment for the Challenge

2-Propanone, reaction products with diphenylamine

Chemical Abstracts Service Registry Number
68412-48-6

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 of 2-Propanone, reaction products with diphenylamine, hereinafter referred to as PREPOD, Chemical Abstracts Service Registry Number[1] 68412-48-6. This substance was identified as a high priority for a screening assessment and included in the Challenge because it was found to meet the ecological categorization criteria for persistence, bioaccumulation potential and inherent toxicity to non-human organisms and is believed to be in commerce in Canada.

The substance, PREPOD, 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.

PREPOD is an organic UVCB (Unknown or Variable Composition, Complex Reaction Products or Biological Materials) substance that is used in Canada and elsewhere as an antioxidant in the manufacture of rubber products such as car tires. The substance is not naturally produced in the environment. Between 100 000 and 1 000 000 kg of PREPOD were manufactured in, and imported into Canada in 2006. In addition, between 100 and 1000 kg of PREPOD were imported into Canada in 2006 as a component of vehicle parts and already assembled vehicles in the automobile industry. The quantity of PREPOD manufactured, imported, and present in products in Canada indicates significant potential for release into the Canadian environment.

Based on reported use patterns and certain assumptions, most of the substance is expected to end up in waste disposal sites. Proportions are estimated to be released to wastewater (6.2 %) and air (0.1 %). PREPOD is not soluble in water, is not volatile and has a tendency to partition to particles and lipids (fat) of organisms because of its hydrophobic nature. For these reasons, PREPOD will most likely be found in soil and sediments. It is not expected to be significantly present in other media.

Based on their physical and chemical properties, the components of PREPOD are not expected to degrade rapidly in the environment, except in air. They are, therefore, considered to be persistent in water, soil and sediments. One significant component of PREPOD has been identified as having the potential to accumulate in organisms. In addition, modelled acute aquatic toxicity data indicate that PREPOD is potentially highly hazardous to aquatic organisms.

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For this screening assessment, three site-specific exposure scenarios with discharge into the aquatic environment were considered, representing both the manufacture and industrial use of PREPOD. Predicted environmental concentrations in water were compared with predicted no-effect concentrations for harm to aquatic organisms for the different components of PREPOD. The highest ratios of these values were found for the component of PREPOD that was additionally determined to be both highly persistent in the environment and highly bioaccumulative. Results of this comparison, especially when recognizing the likelihood of underestimating risk for substances with high persistence and bioaccumulation potential, indicate a potential for harm to aquatic organisms from PREPOD.

Based on the information available, it is proposed that PREPOD is 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.

Exposure of the general population to PREPOD through environmental media (air, drinking water and soil) is expected to be low. General population exposure to PREPOD from food or beverages or from use of consumer products is not expected.

Limited studies on PREPOD components and analogues of a component did not indicate a potential for genotoxicity or carcinogenicity. Based on the information available, the margin of exposure between the upper-bounding estimate of exposure via environmental media for PREPOD and the most sensitive health effect level of PREPOD components is considered to be adequate to address uncertainties in the health effects and exposure databases.

Based on the information presented in this final screening assessment, it is concluded that PREPOD is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Based on the information available, it is concluded that PREPOD meets one or more of the criteria set out in section 64 of CEPA 1999. In addition, components of PREPOD are persistent and one significant component is bioaccumulative in accordance with the *Persistence and Bioaccumulation Regulations*. The presence of PREPOD in the environment results primarily from human activity and it is not a naturally occurring radionuclide or a naturally occurring inorganic substance.

Where relevant, research and monitoring will support verification of assumptions used during the screening assessment and, where appropriate, the performance of potential control measures identified during the risk management phase.

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 2-Propanone, reaction products with diphenylamine, was identified as a high priority for assessment of ecological risk as it was found to be persistent, bioaccumulative and inherently toxic to aquatic organisms and is believed to be in commerce in Canada. The Challenge for this substance was published in the *Canada Gazette* on September 26, 2009 (Canada 2009). 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 related to exposure of the substance were received.

Although 2-Propanone, reaction products with diphenylamine was determined to be a high priority for assessment with respect to the environment, it did not meet the criteria for GPE or IPE.

Screening assessments focus on information critical to determining whether a substance meets the criteria for defining a chemical as toxic 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 the additional information related to exposure 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 December 2010 for the ecological sections and June 2010 for the human health sections of the document. Modelling results were used to reach conclusions. When available and relevant, information presented in hazard assessments from other jurisdictions was considered. The final 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. Although external comments were taken into consideration, the final content and outcome of the screening risk 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 final 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 PREPOD, derived from the DSL name 2-***P***ropanone, ***re***action ***p***r***o***ducts with ***d***iphenylamine.

PREPOD is the reaction product of *N*-phenyl-benzeneamine (diphenylamine (DPA)) and 2-propanone (acetone). It is a UVCB (Unknown or Variable Composition, Complex Reaction Products, or Biological Materials) mixture, and, as such, contains a number of components in different concentrations.

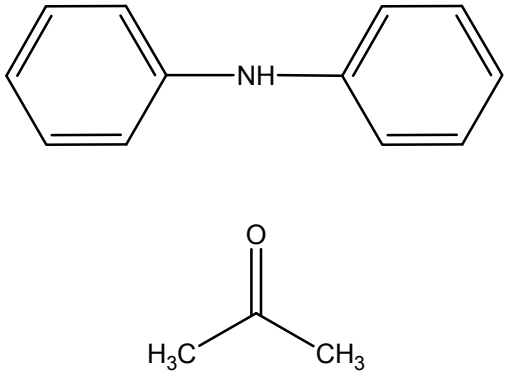
Table 1a shows the substance identity for PREPOD, the UVCB. Table 1b shows the identity information (e.g., CAS RN) and structure for the main components in PREPOD that are being evaluated as representative for the purposes of this assessment. Not all components of PREPOD are shown; in particular, the higher molecular weight components are not readily identifiable and their exact identities are uncertain. In addition to the components in Table 2b, it is known that the following components may also be present based on information available for one commercial product: 4-isopropyl-diphenylamine, diisopropyldiphenylamine, and 3-isopropyl-dimethylacridan (CRA 2010).

The only non-reaction component in PREPOD is DPA (CAS RN 122-39-4); product datasheets indicate that DPA is present in PREPOD, as a residual component, in concentrations up to 20% (PMC Rubber Chemicals India Private Limited 2006b). It should be noted that the type of component, and/or its relative concentration in the mixture of reaction products formed when DPA and acetone are reacted, depends on manufacturing conditions, such as temperature. In other words, a higher manufacturing temperature will yield a different mixture of components, some of which are not present in a lower temperature mixture, and some of them being present in the lower temperature mixture but in a different relative concentration (NOCIL Limited 2008).

In this assessment, the UVCB substance will be referred to as PREPOD, and the individual reaction products will be referred to as components.

Table 1a. Substance identity for 2-Propanone, reaction products with DPA

Chemical Abstracts Service Registry Number (CAS RN)	**68412-48-6**
DSL name	**2-Propanone, reaction products with DPA**
National Chemical Inventories (NCI) names[1]	*Reaction product from diphenylamine and acetone* (ENCS) *Condensate, acetone-diphenylamine* (PICCS) *Reaction product, diphenylamine-acetone* (PICCS) *Diphenylamine-acetone condensation product* (PICCS)
Other names including	*Acetone, diphenylamine condensation product*

tradenames	*Acetone diphenylamine condensation products* [2] *acetone; dicyclohexylamine* [2] *acetone; N-cyclohexylcyclohexanamine* [2] *ADPAL* [3] *BLE* [4] *CID162214* [2] *Diphenylamine, acetone reaction product* *EINECS 270-192-0* [2] *LS-123178* [2] *N-cyclohexylcyclohexanamine; propan-2-one* [2] *N-Phenylbenzeneamine, 2-propanone reaction product* *Rubber Antioxidant BLE* [2]
Chemical group (DSL Stream)	Organic UVCB [5]
Major chemical class or use	Amines
Major chemical sub-class	Aromatic amines
Chemical formulae of reactants	$C_{12}H_{11}N$; C_3H_6O
Structure of reactants	

[1] National Chemical Inventories (NCI). 2009: ENCS (Japanese Existing and New Chemical Substances); PICCS (Philippine Inventory of Chemicals and Chemical Substances)

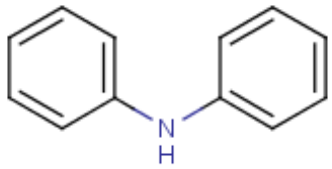
[2] ChemIndustry.com Inc 2008

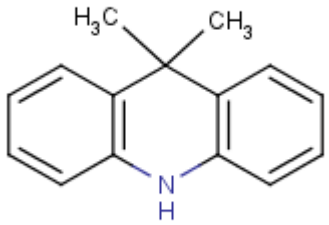
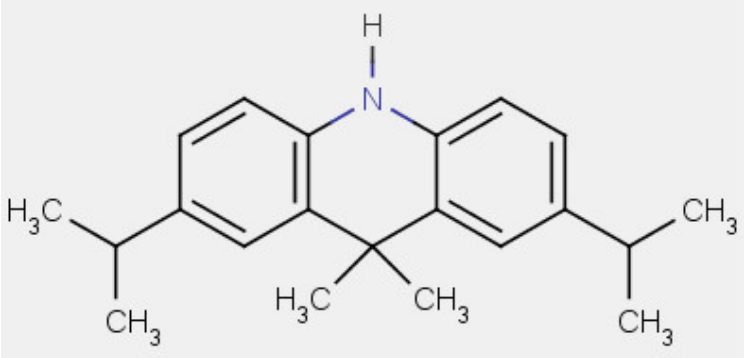
[3] Chemicalland 2010

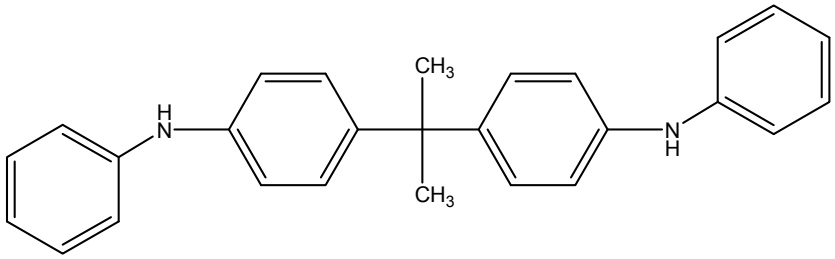
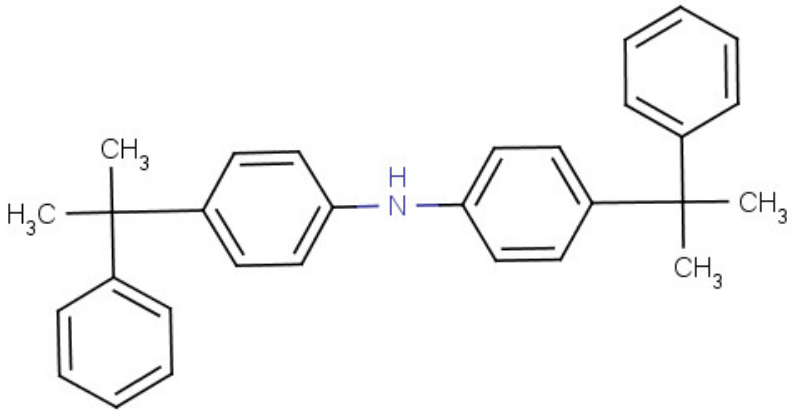
[4] Chemtura Corporation 2007.

