Screening Assessment for the Challenge

Benzene, 1,3-bis(1-isocyanato-1-methylethyl)-
(Tetramethyl-*m*-xylylene diisocyanate)

Chemical Abstracts Service Registry Number
2778-42-9

Environment Canada
Health Canada

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Synopsis

Pursuant to section 74 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment on benzene, 1,3-bis(1-isocyanato-1-methylethyl)- (tetramethyl-*m*-xylylene diisocyanate), Chemical Abstracts Service Registry Number 2778-42-9. This substance was identified as a high priority for screening assessment and included in the Ministerial 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 tetramethyl-*m*-xylylene diisocyanate 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 by Health Canada for categorization of substances on the Domestic Substances List. Therefore, this assessment focuses on information relevant to the evaluation of ecological risks.

The substance tetramethyl-*m*-xylylene diisocyanate is an organic substance that is used as an industrial intermediate which is incorporated into various polymers. The substance is not naturally produced in the environment. No reports of manufacture in or import into Canada of this substance at or above the reporting threshold of 100 kg in the 2005 or 2006 calendar year were received in response to notices published under section 71 of CEPA 1999. However, six Canadian and two foreign companies voluntarily reported having a stakeholder interest in this substance in 2005 and 2006. Further information was not provided.

Since there were no reports of import or manufacture at or above the reporting threshold of 100 kg in 2005 or 2006, releases of this substance into the Canadian environment are presumed to be very low. Tetramethyl-*m*-xylylene diisocyanate reacts with water and is expected to hydrolyze rapidly in the presence of water or moisture. It is semi-volatile, and may have a tendency towards sizable losses via advection when released into the air.

Based on its reactivity in the presence of moisture, tetramethyl-*m*-xylylene diisocyanate is not expected to be persistent in the environment. Additional consideration of the hydrolysis data for this compound suggests that this compound is rapidly degraded in water and moist environments, such as sediment and moist soils. Similarly, the role of hydrolysis and the potential metabolism/degradation of tetramethyl-*m*-xylylene diisocyanate in the gut has been considered further. The substance is thus no longer expected to meet the persistence or bioaccumulation criterion as set out in the *Persistence and Bioaccumulation Regulations*.

For this screening assessment, a conservative exposure scenario was selected in which an industrial operation discharges into the aquatic environment. The predicted environmental concentration in water (PEC) was many orders of magnitude below predicted no-effect concentrations (PNECs) calculated for fish.

In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment.

Based on the information available, tetramethyl-*m*-xylylene diisocyanate does not meet any of the criteria set out in section 64 of the Canadian Environmental Protection Act, 1999.

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 human health. Based on the results of a screening assessment, the Ministers can propose to take no further action with respect to the substance, to add the substance to the Priority Substances List (PSL) for further assessment, or to recommend that the substance be added to the List of Toxic Substances in Schedule 1 of the Act and, where applicable, the implementation of virtual elimination.

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 benzene, 1,3-bis(1-isocyanato-1-methylethyl)- was identified as a high priority for assessment of ecological risk as it had been found to be persistent, bioaccumulative and inherently toxic to aquatic organisms and is believed to be in commerce in Canada. The Challenge for this substance was published in the *Canada Gazette* on May 12, 2007 (Canada 2007). 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, no submissions of new information were received for this substance.

Although benzene, 1,3-bis(1-isocyanato-1-methylethyl)- was determined to be a high priority for assessment with respect to the environment, it did not meet the criteria for GPE or IPE and high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or

reproductive toxicity. Therefore, this assessment focuses principally on information relevant to the evaluation of ecological risks.

Under CEPA 1999, 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 the Act, where

> "64. […] a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
>
> (*a*) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
>
> (*b*) constitute or may constitute a danger to the environment on which life depends; or
>
> (*c*) constitute or may constitute a danger in Canada to human life or health."

Screening assessments examine scientific information and develop conclusions by incorporating a weight of evidence approach and precaution.

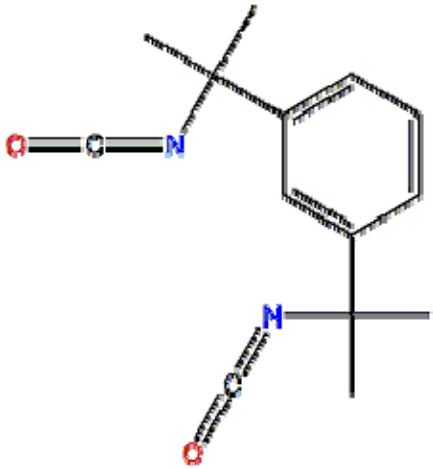
This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, stakeholder research reports and from recent literature searches, up to February 2008 for the ecological sections of the document. Key studies were critically evaluated; modelling results may have been used to reach conclusions. When available and relevant, information presented in hazard assessment from other jurisdictions was considered. The screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents the most critical studies and lines of evidence pertinent to the conclusion.