[5] This substance is a UVCB (**U**nknown or **V**ariable Composition, **C**omplex Reaction Products, or **B**iological Materials); i.e., it is not a discrete chemical and may be characterized by a variety of structures

Table 1b. Identity and structure of the main components in PREPOD and the analogue used in this assessment

Component A [1]	
Chemical Abstracts Service Registry Number (CAS RN)	122-39-4
DSL name	Benzenamine, *N*-phenyl-
Common name	Diphenylamine (DPA)
Chemical formula	$C_{12}H_{11}N$
Structure (used to run the estimation models)	
SMILES used to run the estimation models [2]	c1(Nc2ccccc2)ccccc1
Molecular mass	169.226 g/mol
Component B [1]	
Chemical Abstracts Service Registry Number (CAS RN)	6267-02-3
DSL name	Acridine, 9,10-dihydro-9,9-dimethyl-
Common name	9,9-dimethylacridan
Chemical formula	$C_{15}H_{15}N$

Structure (used to run the estimation models)	
SMILES used to run the estimation models [2]	c12C(c3c(cccc3)Nc1cccc2)(C)C
Molecular mass	209.29 g/mol
Component C [1]	
Chemical Abstracts Service Registry Number (CAS RN)	None
DSL name	Not on DSL
Common name	Diisopropyldimethylacridan
Chemical formula	$C_{21}H_{27}N$
Structure (used to run the estimation models)	
SMILES used to run the estimation models [2]	N1c3ccc(cc3C(C)(C)c2c1ccc(c2)C(C)C)C(C)C
Molecular mass	293.46
Component D	This component is the one whose structure is shown in EPIsuite (2008).
Chemical Abstracts	None

Service Registry Number (CAS RN)	
DSL name	Not on DSL
Common name	-
Chemical formula	$C_{27}H_{26}N_2$
Structure (used to run the estimation models)	
SMILES used to run the estimation models [2]	c1ccccc1Nc2ccc(cc2)C(C)(C)c3ccc(cc3)Nc4ccccc4
Molecular mass	378.52 g/mol
Component D Analogue [3]	
Chemical Abstracts Service Registry Number (CAS RN)	10081-67-1
DSL name	Benzenamine, 4-(1-methyl-1-phenylethyl)-N-(4-(1-methyl-1-phenylethyl)phenyl)-
Common names	4-(1-Methyl-1-phenylethyl)-N-(4-(1-methyl-1-phenylethyl)phenyl)aniline DCDPA
Chemical formula	$C_{30}H_{31}N$
Structure (used to run the estimation models)	

SMILES used to run the estimation models [2]	N(c1ccc(cc1)C(c1ccccc1)(C)C)c1ccc(cc1)C(c1ccccc1)(C)C
Molecular mass	405.58

[1] CRA 2010.

[2] Simplified Molecular Line Input Entry System.

[3] This analogue is not known to be a component of PREPOD.

Physical and Chemical Properties

There are no empirical physical or chemical properties data available for PREPOD, other than those shown in Table 2a. Physical and chemical properties of the PREPOD components were modelled and the results are presented in Table 2b. In addition, a "read-across" approach which employs close analogues, was used to determine the approximate physical and chemical properties as well as other characteristics, such as persistence and bioaccumulation potential. A search of the ChemIDPlus (2009) database yielded analogue data for Component A (DPA) and Component D only. Since there are experimental data for Component A, the experimental data for analogues of Component A are not presented or used in this assessment.

Table 2a. Physical and chemical properties for PREPOD

Property	**Value**	**Temperature (°C)**	**Reference**
Physical state	Dark brown viscous liquid [1]	unknown	Chemicalland 2010
Specific gravity	1.06 – 1.12	unknown	Chemicalland 2010

[1] There are two different types of condensates: low temperature reaction products and high temperature reaction products.

Table 2b. Physical and chemical properties for PREPOD components

Property	**Substance**	**Value**[1]	**Temperature (°C)**	**Reference**
Melting point (ºC)	Component A	52.9 [2]		Jones 1960
	Component B	112.66		MPBPWIN 2008
	Component C	144.78		MPBPWIN 2008

Property	Substance	Value[1]	Temperature (°C)	Reference
	Component D	215.19		MPBPWIN 2008
	Component D Analogue	214.52		MPBPWIN 2008
Boiling point (ºC)	Component A	302 [2]		Jones 1960
	Component B	329.80		MPBPWIN 2008
	Component C	386.18		MPBPWIN 2008
	Component D	505.55		MPBPWIN 2008
	Component D Analogue	507.08		MPBPWIN 2008
Vapour pressure (Pa)	Component A	8.93×10^{-2} [2]	25	Jones 1960
	Component B	7.2×10^{-3} (5.41×10^{-5} mm Hg)	25	MPBPWIN 2008
	Component C	1.5×10^{-4} (1.1×10^{-6} mm Hg)	25	MPBPWIN 2008
	Component D	2.49×10^{-8} (1.87×10^{-10} mm Hg)	25	MPBPWIN 2008
	Component D Analogue	2.32×10^{-8} (1.74×10^{-10} mm Hg)	25	MPBPWIN 2008
Henry's Law constant ($Pa \cdot m^3/mol$)	Component A	0.273 [2]		Jones 1960 Yalkowsky & He 2003

Property	Substance	Value[1]	Temperature (°C)	Reference
	Component B	7.59×10^{-2} (7.49×10^{-7} mm Hg)	25	HENRYWIN 2008
	Component C	0.287 (2.83×10^{-6} mm Hg)	25	HENRYWIN 2008
	Component D	3.26×10^{-6} (3.22×10^{-11} atm·m^3/mol)	25	HENRYWIN 2008
	Component D Analogue	2.62×10^{-3} (6.11×10^{-7} atm·m^3/mol)	25	HENRYWIN 2008
Log K_{ow} (Octanol-water partition coefficient) (dimensionless)	Component A	3.5 [2]		Hansch et al. 1995
	Component B	4.14	25	KOWWIN 2008
	Component C	7.05	25	KOWWIN 2008
	Component D	7.2	25	KOWWIN 2008
	Component D Analogue	8.51	25	KOWWIN 2008
Log K_{oc} (Organic carbon-water partition coefficient) (dimensionless)	Component A	2.78 [2]		Schuurman et al. 2006
	Component B	3.17	25	PCKOCWIN 2008
	Component C	4.93	25	PCKOCWIN 2008
	Component D	6.91	25	PCKOCWIN 2008

Property	Substance	Value[1]	Temperature (°C)	Reference
	Component D Analogue	7.31	25	PCKOCWIN 2008
Water solubility (mg/L)	Component A	53 [2]		Yalkowsky & He 2003
	Component B	0.89	25	WSKOWWIN 2008
		1.5 [3]	25	WATERNT [3]
	Component C	0.001	25	WSKOWWIN 2008
		0.004	25	WATERNT 2008
	Component D	0.003	25	WSKOWWIN 2008
		0.0005	25	WATERNT 2008
	Component D Analogue	1.52×10^{-4}	25	WSKOWWIN 2008
		6.77×10^{-6}	25	WATERNT 2008
pK_a (Acid dissociation constant) (dimensionless)	All PREPOD components	No Acid pKa No Base pKa		ACD/pKaDB 2005

Abbreviations: K_{oc}, organic carbon-water partition coefficient; K_{ow}, octanol–water partition coefficient.
[1] Values in parentheses represent the original ones as reported by the authors or as estimated by the models.
[2] This value is empirical.
[3] Using the EVA (Experimental Value Adjusted) method and the experimental water solubility for Component A. In the EVA approach, the estimate begins with the experimental value of the similar compound. The similar structure is then modified by subtracting and adding fragments to "build" the compound being estimated. The estimate then becomes the sum of the experimental value and the value of the fragment modifications (WSKOWWIN 2008).

Modelled data for the physical/chemical properties of the PREPOD components indicate the following general qualities: moderate to very low water solubility, moderate to very low or negligible vapour pressure and Henry's law constant, moderate to very high log K_{oc} and moderate to high log K_{ow}. Moreover, based on the results obtained from the modelling program pKa DB from ACD (2005), all PREPOD components ionize very little in water and are treated in this assessment as non-ionizing.

Sources

PREPOD is not reported to be naturally produced in the environment.

Information gathered from the CEPA 1999 Section 71 notices for the 2006 calendar year indicates that the total quantity of PREPOD that was manufactured in Canada was in the 100 000 to 1 000 000 kg/year range (Environment Canada 2010a).

For the 2006 calendar year, fewer than four Canadian companies reported importing PREPOD (as a component of vehicle parts and already assembled vehicles in the automobile industry) and the total quantity imported was in the 100 to 1 000 kg/year range (Environment Canada 2010a).

During the 1986 calendar year, it was reported that between 100 kg and 1000 kg of PREPOD was manufactured, imported or in commerce in Canada (Environment Canada 1988). The number of notifiers for the calendar years 1984-86 was fewer than 4.

Products containing PREPOD may enter the country even if they are not identified as such in the section 71 survey responses because they may be imported unknowingly in manufactured items, or in quantities below the 100 kg reporting threshold for the survey. Available information is currently not sufficient to derive a quantitative estimate of the importance of this source.

Uses

According to submissions made in response to a notice under section 71 of CEPA, 1999, between 100 000 and 1 000 000 kg of PREPOD were used in Canada in 2006 (Environment Canada 2010a).

The main use of PREPOD is as an antioxidant in rubber products, including tires. Given the large number of tires that are imported into Canada (Statistics Canada 2011), it is likely that PREPOD was used in the manufacture of some of them. However, no data were found which specifies the exact number of tires imported into Canada that contain PREPOD.

The industrial functions of PREPOD reported in the responses to the CEPA 1999 Section 71 notices for the 2005 and 2006 calendar years (Environment Canada 2006;

Environment Canada 2010a) are: antioxidant, paint additive and coating additive, plasticizer, abrasives, oxidizing or reducing agent.

The use codes for PREPOD, identified when the DSL was compiled in 1984-86, are shown below:

> 07- Antioxidant/corrosion inhibitor/tarnish inhibitor/scavenger/antiscaling agent
> 76- Organic Chemicals, Industrial

PREPOD is present in imported vehicle parts, namely in the front mounting bracket for engines and in brake components, and in already assembled automobiles at concentrations of 0.0023% by weight and 0.0003% by weight, respectively (Environment Canada 2010a).

PREPOD was not notified as an ingredient in cosmetic products in Canada (CNS 2010) and does not appear on the Cosmetic Ingredient Hotlist, Health Canada's administrative list of ingredients that are intended to be prohibited or restricted for use in cosmetics in Canada (Health Canada 2009). PREPOD is not currently used in any pest control products registered for use in Canada as either an active ingredient or a formulant (PMRA 2007). PREPOD is not listed as an approved food additive under Division 16 of the *Food and Drug Regulations* (Canada 1978). Diphenylamine acetone resin, a common name that may refer to PREPOD, was last submitted as a component of a food packaging material in 1995 (May 2010 email from Food Directorate, Health Canada to Risk Management Bureau, Health Canada; unreferenced). However, PREPOD was not identified in current food packaging applications or in incidental additives (April 2010 email from Food Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced). PREPOD is not listed in the Drug Product Database (DPD), the Therapeutic Products Directorate's internal Non-Medicinal Ingredient Database, the Natural Health Products Ingredients Database or the Licensed Natural Health Products Database as a medicinal or a non-medicinal ingredient present in final pharmaceutical products, natural health products or veterinary drugs (DPD 2010; NHPID 2010; LNHPD 2010; April 2010 email from Therapeutic Products Directorate, Natural Health Products Directorate and Veterinary Drugs Directorate, Health Canada, to Risk Management Bureau, Health Canada; unreferenced).

The "Handbook of Preservatives" by Michael Ash and Irene Ash (2004) indicated that diphenylamine acetone resin (CAS RN 68412-48-6 and 9003-79-6) has been approved by US FDA for use as an indirect food additive (antioxidant for rubber and components of adhesives; US FDA 2009a, 2009b), however, US FDA evaluations of these applications were not available for this assessment.

Releases to the Environment

A method has been developed by Environment Canada to estimate a substance's potential 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 available for the substance. Starting with an identified mass of the substance in commerce, each life cycle stage is subsequently evaluated until all of the mass is accounted for. Relevant factors are considered, uncertainties recognized and assumptions may be made during each stage, depending on information available. The estimated losses represent a complete mass balance for the substance over the life cycle of the substance 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.

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 any treatment, whether it be on-site industrial wastewater treatment or off-site municipal 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 PREPOD over its lifecycle are presented in Table 3 (Environment Canada 2010b).

Table 3. Mass Balance of PREPOD During Its Lifecycle [1]

Type of Loss	Proportion (%)	Pertinent Lifecycle Stages
Wastewater	6.2	Manufacture, industrial use, consumer/ commercial use
Land	-	–

Air	0.1	Manufacture, industrial use
Chemical transformation	Non-zero [2]	Industrial use, consumer/commercial use
Incineration	3.3	Industrial use, consumer/commercial use
Landfill	82.9	Manufacture, industrial use, consumer/commercial use
Recycling	7.6	–
Export	0	–

[1] For PREPOD, information from OECD 2004 was used to estimate releases to the environment and the distribution of the substance, as summarized in this table. Other documentation may have provided information for some assumptions.
[2] Potential chemical transformation of PREPOD stemming from the process of oxidation is acknowledged; however, at the present time the extent to which it occurs is not adequately documented in the available literature to allow quantification.

The above loss estimates indicate that PREPOD has a potential for release to the environment:

- Due to the very low concentrations of PREPOD in finished vehicles and car parts, its function, and the anticipated recycling or incineration of many of these vehicle parts, significant losses are not expected from these sources.
- In general, wastewater is a common source for releases of a substance to water and soil through wastewater treatment facilities and the subsequent waste management of sludge.
- Landfills, where the majority of the substance ends up, have the potential to leach the substance into groundwater. In areas where landfill leachate is collected and sent to a local sewage treatment plant for treatment, the substance can enter the receiving water via the effluent as well as the soil applied with the biosolids from the plant.

Although there is the possibility that other consumer/commercial products containing PREPOD may be imported into Canada in addition to those reported as a result of industry surveys conducted pursuant to Section 71 of CEPA 1999, no information is available on the quantity of such imports. It is anticipated that the life cycle stages and proportional losses resulting from use of these other products would not be significantly different from those considered and estimated above.

Rubber tire wear particles (TWP) containing PREPOD could be released into the environment, specifically, deposited on the side of roads and washed into sewers. There is some evidence that antioxidants can leach from TWP once the rubber particles come into contact with water (Wik 2007).

Environmental Fate

The results of Level III fugacity modelling (Table 4), based on the physical and chemical properties of the PREPOD components, are shown in Table 2. PREPOD is a UVCB mixture that is used primarily as a rubber additive. There is evidence that some rubber additives can leach from rubber tire wear particles (TWPs) into the environment (Wik 2007). However, it is uncertain which individual components in PREPOD could be released to the environment and this should be kept in mind when considering the results of the fugacity modelling. These results represent the partitioning of the PREPOD components in a hypothetical evaluative environment resulting from intermedia partitioning, and loss by both advective transport (out of the modelled region) and degradation/transformation (reaction) processes. The partitioning values shown in Table 4 represent the net effect of these processes under conditions of continuous release when a non-equilibrium "steady-state" has been achieved.

Table 4. Results of the Level III-fugacity modelling (EQC 2003)

	Percentage of Substance Partitioning into Each Compartment			
Component A released to	**Air**	**Water**	**Soil**	**Sediment**
Air (100%)	14.2	7.51	77.5	0.71
Water (100%)	negligible	91.4	0.01	8.62
Soil (100%)	negligible	0.67	99.3	0.06
Component B released to	**Air**	**Water**	**Soil**	**Sediment**
Air (100%)	34.1	12.5	47.4	6.00
Water (100%)	negligible	67.5	0.01	32.5
Soil (100%)	negligible	0.14	99.8	0.07
Component C released to	**Air**	**Water**	**Soil**	**Sediment**
Air (100%)	6.41	0.72	56	36.8
Water (100%)	negligible	1.91	Negligible	98.1
Soil (100%)	negligible	negligible	99.9	0.12
Component D released to	**Air**	**Water**	**Soil**	**Sediment**
Air (100%)	0.46	0.33	81.5	17.7
Water (100%)	negligible	1.85	0.0	98.2
Soil (100%)	negligible	0.0	99.9	0.13
Component D Analogue released to	**Air**	**Water**	**Soil**	**Sediment**
Air (100%)	0.05	0.05	94.9	5.05
Water (100%)	negligible	0.94	negligible	99.1
Soil (100%)	negligible	negligible	99.7	0.3

Except for Component A and Component B, all PREPOD components will have low or negligible partitioning to air, regardless of the medium of release. Component A and Component B will partly remain in air (14.2 % and 34.1 %, respectively) if released to air. All PREPOD components, if released solely to air, will tend to partition significantly to soil by deposition from air.

If released to water, Component A and Component B will remain in that medium to a significant degree. The other PREPOD components will not partition significantly to water, regardless of medium of release. If released into water, PREPOD Components C, D, and D Analogue are expected to strongly adsorb to suspended solids and sediment; Components A and B are also expected to adsorb, but to a lesser degree. Volatilization from water surfaces is expected to be a relatively insignificant fate process for all components except Component A, based on their estimated Henry's Law constants

If released to soil, all PREPOD components are expected to be highly sorbed to soil and, consequently, relatively immobile in that medium. Volatilization from dry and moist soil surfaces is expected to be a relatively insignificant fate process for all components except Component A, based on their estimated Henry's Law constants

The scenario for release to soil would be the most relevant based on the losses predicted by the MFT (see Table 3, above).

Persistence and Bioaccumulation Potential

Environmental Persistence

Table 5a presents the empirical biodegradation data (NITE 2002) that shows 0 and 5 percent biodegradation over 14 days in a ready-biodegradation test for Component A. This test indicates that the half-life of Component A in water is likely to be longer than 182 days (6 months) and that the substance is therefore likely to persist in that environmental compartment. Also shown in Table 5a, is the empirical biodegradation data (NITE 2002) that shows 0 and 1 percent biodegradation over 28 days in a ready-biodegradation test for the analogue of Component D. This test indicates that the half-life of Component D in water is likely to be longer than 182 days (6 months) and that the substance is therefore likely to persist in that environmental compartment.

Table 5a. Empirical data for persistence of PREPOD components

PREPOD substance	Medium	Fate Process	Degradation Value	Degradation Endpoint	Reference
Component A	Water	Biodegradation	0	BOD, % (14 days)	NITE 2002 (indirect analysis)
			5	UV-Vis, % (14 days)	NITE 2002 (direct analysis)
Component D Analogue	Water	Biodegradation	0	BOD, % (28 days)	NITE 2002 (indirect analysis)
			1	UV-Vis, % (28 days)	NITE 2002 (direct analysis)

Since few experimental data on the degradation of PREPOD components are available, a QSAR-based weight-of-evidence approach (Environment Canada 2007) was also applied using the degradation models shown in Table 5b below. None of the PREPOD components contain functional groups expected to undergo hydrolysis.

Tables 5b and 5c summarize the results of available QSAR models for degradation in air and water, respectively.

Table 5b. Modelled data for degradation of PREPOD components in air

Fate Process	Model	PREPOD substance	Model Result and Prediction $t_{1/2}$ (days)	Extrapolated Half-life (days)
Atmospheric oxidation	AOPWIN 2008 [1]	Component A	0.053	≤ 2
		Component B		
		Component D		
		Component D Analogue		
		Component C	0.052	
Ozone reaction	AOPWIN 2008 [1]	All PREPOD components	n/a [2]	n/a

[1] EPIsuite (2008)
[2] Model does not provide an estimate for this type of structure.

In air, all PREPOD components have a predicted atmospheric oxidation half-life value between 0.052 and 0.053 days (see Table 5b), which indicates that PREPOD components are likely to be rapidly oxidized. None of the PREPOD components are expected to react with other photo-oxidative species in the atmosphere, such as O_3 nor are they likely to degrade via direct photolysis. Therefore, it is expected that reactions with hydroxyl radicals will be the most important fate process in the atmosphere for PREPOD components. With a half-life of 0.052 to 0.053 days via reactions with hydroxyl radicals, PREPOD components are considered not persistent in air.