This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. Additionally, the draft of this screening assessment was subject to a 60-day public comment period. The critical information and considerations upon which the assessment is based are summarized below.

Substance Identity

For the purposes of this document, this substance will be referred to as tetramethyl-*m*-xylylene diisocyanate, which has been derived from the DSL inventory name. Other names and identifying characteristics of the substance are presented in Table 1.

Table 1. Substance identity

Chemical Abstracts Service Registry Number (CAS RN)	**2778-42-9**
Name on Domestic Substances List (DSL)	**Benzene, 1,3-bis(1-isocyanato-1-methylethyl)-**
Inventory names[1]	*Benzene, 1,3-bis(1-isocyanato-1-methylethyl)-* (TSCA, AICS, ASIA-PAC, NZIoC, DSL) *1,3-Bis(1-isocyanato-1-methylethyl)benzene* (EINECS, ENCS, ECL)
Other names	*α,α,α′,α′-Tetramethyl-m-phenylenedimethylene diisocyanate; α,α,α′,α′-Tetramethyl-m-xylylene diisocyanate; 1,3-Bis(a-isocyanatoisopropyl)benzene; Isocyanic acid, a,a,a',a'-tetramethyl-m-xylylene ester; Isocyanic acid, m-phenylenediisopropylidene ester; m-Bis(1-isocyanato-1-methylethyl)benzene; m-TMXDI; Tetramethyl-m-xylylene diisocyanate*
Chemical group (DSL stream)	Discrete organics
Major chemical class or use	Isocyanate
Chemical formula	$C_{14}H_{16}N_2O_2$
Chemical structure	
Simplified Molecular Input Line Entry System (SMILES)	O=C=NC(c1cc(ccc1)C(N=C=O)(C)C)(C)C
Molecular mass	244.30 g/mol

[1] National Chemical Inventories (NCI), 2007: AICS (Australian Inventory of Chemical Substances); ECL (Korean Existing Chemicals List); EINECS (European Inventory of Existing Chemical Substances); ENCS (Japanese Existing and New Chemical Substances); TSCA (Toxic Substances Control Act Chemical Substance Inventory); ASIA-PAC (Asia-Pacific Substances Lists); NZIoC (New Zealand Inventory of Chemicals).

Physical and Chemical Properties

Table 2 contains experimental and modelled physical and chemical properties of tetramethyl-*m*-xylylene diisocyanate that are relevant to its environmental fate.

Table 2. Physical and chemical properties for tetramethyl-*m*-xylylene diisocyanate

Property	Type	Value[1]	Temperature (°C)	Reference
Melting point (ºC)	Experimental	-10	--	Cytec Industries 2005
Boiling point (ºC)	Experimental	292	--	Cytec Industries 2005
	Modelled	320	--	MPBPWIN 2000
Density (kg/m^3)	No information available			
Vapour pressure (Pa)	Experimental	0.43 *(3.2E-3 mm Hg)*	25	Cytec Industries 2005
	Modelled	0.39 *(2.98E-3 mm Hg)*	25	MPBPWIN 2000 (using experimental boiling point and melting point in calculation)
	Modelled	1.4E-2 *(1.05 E-4 mm Hg)*	25	MPBPWIN 2000
Henry's Law constant (Pa·m^3/mol)	Modelled	3.26E-1 *(3.22 E-6 atm·m^3/mol)*	25	HENRYWIN 2000
Log K_{ow} (Octanol-water partition coefficient) (dimensionless)	Modelled	4.74	25	KOWWIN 2000
Log K_{oc} (Organic carbon-water partition coefficient) (dimensionless)	Modelled	5.05		PCKOCWIN 2000
Water solubility (mg/L)	Experimental	insoluble (reacts with water)		Cytec Industries 2005
	Modelled	2.289	25	WSKOWWIN 2000
	Modelled	5.83	25	WSKOWWIN 2000 (using experimental melting point in calculation)
	Modelled	5.94	25	WATERNT 2002
Other solubilities (g/L)	Experimental	n/a		
	Modelled	n/a		
pK_a (Acid dissociation constant) (dimensionless)	Experimental	n/a		
	Modelled	n/a		

[1] If different, values in brackets represent the original values as reported by the authors or as estimated by the models.