Table 5c. Modelled data for degradation of PREPOD components in water

Fate Process	Model and model basis	PREPOD substance	Model Result and Prediction	Extrapolated Half-life (days)
Hydrolysis	HYDROWIN 2008[1]	All PREPOD components	n/a [2]	n/a
Primary biodegradation (aerobic) [3]	BIOWIN 2008 [1] Sub-model 4: Expert Survey (qualitative results [4])	Component A	3.51 "biodegrades fast"	<182
		Component B	3.29 "biodegrades relatively fast"	<182
		Component C	3.03 "biodegrades relatively slowly"	<182
		Component D	2.94 "biodegrades relatively fast"	≥182
		Component D Analogue	2.86 "biodegrades relatively slowly"	≥182
Ultimate biodegradation (aerobic)	BIOWIN 2008[1] Sub-model 3: Expert Survey (qualitative results [4])	Component A	2.73 "biodegrades relatively slowly"	≥ 182
		Component B	2.39 "biodegrades relatively slowly"	≥ 182
		Component C	2.05 "biodegrades slowly"	≥ 182
		Component D	1.92 "biodegrades slowly"	≥ 182
		Component D Analogue	1.79 "biodegrades slowly"	≥ 182
	BIOWIN 2008[1] Sub-model 5: MITI linear probability [5]	Component A	0.13 "biodegrades slowly"	≥ 182
		Component B	0.07 "biodegrades very slowly"	≥ 182
		Component C	0.22 "biodegrades slowly"	≥ 182
		Component D	-0.51 "biodegrades very slowly"	≥ 182

		Component D Analogue	- 0.37 “biodegrades very slowly”	≥ 182
	BIOWIN 2008[1] Sub-model 6: MITI non-linear probability [5]	Component A	0.08 “biodegrades very slowly”	≥ 182
		Component B	0.03 “biodegrades very slowly”	≥ 182
		Component C	0.004 “biodegrades very slowly”	≥ 182
		Component D	0.0003 “biodegrades very slowly”	≥ 182
		Component D Analogue	0.0006 “biodegrades very slowly”	≥ 182
	CPOPs 2008 % BOD (biological oxygen demand) [3]	Component A	0.84 “biodegrades very slowly”	≥ 182
		Component B	2.12 “biodegrades very slowly”	≥ 182
		Component C	2.97 “biodegrades very slowly”	≥ 182
		Component D	2.58 “biodegrades very slowly”	≥ 182
		Component D Analogue	14.35 “biodegrades slowly”	≥ 1
	TOPKAT 2004 Probability	Component A	% BOD = 0 “biodegrades very slowly”	≥ 182
		Component B	% BOD = 0 “biodegrades very slowly”	≥ 182
		Component C	% BOD = 0 “biodegrades very slowly”	≥ 182
		Component D	% BOD = 2.6 “biodegrades very slowly”	≥ 182
		Component D Analogue	% BOD = 0 “biodegrades very slowly”	≥ 182

[1] EPIsuite (2008)
[2] Model does not provide an estimate for this type of structure.
[3] This result is interpreted from the perspective of ultimate degradation and without knowledge of the biodegradation products.
[4] Output is a numerical score from 0 to 5.
[5] Output is a probability score.

Results for the three BIOWIN ultimate biodegradation models (BIOWIN Sub-models 3, 5 and 6) indicate that biodegradation is slow for all PREPOD components and that the half-life of these components in water is ≥ 182 days. The results from BIOWIN Sub-model 4 indicates that primary biodegradation of PREPOD Components A, B, and C is not fast enough to suggest that complete mineralization is expected in less than 182 days. The identity of the degradation products resulting from primary degradation is also not known. In addition, the ultimate degradation predictions from TOPKAT and CPOPs indicate a slow rate of biodegradation for all PREPOD components. Also, PREPOD contains structural features associated with chemicals that are not easily biodegraded (e.g., aromatic amine). Therefore, considering all model results and structural features, there is reliable evidence to indicate that the ultimate biodegradation half-life of all PREPOD components is ≥ 182 days in water.

Using an extrapolation ratio of 1:1:4 for water: soil: sediment biodegradation half-life (Boethling et al. 1995), the ultimate biodegradation half-life of all PREPOD components in soil is also ≥182 days and the half-life of all PREPOD components in sediments is ≥365 days. This indicates that all PREPOD components are expected to be persistent in soil and sediment.

Based on the consistency between and among the empirical and modelled data (see Tables 5a, 5b, and 5c), the components of PREPOD meet the criteria for persistence in water, soil, and sediment (half-lives in soil and water ≥ 182 days and half-life in sediment ≥ 365 days), but do not meet the criteria for persistence in air (half-life in air ≥ 2 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential for Bioaccumulation

The modelled log K_{ow} values for PREPOD components indicate that they have moderate (Component A) to high (Component D Analogue) potential to bioaccumulate in biota (see Table 2).

Empirical BCF data for one PREPOD component and the analogue for Component D are presented below (Table 6a).

Table 6a. Empirical data for bioaccumulation of PREPOD components

PREPOD substance	Test organism	Endpoint	Value wet weight (L/kg)	Reference
Component A	Carp (*Cyprinus carpio*)	BCF	51-253	NITE 2002
Component D Analogue	Carp (*Cyprinus carpio*)	BCF	53-124	NITE 2002

Since BCF data are limited and no experimental bioaccumulation factor (BAF) data for PREPOD or its components were available, a predictive approach was applied using the Arnot-Gobas (2003, 2004) kinetic mass-balance model, as shown in Table 6b. A kinetic mass-balance model is, in principle, considered to provide the most reliable prediction

method for determining bioaccumulation potential because it allows for correction of the kinetic rate constants and bioavailability parameters, when possible. BCF and BAF model predictions are considered "in domain" for PREPOD and its analogues because it is based on first principles, and, as long as the mechanistic domain (passive diffusion), global parameter domain (range of empirical log K_{ow} and MW) as well as metabolism domain (corrected k_M) are satisfied, predictions are considered valid (Arnot and Gobas 2003, Arnot and Gobas 2006).

Since some empirical BCFs are known, in order to provide the best possible predictions of BCF and BAF, the kinetic mass-balance model was re-parameterized using metabolic rate constants normalized to fit the conditions of the study according to the procedures outlined in Arnot et al. (2008a). The study normalized kinetic rate constants and predicted BCF and BAF values are given in Table 6b.

From Table 6b it can be seen that, when the mass-balance model (v 1.1) is fitted to the available BCF data, model output closely predicts the measured BCF results from the NITE 2002 study. The kinetic rate constants are thus optimized for further model prediction. The BAFs for Components A,D and D Analogue were also predicted using the adjusted kinetic parameters. For Component A, at log K_{ow} 3.5 uptake via the diet is 0%, hence the model predictions for BAF are equal to the BCF predictions. The predicted BAFs for Component D and Component D Analogue are only low level and reflects the fact that ~35% and ~87% of the total exposure to fish is expected to occur via the diet, respectively.

The metabolic competency of an organism can be related to body weight and temperature (e.g., Hu and Layton 2001, Nichols et al. 2007). Metabolic rate constants (k_M) from Table 6b were therefore further normalized to the conditions of the middle trophic level fish. For Components B and C, no empirical BCF data were available to fit rate constants. Therefore, for metabolism rate, the QSAR method was used (Table 6c) (Arnot et al. 2009).

BCF and BAF estimates were then generated for all PREPOD components using a generic middle trophic level (MTL) fish (weight = 184g, lipid content = 6.8%, temperature = 10^{o}C) representative of Canadian waters which is also used in the Arnot-Gobas bioaccumulation model (Arnot and Gobas 2003, 2004). In addition, the CPOPs model (CPOPs 2008), which also takes metabolism into account, was used to predict the BCF of the PREPOD components.

Table 6b: Empirical study normalized rate constants and BCF/BAF predictions for components of PREPOD

Substance	Measured BCF[a]	Log K_{ow}	Uptake Rate Constants day^{-1} (k_1)[b]	Gill Elimination Rate Constant day^{-1} (k_2)[b]	Metabolic Rate Constant day^{-1} (k_M)[b]	Growth Rate Constant day^{-1} (k_G)[b]	Fecal Egestion Rate Constant day^{-1} (k_E)[b]	BCF[c]	BAF[c]	Reference
Component A	114	3.5	394	2.651	0.794	0.001	0.008	115	115	NITE 2002
Component D[f]	81	6.4	407	0.003	3.247[e]	0.001	0.007	81	100	NITE 2002
Component D Analogue	81	7.3	407	0.0004	0.978	0.005	0.007	81	407	NITE 2002

[a] geometric mean of available BCF steady state values reported
[b] calculated using mass-balance approach as outlined in Arnot et al. (2008a) when BCF is known and correcting for log K_{ow}, fish body weight, temperature and lipid content of fish from cited study
[c] BCF and BAF predictions calculated using kinetic parameters normalized to study conditions
[d] $k_T = (k_2 + k_M + k_G + k_E)$
[e] k_M estimated using QSAR method and normalized to conditions of middle trophic level fish
[f] rate constants based on BCF data for Component D Analogue

Table 6c: Modelled data for bioaccumulation of PREPOD components in fish using BCFBAF 2008 and CPOPs (2008)

PREPOD substance	LogK_{ow}	Metabolic Rate Constant MTL Fish[a]	BCF MTL Fish[b]	BAF MTL Fish[b]	BCF with Mitigating Factors[c]
Component A	3.5	0.448	144	144	112
Component B	4.1	0.280	398	407	331
Component C	7.1	0.077	676	18620	523
Component D	6.4	1.830	71	91	292
Component D Analogue	7.3	0.551	71	447	133

[a] k_M normalized to a representative middle trophic level fish (W=184g, L=6.8%, T=10°C)
[b] BCF reported for a representative middle trophic level fish (W=184g, L=6.8%, T=10°C)
[c] BCF model with Mitigating Factors (Dimitrov et al. 1995)

The modelled evidence indicates that all of the PREPOD components are not expected to bioconcentrate from water, as uptake rates via the gills are not sufficient to overcome elimination rates. The modelled BCFs for the middle trophic level fish are very comparable among all models and compare well with the empirical and analogue BCFs for Component A, D and D Analogue.). Metabolism corrected BCF values for all PREPOD components are well below 5000 the BCF criterion set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

However, PREPOD Component C has a predicted BAF greater than 5000, the BAF criterion set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000). It is expected that uptake via the diet for this component, which is expected to be ~73%, contributes significantly to the bioaccumulation of this compound. The predicted metabolism rate for this component for the middle tropic level fish is low (<0.1 day^{-1}) which suggests that the elimination rate is not sufficient to prevent bioaccumulation in tissues via the gastrointestinal tract (GIT). No information on the dietary uptake efficiency (E_D) of the Component C is available and the default model value used was 38%, which is not unreasonable given the structure and predicted rate of metabolism.

Arnot and Gobas (2006) critically evaluated available bioaccumulation data (BCF and BAF) for fish and other organisms. Part of this effort was stimulated by DSL Categorization efforts starting in 2000 and lead to an empirical database of quality BCF and BAF values that Canada has used for categorization and is now using for the Challenge (Arnot and Gobas 2003b). In Arnot and Gobas (2006), at a log K_{ow} of ~7.1 (i.e., Component C), the empirical distribution of "acceptable" fish BAF data shows that there are several chemicals with fish BAFs exceeding the Canadian criterion of BAF ≥5000 and thus, at this log K_{ow}, bioavailability is not overly restricted.

BCF and BAF modeling of PREPOD components is considered "in domain" for the Arnot-Gobas mass-balance model because, although the model has been parameterized based largely on halogenated neutral organism chemicals, the model is based on first principles and as long as the mechanistic domain (passive diffusion), global parameter domain (range of empirical log K_{ow} and molecular weight as well as metabolism domain (corrected k_M) are satisfied, predictions are considered valid. All of these domains have been satisfied in this assessment.

In conclusion, based on the available kinetic-based modelled BCF values corrected for metabolism, all PREPOD components have low potential to bioconcentrate from water exposures. However, the available kinetic-based modelled BAF values, corrected for metabolism, indicate that Component C has high potential to bioaccumulate via the diet. Therefore, PREPOD Component C (diisopropyldimethylacridan) meets the bioaccumulation criteria (BCF or BAF > 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 Component A are shown in Table 7a.

Table 7a. Experimental data for aquatic toxicity of PREPOD components

PREPOD component	Test organism	Type of test	Endpoint	Value	Reference
Component A	Medaka (Rice Fish) (*Oryzias latipes*)	Acute (48 hours)	LC_{50} [1]	5.1 mg/L	NITE 2002

[1] LC_{50} – The concentration of a substance that is estimated to be lethal to 50% of the test organisms.

Since there are limited experimental data available for the aquatic toxicity of PREPOD components, modelled data were used to estimate the potential for aquatic toxicity. Some of the values predicted by ECOSAR (neutral organic SAR), particularly those for acute toxicity, are higher than the predicted water solubility of the PREPOD components. However, an estimation error factor of 10, applied to the water solubility value, brings these toxicity values within the domain of the predicted water solubility. Table 7b contains the predicted ecotoxicity values that were considered as reliable and that were used in the QSAR weight-of-evidence approach for aquatic toxicity (Environment Canada 2007).

Table 7b. Modelled data for aquatic toxicity of PREPOD components using ECOSAR (neutral organic SAR)

Test organism	Type of test	Endpoint	PREPOD substance	Value (mg/L)
Fish	Acute (96 hours)	LC_{50}	Component A	6.2
			Component B	2.1
			Component C	0.008
			Component D	0.008
			Component D Analogue	0.00058 [1]
Fish	Acute (14 day)	LC_{50}	Component A	6.5
			Component B	2.2
			Component C	0.009
			Component D	0.009
			Component D Analogue	0.00065 [1]
Daphnid	Acute (48 hours)	EC_{50}	Component A	4.4
			Component B	1.6
			Component C	0.01
			Component D	0.009

			Component D Analogue	0.00086 [1]
Green algae	Acute (96 hours)	EC_{50}	Component A	4.0
			Component B	2.0
			Component C	0.041
			Component D	0.043 [1]
			Component D Analogue	0.007 [1]
Mysid Shrimp	Acute (96 hours)	LC_{50}	Component A	2.1
			Component B	0.46
			Component C	0.0002
			Component D	0.00019
			Component D Analogue	5.6×10^{-6}
Fish	Chronic (30 days)	ChV	Component A	0.72
			Component B	0.26
			Component C	0.001
			Component D	0.0011
			Component D Analogue	9.4×10^{-5} [1]
Daphnid	Chronic (16 days)	ChV	Component A	0.65
			Component B	0.27
			Component C	0.003
			Component D	0.002
			Component D Analogue	0.00028 [1]

LC_{50} – The concentration of a substance that is estimated to be lethal to 50% of the test organisms.
EC_{50} – The concentration of a substance that is estimated to cause some effect on 50% of the test organisms.
ChV– Chronic toxicity value
[1] Exposure value is at least ten times higher than the estimated water solubility.

A range of aquatic toxicity predictions for all PREPOD components were obtained from ECOSAR (2008). All acute and chronic toxicity values for Component D and its analogue and Component C were well below 1.0 mg/L. Since the results indicate a high hazard for at least two components, PREPOD is considered to be highly hazardous to aquatic organisms (acute $LC/EC_{50} \leq 1.0$ mg/L).

B - In Other Environmental Compartments

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

Ecological Exposure Assessment

Based on physical-chemical properties and predicted release patterns, the greatest environmental exposure to PREPOD is expected to be from soil and sediment. No data concerning concentrations of this substance in any medium in Canada have been

identified; therefore, environmental concentrations are estimated from available information, including estimated substance quantities, release rates, and size of receiving water bodies. The high quantity of this substance that is manufactured and used in Canada suggests that releases into the Canadian environment are likely occurring.

Industrial Release

The aquatic exposure of PREPOD is expected if the substance is released from industrial use to a wastewater treatment plant which 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 site-specific exposure analysis was conducted for the aquatic compartment at a total of 3 sites where PREPOD was manufactured, or used as a rubber additive. The days of operation were assumed to be 350 for manufacture and 250 for use, respectively. The quantity of the substance manufactured or used at each site was in the range of 10 000 to 500 000 kg/year (Environment Canada 2010a). Quantities for each of the four components were estimated based on compositional percentages reported for components in one commercial product (CRA 2010). A release of 0.05% was assumed for the manufacturing site, based on OECD (2009), and a release of 2.00% was assumed for the two use sites, based on 1% release from container handling (OECD 2004a) and 1% release from formulation of product (OECD 2004b). The wastewater containing PREPOD was then treated by off-site secondary wastewater treatment systems with model predicted removal rates ranging of 32.8% (Component A); 45.3 % (Component B); 80.2 % (Component C); and 80.6% (Component D) (ASTreat 2006). The effluents from these treatment systems were then released to rivers, lakes or coastal waters and site-specific dilution factors, limited to a factor of ten, were used in deriving the predicted environmental concentrations (PECs) from the effluent concentrations.

The estimated PECs for all components at the three industrial sites are shown in Table 8 (Environment Canada 2011). These PEC values represent the level of exposure in the

receiving water near the point of the discharge from the wastewater treatment plant for each site.

Characterization of Ecological Risk

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

Given the information on the quantity of PREPOD that is manufactured, imported, and used in Canada, and on the nature of its reported uses, release of PREPOD into the Canadian environment is expected. Once released in the environment, because of their resistance to degradation, Components A, B, C, and D of PREPOD are expected to remain in water, sediment and soil for a long time. Because of the lipophilic character of Component C, and as it also persists in the environment, this component will likely bioaccumulate. Modelled data suggest that Components C and D may have high acute and chronic aquatic toxicity. This information indicates that PREPOD has the potential to cause ecological harm in Canada.

A site-specific risk quotient analysis, integrating estimates of exposure with toxicity information, was performed for the aquatic medium at three sites to determine whether there is potential for ecological harm in Canada. The estimated PECs for all components at all three sites are shown in Table 8. The critical toxicity values (CTVs) chosen are the modelled 30-day chronic values (ChV) for rainbow trout, ranging from 1.1 µg/L to 720 µg/L. To derive the PNECs, the CTVs are divided by an assessment factor of 10 (to account for interspecies and intraspecies variability in sensitivity), to give values ranging from 0.11 µg/L to 72 µg/L. The resulting risk quotients (PEC/PNEC) are shown in Table 8,

Table 8: Risk Quotients for PREPOD Components

PREPOD Component	PEC (µg/L)	PNEC (µg/L)	RQ (PEC/PNEC)
Component A: site 1 (manufacture)	2.43	72	0.034
Component A: site 2 (use)	0.063		0.0009
Component A: site 3 (use)	0.535		0.007
Component B: site 1 (manufacture)	1.03	26	0.04
Component B: site 2 (use)	0.026		0.001
Component B: site 3 (use)	0.23		0.009
Component C: site 1	0.215	0.1	2.15

(manufacture)			
Component C: site 2 (use)	0.005		0.05
Component C: site 3 (use)	0.0473		0.47
Component D: site 1 (manufacture)	0.028	0.11	0.25
Component D: site 2	0.0007		0.006
Component D: site 3	0.0062		0.056

This information indicates that PREPOD, influenced in particular by Component C, could be causing ecological harm in Canada. An additive approach, in which the risk quotients for each of the four components is summed to estimate an overall risk quotient for the UVCB could be applied. However, it is not clear whether effects caused by these components would be fully additive.

As indicated above, Component C, in addition to having a risk quotient greater than 1 at the manufacturing site, is also expected to have high persistence in the environment and have a high bioaccumulation potential. For substances that are both persistent and bioaccumulative, risk quotients likely underestimate the potential for ecological harm. Substances that are persistent remain in the environment for a long time after being released, increasing the potential magnitude and duration of exposure. Substances that have long half-lives in mobile media (air and water) and partition into these media in significant proportions have the potential to cause widespread contamination. Releases of small amounts of bioaccumulative substances may lead to high internal concentrations in exposed organisms. The extent of bioaccumulation may not be fully reached over the duration of standard laboratory ecotoxicity tests.

Highly bioaccumulative and persistent substances are of special concern, since they may biomagnify in food webs, resulting in very high internal exposures, especially for top predators. Evidence that a substance is highly persistent and bioaccumulative, as defined in the *Persistence and Bioaccumulation Regulations* of CEPA 1999 (Canada 2000), when taken together with potential for environmental release or formation and potential for toxicity to organisms, provides a significant indication that it may be entering the environment under conditions that may have harmful long-term ecological effects.

Given that long term risks associated with persistent and bioaccumulative substances cannot at present be reliably predicted, quantitative risk estimates have increased uncertainty. Furthermore, since accumulations of such substances may be widespread and are difficult to reverse, a protective response to uncertainty is necessary.

Uncertainties in Evaluation of Ecological Risk

All modelling of a substance's physical and chemical properties and persistence, bioaccumulation potential, and aquatic toxicity characteristics is based on chemical

structures. As this substance is a UVCB, it cannot be completely represented by a single, discrete chemical structure. It is recognized that uncertainties exist when relating the results of this assessment for the individual components in PREPOD to the whole substance.

Uncertainty with the release and exposure characterization exists due to the lack of information on environmental concentrations in Canada of the PREPOD components. The high quantity of this substance manufactured and used in Canada indicates that releases into the Canadian environment are likely occurring.

There is uncertainty associated with the fact that few experimental data are available for the bioaccumulation potential and persistence of the PREPOD components and modelled results were used.

Regarding ecotoxicity, based on the predicted partitioning behaviour of this chemical, the significance of soil and sediment as important media of exposure is not well addressed by the effects or bioaccumulation data available. Indeed, the only effects and bioaccumulation data identified apply to pelagic aquatic exposures, although the water column may not be the medium of primary concern based on partitioning estimates.

Potential to Cause Harm to Human Health

Exposure Assessment

Environmental Media

Empirical data on concentrations in environmental media in Canada for PREPOD were not identified. PREPOD is not expected to be found in food or beverages. Environmental concentrations were estimated using the loss percentages summarized in the Mass Flow tool (see Table 3) (Environment Canada 2010b). The percentages were applied to the total quantity of PREPOD in Canadian commerce in 2006. The total quantity in commerce was conservatively assumed to be up to 1 000 000 kg (Environment Canada 2010a). The loss quantities are estimated to be 62 000 kg to water from wastewater, 1 000 kg to air from air emissions and 828 000 kg to soil from loss to landfill. These loss quantities to water and soil are considered to be overestimates, as explained in the Releases to the Environment section.

The estimated losses were used in ChemCAN, a Canada-specific environmental exposure model, to estimate concentrations in various environmental media (ChemCAN 2003). This model differs from the point source models used in the ecological assessment section of the document, which provide estimates of exposure near release points, in that it is a regional far-field level III fugacity model that is used to estimate average concentrations in various media to inform human exposure estimates. The estimated environmental concentations are presented in Appendix 2. Conservative upper-bounding daily intakes of PREPOD for the general population in Canada were derived based on the estimated environmental concentrations, resulting in an upper-bounding estimate of exposure from environmental media of 0.14 μg per kg-bw (kilogram of body weight) per day for toddlers (0.5 – 4 years) (see Appendix 3).

Consumer Products

No consumer product uses were identified. One commercial use was identified in response to a notice issued under section 71 of CEPA 1999. PREPOD is present in imported vehicle parts, namely in the front mounting bracket for engines, in brake components, and in already assembled automobiles at concentrations of 0.0023% by weight and 0.0003% by weight respectively (Environment Canada 2010a). Due to the very low concentrations of PREPOD in finished vehicles and car parts, and its function, exposure to vehicle passengers or drivers is not expected. In addition, while PREPOD may be present in some imported rubber tires, any incidental dermal contact with the tire is anticipated to result in negligible exposure.

Health Effects Assessment

The available health effect information for Components A, B, C and D of PREPOD, as described in Table 1b, were considered in this assessment.

As a precursor of PREPOD, DPA (Component A) is present in the PREPOD mixture as a residual component. It was classified by the US EPA (1998) as "not likely" to be a human carcinogen based on a lack of evidence of carcinogenicity**.** Orally administered, it is well absorbed (80-90 %) from the gastrointestinal tract in man and in several animal species. DPA is readily biotransformed to hydroxylated metabolites and their conjugates and excreted; no potential for bioaccumulation is expected (European Commission 2008). Regarding acute toxicity, the lowest oral LD_{50} value for DPA is 600 mg/kg-bw in hamster and the lowest dermal LD_{50} is greater than 2000 mg/kg-bw in rabbit. Based on the results of toxicity studies, DPA is not a skin sensitizer; however, it can cause serious damage to eyes (EURAR 2008). Due to predominantly negative results obtained from a wide range of *in vivo* and *in vitro* genotoxicity studies, and no evidence of increased tumour incidence in long term oral studies in various animal species, DPA is not considered to be genotoxic nor is it considered to be carcinogenic by EURAR (2008). The US EPA (1998) concluded that there was no developmental toxicity observed for DPA, and the European Commission (2008) concluded that the impairment of reproduction as well as any specific embryo-/fetotoxic or teratogenic potential capability of DPA are unlikely to occur in the absence of parental toxicity. Repeated dose toxicity studies indicated that the primary target organs in experimental animals after short- and long-term dietary exposure to DPA are the haematological system, kidneys, spleen and liver (EURAR 2008). Increase in the relative kidney weight as a systemic effect was also observed in rats due to subchronic dermal exposure (EURAR 2008). The LOAEL for the most sensitive toxicological effect of Component A of PREPOD (DPA), haematotoxicity (a slight anemia and formation of Heinz bodies), was determined to be 25 mg/kg-bw per day based on a 2-year oral toxicity study in rats (EURAR 2008). No marked species differences were evident for either the LOAEL or its correlated health effects. No inhalation toxicity study was identified for Component A (European Commission 2008; EURAR 2008; JMPR 1998).

No health effects information was identified for Components B and C. Potential analogues for Components B and C were not found to be associated with any additional health effects information. (Q)SAR models (Derek, TopKat, CaseTox and Leadscope Model Applier) were applied to Components B and C but outputs were mainly inconclusive or the structures of the components were out of the domain of applicability for the models.

Very limited health effects information was identified for Component D of PREPOD. Acute toxicity evaluation by Bayer AG (Bomhard 1977) indicates that Component D is neither a skin nor an eye irritant when tested on rabbits. The oral LD_{50} for Component D

tested in rats is greater than 10 000 mg/kg-bw. The outputs of (Q)SAR models (Derek, TopKat, CaseTox and Leadscope Model Applier) for Component D were mixed; results were mainly negative or inconclusive except for a positive prediction for chromosome aberrations *in vitro* in Casetox and Model Applier (see Appendix 6).

The health effects information available for Component D was limited and relevant toxicity data on analogues were also considered. Two analogues were identified for Component D based on their structural similarity: Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl) phenyl]- (CAS RN10081-67-1, referred to as DCDPA) and styrenated diphenylamine (CAS RN 68442-68-2, referred to as SDPA), as shown in Appendix 5. The degree of structural similarity is quantified using the Tanimoto association coefficient in SciFinder; this coefficient was 87% both between Component D and DCDPA, and Component D and SDPA. Additionally, one physico-chemical property (i.e., water solubility) fell within comparable range for Component D and its analogues.

A summary of the available health effects data for DCDPA and SDPA is provided in this section (with more details presented in Appendix 4). Regarding genotoxicity, SDPA was negative in an *in vivo* micronucleus test in mice bone marrow. Both DCDPA and SDPA were negative in inducing gene mutation in *Salmonella typhimurium* or *Escherichia coli* strains in both the presence and absence of metabolic activation. SDPA also tested negative in *Escherichia coli* strains in an *in vitro* DNA damage/repair study (CCR 1993; Goodyear 1980; Jones et al. 1985; US EPA 2009).

In a combined reproductive/developmental toxicity study, Sprague-Dawley rats were exposed to the analogue SDPA via gavage at 0, 50, 250 and 600 mg/kg-bw per day (43 days for males and 54 days for females). A higher percentage of pre-implantation losses, reduced offspring/litter and reduced litter weights were reported in dams treated at the high dose. Hepatotoxic effects were also reported in dams at this dose level. Developmental delays were noted as indicated by a delayed acquisition of surface righting reflex in high dose offspring; however, no treatment-related differences were observed in pinna unfolding tests (US EPA 2009).

In a repeated-dose oral toxicity study in Sprague-Dawley rats, SDPA was observed to cause hepatotoxicity, as indicated by increased relative liver weight, elevated alkaline phosphatise activity, vacuolisation of the periportal /centrilobular hepatocytes and reduced cholesterol level at 300 (LOAEL) and 1000 mg /kg-bw per day in a 28-day study (HRC 1994b). Similar hepatotoxic effects were also observed at higher dose levels in the 43-54 day study mentioned above (US EPA 2009). In addition to the liver effects, impaired blood clotting and kidney damage were also reported in rats treated at the high dose (1000 mg/kg-bw per day) in the 28-day study (HRC 1994b).

No chronic toxicity/carcinogenicity studies were identified for SDPA or DCDPA.

The confidence in the health effects database of PREPOD is considered to be very low as very limited empirical data were identified for the Component D and no health effects

information were available for Components B and C. However, the health effects information for Component A of PREPOD and for analogues of Component D, with limited additional (Q)SAR model results informed the hazard characterization of PREPOD.

Characterization of Risk to Human Health

The limited empirical health effect information identified for PREPOD components indicated a low potential for acute hazard by the oral route. Component A of PREPOD did not demonstrate genotoxic or carcinogenic potential. The outputs of (Q)SAR models (TopKat, CaseTox, Derek and Leadscope Model Applier) for genotoxicity and carcinogenicity for Component D of PREPOD were mainly negative or inconclusive. Empirical data for the analogues of Component D did not demonstrate genotoxic potential.

Component A was found to have no developmental toxicity potential by the US EPA (1998) and it was found unlikely to induce reproductive/developmental impairments in the absence of parental toxicity by the European Commission (2008). Additional reproductive toxicity studies for the analogue (SDPA) of Component D indicate that it induced the pre-implantation losses only at the high dose level (600 mg/kg-bw per day).

The most sensitive toxicological effect for PREPOD was determined to be haematotoxicity (slight anemia and the formation of Heinz bodies) induced by Component A, and a LOAEL of 25 mg/kg-bw per day was derived based on a 2-year oral toxicity study in rats. Comparison of the upper bounding estimate of exposure to PREPOD from environmental media (0.14 μg/kg-bw per day) and the oral LOAEL (25 mg/kg-bw per day) for haematotoxicity in rat for Component A, results in a margin of exposure of 178 570. This margin of exposure is considered adequate to address uncertainties in the health effects and exposure databases. General population exposure to PREPOD from use of consumer products is not expected.

Uncertainties in Evaluation of Risk to Human Health

Confidence in the environmental exposure estimate for PREPOD is low. Data in the literature were not identified for concentrations of this substance in environmental media. However, quantities in commerce for the 2006 calendar year are known and were combined with estimated loss percentages from Environment Canada's Mass Flow tool to model environmental concentrations. As the maximum value of the quantity in commerce range was used in the modeling, it is likely that the modeled results are conservative estimates of environmental exposure.

Based on the limited health effects data available, the confidence in the health effects assessment for PREPOD is considered to be low. However, the margin between an upper-bounding estimate of exposure from environmental media and the most sensitive

health effect level identified in the literature was adequate to address uncertainties in the health effects and exposure databases.

Conclusion

Based on the information presented in this final screening assessment, it is concluded that PREPOD is entering or may be 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. Based on combined experimental and modeled evidence, PREPOD likely contains many components that are persistent in the environment based on criteria set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000). Additionally, PREPOD contains at least one component (Diisopropyldimethylacridan) that also meets the bioaccumulation criteria.

Based on the information presented in this final screening assessment, it is concluded that PREPOD is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that PREPOD meets one or more 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 and, where appropriate, the performance of potential control measures identified during the risk management phase

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Appendix 1: PBT model inputs summary table for PREPOD components.

	Phys-Chem/Fate	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**PBT Profiling**	**Ecotoxicity**
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type 1 vs. Type 2 chemical)	OECD POPs Tool	Arnot-Gobas BCF/BAF Model	Gobas Wolf BMF Model	Canadian-POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER
SMILES Code									
Component A	N(c(ccc c1)c1)c(cccc 2)c2							N(c(ccc c1)c1)c(cccc2)c 2	N(c(cccc1) c1)c(cccc2)c2
Component B	N(c(c(ccc1)C (c2ccc c3)(C) C)c1)c 23							N(c(c(c cc1)C(c 2cccc3) (C)C)c1)c23	N(c(c(ccc1)C(c2cccc 3)(C)C)c1) c23
Component C	N1c3c cc(cc3 C(C)(C)c2c1c cc(c2) C(C)C) C(C)C							N1c3cc c(cc3C(C)(C)c2 c1ccc(c 2)C(C) C)C(C) C	N1c3ccc(c c3C(C)(C) c2c1ccc(c 2)C(C)C)C (C)C
Component D	c1cccc c1Nc2 ccc(cc 2)C(C) (C)c3c cc(cc3)Nc4cc ccc4							c1ccccc 1Nc2cc c(cc2)C (C)(C)c 3ccc(cc 3)Nc4c cccc4	c1ccccc1N c2ccc(cc2) C(C)(C)c3 ccc(cc3)N c4ccccc4
Component D Analogue	N(c2cc c(cc2) C(c3cc ccc3)(C)C)c4 ccc(cc 4)C(c1 ccccc1)(C)C							N(c2ccc (cc2)C(c3ccccc 3)(C)C) c4ccc(c c4)C(c1 ccccc1) (C)C	N(c2ccc(c c2)C(c3cc ccc3)(C)C) c4ccc(cc4) C(c1ccccc 1)(C)C
Molecular weight (g/mol)									
Component A		169.23	169.23						
Component B		209.29	209.29						

	Phys-Chem/Fate	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**PBT Profiling**	**Ecotoxicity**
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type 1 vs. Type 2 chemical)	OECD POPs Tool	Arnot-Gobas BCF/BAF Model	Gobas Wolf BMF Model	Canadian -POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER
Component C		293.46	293.46						
Component D		378.52	378.52						
Component D Analogue		405.58	405.58						
Melting point (ºC)									
Component A	52.90		52.90						
Component B			112.66						
Component C			144.78						
Component D			215.19						
Component D Analogue			214.52						
Boiling point (ºC)									
Component A									
Component B									
Component C									
Component D									
Component D Analogue									
Data temperature (ºC)									

	Phys-Chem/Fate	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**PBT Profiling**	**Ecotoxicity**
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type 1 vs. Type 2 chemical)	OECD POPs Tool	Arnot-Gobas BCF/BAF Model	Gobas Wolf BMF Model	Canadian -POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER
All Components			25						
Density (g/cm^3)									
All Components		1							
Vapour pressure (Pa)									
Component A			8.93×10^{-2}						
Component B			7.2×10^{-3}						
Component C			1.5×10^{-4}						
Component D			2.49×10^{-8}						
Component D Analogue			2.32×10^{-8}						
Henry's Law constant ($Pa \cdot m^3/mol$)									
Component A	0.273								
Component B									
Component C									
Component D									
Component D Analogue									
Log K_{aw} (Air-water partition coefficient; dimensionless)									

	Phys-Chem/Fate	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**PBT Profiling**	**Ecotoxicity**
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type 1 vs. Type 2 chemical)	OECD POPs Tool	Arnot-Gobas BCF/BAF Model	Gobas Wolf BMF Model	Canadian -POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER
All Components									
Log K_{ow} (Octanol-water partition coefficient; dimensionless)									
Component A	3.5	3.5 (1)	3.5			3.5			
Component B		4.14 (1)	4.14			4.1			
Component C		7.05 (1)	7.05			7.1			
Component D		7.2 (1)	7.2			6.4			
Component D Analogue		8.51 (1)	8.51			7.3			
Log K_{oc} (Organic carbon-water partition coefficient – L/kg)									
Component A									
Component B									
Component C									
Component D									
Component D Analogue									
Water solubility (mg/L)									
Component A	53		53						

	Phys-Chem/Fate	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**PBT Profiling**	**Ecotoxicity**
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type 1 vs. Type 2 chemical)	OECD POPs Tool	Arnot-Gobas BCF/BAF Model	Gobas Wolf BMF Model	Canadian -POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER
Component B			0.89						
Component C			4.0×10^{-3}						
Component D			3.0×10^{-3}						
Component D Analogue			6.77×10^{-6}						
Log K_{oa} (Octanol-air partition coefficient; dimensionless)									
All Components									
Soil-water partition coefficient (L/kg)[1]									
All Components									
Sediment-water partition coefficient (L/kg)[1]									
All Components									
Suspended particles-water partition coefficient (L/kg)[1]									
All Components									
Fish-water partition coefficient (L/kg)[2]									
All Components									

	Phys-Chem/Fate	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**PBT Profiling**	**Ecotoxicity**
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type 1 vs. Type 2 chemical)	OECD POPs Tool	Arnot-Gobas BCF/BAF Model	Gobas Wolf BMF Model	Canadian -POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER
Aerosol-water partition coefficient; dimensionless[3]									
All Components									
Vegetation-water partition coefficient; dimensionless[1]									
All Components									
Enthalpy (K_{ow})									
All Components									
Enthalpy (K_{aw})									
Half-life in air (days)									
Component A			0.053						
Component B			0.053						
Component C			0.052						
Component D			0.053						
Component D_Analogue			0.053						
Half-life in water (days)									
Component A			187.33						
Component B			183						

	Phys-Chem/Fate	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**PBT Profiling**	**Ecotoxicity**
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type 1 vs. Type 2 chemical)	OECD POPs Tool	Arnot-Gobas BCF/BAF Model	Gobas Wolf BMF Model	Canadian -POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER
Component C			183						
Component D			183						
Half-life in sediment (days)									
Component A			749.33						
Component B			732						
Component C			732						
Component D			732						
Half-life in soil (days)									
Component A			187.33						
Component B			183						
Component C			183						
Component D			183						
Half-life in vegetation (days)[4]									
Metabolic rate constant (1/days)									
Component A						0.448			
Component B						0.28			

	Phys-Chem/Fate	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**PBT Profiling**	**Ecotoxicity**
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type 1 vs. Type 2 chemical)	OECD POPs Tool	Arnot-Gobas BCF/BAF Model	Gobas Wolf BMF Model	Canadian -POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER
Component C						0.077			
Component D						1.83			
Component D_Analogue						0.551			
Biodegradation rate constant (1/days) or (1/hr) -specify									
Component A		0.55 (2) (1/d)							
Component B		0.55 (2) (1/d)							
Component C		0.17 (2) (1/d)							
Component D		0.17 (2) (1/d)							
Biodegradation half-life in primary clarifier ($t_{1/2\text{-}p}$) (hr)									
Component A		300							
Component B		300							
Component C		1000							
Component D		1000							
Biodegradation half-life in aeration vessel ($t_{1/2\text{-}s}$) (hr)									
Component A		30							
Component B		30							

	Phys-Chem/Fate	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**Fate**	**PBT Profiling**	**Ecotoxicity**
Model Input Parameters	EPISuite (all models, including: AOPWIN, KOCWIN, BCFBAF BIOWIN and ECOSAR)	STP (1) ASTreat (2) SimpleTreat (3) (required inputs are different depending on model)	EQC (required inputs are different if Type I vs. Type II chemical)	TaPL3 (required inputs are different if Type 1 vs. Type 2 chemical)	OECD POPs Tool	Arnot-Gobas BCF/BAF Model	Gobas Wolf BMF Model	Canadian -POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER
Component C		100							
Component D		100							
Biodegradation half-life in settling tank ($t_{1/2-s}$) (hr)									
Component A		30							
Component B		30							
Component C		100							
Component D		100							

[1] derived from $\log K_{oc}$
[2] derived from BCF data
[3] default value
[4] derived from half-life in water

Appendix 2: Estimated concentrations of PREPOD in environmental media using ChemCAN version 6.00 (ChemCAN 2003).[1]

Medium[2]	Estimated concentration
Ambient air[3]	0.0627 ng/m^3
Surface water	0.310µg/L
Soil	19.5 µg/g solids
Sediment	23.7 µg/g solids

[1]The concentrations were estimated for the area of southern Ontario.
[2]Default inflow concentrations of 2 ng/m^3 in air and 3 ng/L in water were specified by ChemCAN v6.00.
[3]The oxidative degradation half-life in air was assumed to be 0.053 days (AOPWIN 2008).

Appendix 3: Upper-bounding estimates of daily intakes of PREPOD for various age groups.

Route of exposure	Estimated intake (µg/kg-bw per day) of PREPOD by various age groups							
	0–0.5 years[1,2,3]			0.5–4 years[4]	5–11 years[5]	12–19 years[6]	20–59 years[7]	60+ years[8]
	Breast milk fed	Formula fed	Not formula fed					
Air[9]	1.76×10^{-5}	1.76×10^{-5}	1.76×10^{-5}	3.72×10^{-5}	2.94×10^{-5}	1.67×10^{-5}	1.43×10^{-5}	1.25×10^{-5}
Drinking water[10]	N/A	3.31×10^{-2}	1.24×10^{-2}	1.40×10^{-2}	1.10×10^{-2}	6.26×10^{-3}	6.56×10^{-3}	6.89×10^{-3}
Food and beverages[11]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Soil[12]	7.78×10^{-2}	7.78×10^{-2}	7.78×10^{-2}	1.26×10^{-1}	4.08×10^{-2}	9.83×10^{-2}	8.23×10^{-3}	8.11×10^{-3}
Total intake	7.78×10^{-2}	1.11×10^{-1}	9.02×10^{-2}	1.40×10^{-1}	5.18×10^{-2}	1.61×10^{-2}	1.48×10^{-2}	1.50×10^{-2}
Maximum total intake from all routes of exposure: 0.14 µg/kg-bw per day								

N/A, not available

[1] No quantitative data were identified for concentrations of PREPOD in breast milk.

[2] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day, to drink 0.8 L of water per day (formula fed) or 0.3 L/day (not formula fed) and to ingest 30 mg of soil per day (Health Canada 1998).

[3] For exclusively formula-fed infants, intake from water is synonymous with intake from food. No quantitative data on concentrations of PREPOD in drinking water or formula were identified for Canada. The concentration of PREPOD in drinking water was estimated using ChemCAN v6.00 at 0.310 µg/L (ChemCAN 2003). For non-formula-fed infants, approximately 50% are introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW 1990).

[4] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day (Health Canada 1998).

[5] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day (Health Canada 1998).

[6] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).

[7] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).

[8] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).

[9] No quantitative data were identified for concentrations of PREPOD in air. The concentration of PREPOD in air was estimated using ChemCAN v6.00 at 0.0627 ng/m^3 (ChemCAN 2003).

[10] No quantitative data were identified for concentrations of PREPOD in drinking water. The concentration of PREPOD in drinking water was estimated using ChemCAN v6.00 at 0.310 µg/L (ChemCAN 2003).

[11] No quantitative data were identified for concentrations of PREPOD in food or beverages.

[12] No quantitative data were identified for concentrations of PREPOD soil. The concentration of PREPOD in soil was estimated using ChemCAN v6.00 at 19.5 µg/g solids (ChemCAN 2003).

Appendix 4: Summary of health effects information for analogues DCDPA (CAS RN 10081-67-1) and SDPA (CAS RN 68442-68-2)

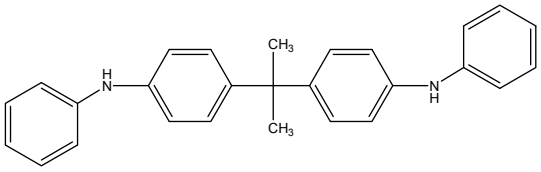
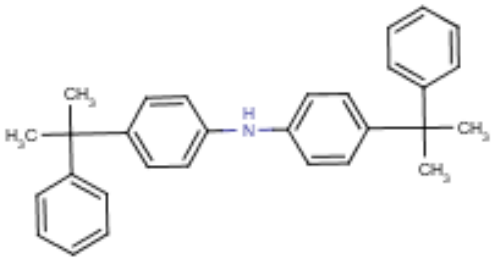
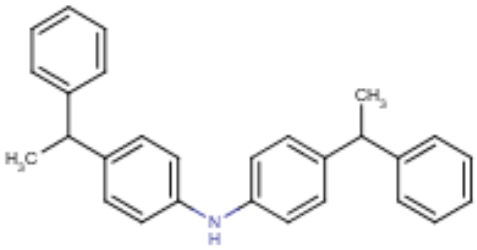
Endpoint	Lowest effect levels[1]/results
Laboratory animals and *in vitro*	
Acute toxicity	**DCDPA (CAS RN 10081-67-1)** **Oral LD_{50}** (rat) > 10 000 mg/kg-bw (US EPA 2003). **SDPA (CAS RN 68442-68-2)** **Oral LD_{50}** (rat) values: 500 to > 20 000 mg/kg-bw (US EPA 2003). **Oral LD_{50}** (rat) > 5000 mg/kg-bw (Bayer 1976**).** **Dermal LD_{50}** (rabbit) **>** 10 000 mg/kg-bw (US EPA 2009). No inhalation LD_{50} was identified for DCDPA or SDPA; no dermal LD_{50} was identified for DCDPA.
Short-term repeated-dose toxicity	**SDPA (CAS RN 68442-68-2)** In a 28-day study, groups of 5 male and 5 female Sprague-Dawley rats were given 0, 100, 300 or 1000 mg/kg-bw per day SDPA by gavage for 28 days. **Lowest oral LOAEL =** 300 mg/kg-bw per day based on reduced body weight gain and increased relative liver weight observed in mid-dose females; significantly increased alkaline phosphatise activity and decreased cholesterol, albumin and calcium level and vacuolisation of the periportal /centrilobular hepatocytes were observed in both sexes of mid-dose groups. Marked liver toxicity, characterised by increased liver weights, changes in enzyme activities, protein, cholesterol and bilirubin levels, impaired blood clotting, macroscopic and microscopic effects and decreased body weight gain were also observed in both sexes of high dose group animals. The high dose also caused kidney damage with changes in plasma electrolytes, urine volume, the specific gravity and pH of the urine and macro and microscopic effects (macro and microscopic effect only seen in one female however, interpreted by the investigators as treatment-related) (HRC 1994b). **Oral LOAEL =** 600 mg/kg-bw per day based on increased absolute and relative liver and adrenal weights in both sexes; and reduced cholesterol levels, increased activity for alkaline phosphatase and follicular cell hypertrophy in the thyroid glands in males in a combined reproductive/developmental toxicity screening test, in which the Sprague-Dawley rats (10 per sex per dose) were exposed to SDPA (suspension in corn oil) via gavage at 0, 50, 250 and 600 mg/kg-bw per day for 43 (males) and 54 (females) days. No deaths or treatment-related changes in body weight, growth, food and water intake or behavioural abnormality were seen in any treatment groups. Histopathological examination of the liver revealed centrilobular hepatocyte enlargement in all SDPA treated females and in mid- and high-dose treated males (US EPA 2009). **Oral LOAEL =** 1000 mg/kg-bw per day based on increased liver weight in both sexes of Sprague-Dawley rats exposed to 0, 100, 300 or 1000 mg/kg-bw per day of SDPA by gavage for 7 days (7-day dose finding study). No clinical abnormalities were seen other than slight, sporadic salivation due to the method

	of dosing (HRC 1994a). No repeated-dose toxicity studies identified for DCDPA (CAS RN 10081-67-1).
Reproductive and developmental toxicity	**SDPA (CAS RN 68442-68-2)** In the combined reproductive/developmental toxicity screening test described above, Sprague-Dawley rats (10 per sex per dose) were exposed to SDPA (suspension in corn oil) via gavage at 0, 50, 250 and 600 mg/kg-bw per day for 43 (males) and 54 (females) days. Females were terminated on day 5 post partum (with exposures before and after mating, during gestation and lactation for 4 days). No adverse effects on mating performance, fertility or gestation were observed. Females treated with 600 mg/kg-bw per day had a higher percentage of pre-implantation losses compared to controls, resulting in less offspring/litter when compared to controls and lower total litter weights. No clinical signs of toxicity were observed in the offspring. The mean offspring weights of treated animals were comparable to controls. Offspring from the 600 mg/kg-bw per day treated animals showed a delay in acquisition of surface righting reflex, however no treatment-related differences were observed in pinna unfolding tests. No treatment-related macroscopic abnormalities were observed at necropsy (US EPA 2009). **LOAEL (reproductive toxicity)** = 600 mg/kg-bw/day (based on higher pre-implantation losses). **LOAEL (developmental toxicity) =** 600 mg/kg-bw per day (based on a delay in acquisition of surface righting reflex). No reproductive or developmental toxicity studies were identified for DCDPA (CAS RN 10081-67-1).
Genotoxicity and related endpoints: *in vivo*	**Micronucleus formation** **SDPA (CAS RN 68442-68-2)** **Negative:** In bone marrow cells of male CD-1 mice after single oral administration of SDPA at 0, 500, 1000 and 2000 mg/kg-bw per day (US EPA 2009). **Negative:** In bone marrow cells of both sexes of NMRI mice after single i.p. injection of SDPA at 0, 400 and 4000 mg/kg-bw per day (mild cytotoxicity at high dose level) (**CCR 1993**). No *in vivo* genotoxicity studies identified for DCDPA (CAS RN 10081-67-1).
Genotoxicity and related endpoints: *in vitro*	**Gene mutation** **DCDPA (CAS RN 10081-67-1)** **Negative:** *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 with and without metabolic activation (Jones et al. 1985). **SDPA (CAS RN 68442-68-2)** **Negative:** *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation (US EPA 2009; Goodyear 1980). **Negative**: *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537; and *Escherichia coli* strain WP2uvrA with and without metabolic activation (US

	EPA 2009). **<u>DNA damage and repair</u>** **SDPA (CAS RN 68442-68-2)** **Negative:** *Escherichia coli* strains W3110 and p3478 with and without metabolic activation (US EPA 2009).
Irritation	**DCDPA (CAS RN 10081-67-1)** **Eye irritation:** In an ocular irritation test, 3 mg of EPRA **(**trade name of DDPA, CAS RN 10081-67-1) were applied to the right eye of each of six albino rabbits (sex and strain not specified), the untreated left eye served as a control. No gross signs of eye irritation were observed at any observation interval (24, 48 and 72 hours) following application of EPRA and no evidence of systemic toxicity from mucous membrane absorption was reported in the study (US EPA 2003). **Skin irritation:** 500 mg of EPRA was applied to skin of each of six albino rabbits (sex and strain not specified). EPRA produced no gross signs of dermal irritation on intact or abraded skin (US EPA 2003). **SDPA (CAS RN 68442-68-2)** **Eye irritation:** Six Albino rabbits (sex not stated) were instilled into one eye with SDPA (concentration not specified); the untreated eye served as the control. The test substance was rinsed out of the eye with water for three of the six rabbits. Mild eye irritation was noted in rabbits for which eyes were not rinsed (US EPA 2009). **Skin irritation:** SDPA has been classified to be a mild irritant to rabbit skin, study details were not provided (US EPA 2009).

[1] LC_{50}, median lethal concentration; LD_{50}, median lethal dose; LOAEL, lowest-observed-adverse-effect level; LOEL, lowest-observed-effect level; NOAEL, no-observed-adverse-effect level.

Appendix 5: PREPOD (Component D) and analogues used for human health assessment

Name / CAS RN / Short Name	Structure	Molecular Formula Molecular Weight (g/mol) Water Solubility (WS)
Component D of 2-Propanone, reaction products with diphenylamine (PREPOD) 68412-48-6		$C_{12}H_{11}N \times C_3H_6O$ MW: 378.52 g/mol WS: 0.002949 mg/L at 25°C (modelled)
Benzenamine, 4-(1-methyl-1-phenylethyl)-N-[4-(1-methyl-1-phenylethyl)phenyl]- 10081-67-1 DCDPA		$C_{30}H_{31}N$ MW: 405.58 g/mol Insoluble in water
Benzenamine, N-phenyl-, styrenated 68442-68-2 SDPA		$C_{28}H_{27}N$ MW: 377.53 g/mol Insoluble in water

Appendix 6: Summary of (Q)SAR results for Component D of PREPOD

(Q)SAR PREDICTIONS ON CARCINOGENICITY

Model/ Species	Mice		Rat		Rat	Mice	Rodent	Mammal
	Male	Female	Male	Female				
Model Applier	N	N	P	N	N	N	N	-
Multicase Casetox	IC	IC	IC	N	IC	IC	N	-
Topkat	IC	IC	IC	IC	-	-	-	-
Derek	-	-	-	-	IC	IC	-	-

P – positive;
N – negative;
'–' no model available in the QSAR suite;
IC – inconclusive (unreliable prediction based on user-defined model specific criteria other than model's applicability domain)

(Q)SAR PREDICTIONS ON GENOTOXICITY

Model/endpoints	chrom. ab.	chrom. ab. other rodent	chrom. ab. rat	micronucleus mice	micronucleus rodent	drosophila	drosophila HT	drosophila SLRL	mam. mutation	mam. mutation DL	UDS	UDS human lymphocytes	UDS rat hepatocytes	mouse lymphoma mut	s. cerevisiae	yeast	hgprt	e. coli	e. coli w	microbial	salmonella	BB cancer alert
MA	P	N	ND	ND	P	N	N	N	N	N	N	ND	N	N	N	N	N	ND	N	N	N	-
CT	P	-	-	N	-	IC	-	-	-	-	IC	-	-	P	-	-	-	-	-	-	IC	-
TK	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	IC	-

MA – model applier;
CT – Multicase Casetox;
TK – Topkat;
BB – Benigni-Bossa rulebase for mutagenicity and carcinogenicity (Toxtree model);
P – positive;
N – negative;
ND – not in domain (model indicates query chemical to be outside of its applicability domain);
'–' no model available in QSAR suite;
IC – inconclusive (unreliable prediction based on user-defined model specific criteria other than model's applicability domain).

(Q)SAR PREDICTIONS ON DEVELOPMENTAL TOXICITY

Model Applier

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

Multicase Casetox

Endpoint/Species	Hamster	Mammal	Miscellaneous
Teratogenicity	-	IC	IC
Developmental	IC	-	-

P – positive;
N – negative;
ND – not in domain (model indicates query chemical to be outside of it's applicability domain);
'–' no model available in QSAR suite;
IC – inconclusive (unreliable prediction based on user-defined model specific criteria other than model's applicability domain).

(Q)SAR PREDICTIONS ON REPRODUCTIVE TOXICITY

Model Applier

Model/ endpoint	Female			Male		
Species	mice	rat	rodent	mice	rat	rodent
repro	ND	ND	ND	ND	ND	ND
sperm	-	-	-	ND	ND	ND

Multicase Casetox

mice	rat	rabbit	human
IC	IC	IC	IC

ND – not in domain (model indicates query chemical to be outside of it's applicability domain);
'–' no model available in QSAR suite;
IC – inconclusive (unreliable prediction based on user-defined model specific criteria other than model's applicability domain).