It is important to note that the modelling technique used to estimate octanol-water partition coefficients (K_{ow}) is a fragment addition method. The fragment addition method does not properly account for the rapid hydrolysis of the isocyanate groups on this compound, and calculates the log K_{ow} based on the isocyanate groups being incorporated in the final K_{ow} prediction. However, as the isocyanate groups are rapidly anticipated to hydrolyse to amines, the K_{ow} prediction is not expected to be environmentally relevant. The log K_{ow} for the compound containing diamines is predicted to be 1.89, as opposed to the log K_{ow} prediction for the diisocyanate compound, which is 4.74. As a result, this chemical type introduces uncertainty into the quantitative structure-activity relationship (QSAR) estimates.

Sources

The substance tetramethyl-*m*-xylylene diisocyanate is not known to be naturally produced in the environment.

Information gathered from the CEPA 1999 section 71 notices for the calendar years 2005 and 2006 indicate that tetramethyl-*m*-xylylene diisocyanate was not manufactured in or imported into Canada in a quantity meeting the 100 kg reporting threshold (Canada 2006b; Environment Canada 2006; Environment Canada 2007a). Six Canadian and two foreign companies identified themselves as having a stakeholder interest in the substance.

Elsewhere, tetramethyl-*m*-xylylene diisocyanate has been identified as a High Production Volume (HPV) chemical by the Organisation for Economic Co-operation and Development (1997), as an HPV in the United States (Sponsor Cytec Industries), and as a Low Production Volume (LPV) chemical in the European Union.

Uses

No uses were identified as a result of the section 71 notice (Canada 2006b; Environment Canada 2006; Environment Canada 2007a). However, tetramethyl-*m*-xylylene diisocyanate is used as a monomer in polymers that are being imported into Canada, as confirmed by the New Substances program. Over 40 such polymers have been identified. Previously, "Organic Chemicals, Industrial" was identified as the one use for this substance on the DSL in 1984–1986.

Additionally, a number of uses have been identified through the U.S. HPV program. Tetramethyl-*m*-xylylene diisocyanate is a versatile aliphatic isocyanate with broad end-use applicability. Tetramethyl-*m*-xylylene diisocyanate is used as an industrial intermediate that is incorporated into various polymers to improve performance. This chemical imparts improved physical properties to polyurethane products, affording higher strength and improved adhesion, appearance and flexibility, resulting in more durable products. Application areas for the polymers incorporating tetramethyl-*m*-xylylene diisocyanate include specialty coatings, aqueous dispersions, automotive coatings, wood

coatings, inks, sealants, adhesives, thermoplastic urethanes and lacquers. Common commercial products that may have been made using tetramethyl-*m*-xylylene diisocyanate include fabric and leather finishes, adhesives, automotive paints, printing inks, sealants and wood coatings. Tetramethyl-*m*-xylylene diisocyanate is approved by the United States Food and Drug Administration for use in food packaging under specific listings in the Code of Federal Regulations (CFR) Title 21 – Food and Drugs, Chapter I – Food and Drug Administration, Department of Health and Human Services (Cytec Industries 2005).

Releases to the Environment

Since there were no reports of import or manufacture at or above the reporting threshold of 100 kg in 2006 in response to a section 71 notice (Environment Canada 2007a), releases of this substance to the Canadian environment are presumed to be very low.

According to Cytec Industries (2005), tetramethyl-*m*-xylylene diisocyanate is not expected to be widely dispersed in the environment as a result of its usage patterns, as it is anticipated that the substance is not used directly but rather reacted into the polymers to which it is added (Cytec Industries 2005).

Once it is incorporated in the polymer, the molecular structure of the monomer is modified and therefore the integral structure of tetramethyl-*m*-xylylene diisocyanate would not be maintained. Even if the polymers containing this substance as a monomer can be released to the environment at different steps of their life cycle and subsequently break down to smaller components, the substance tetramethyl-*m*-xylylene diisocyanate itself would not be released in its structural integrity. Residual material (unreacted tetramethyl-*m*-xylylene diisocyanate) is also not expected to be present in the polymer because of the reactivity of this substance (see Environmental Persistence section).

Environmental Fate

Based on its physical and chemical properties (Table 2) and the results of Level III fugacity modelling (Table 3), tetramethyl-*m*-xylylene diisocyanate is not expected to partition to any significant degree beyond the medium to which it is emitted. This is due to the high reactivity rate (hydrolysis) of the compound overriding intermedia exchange rates. Loss of the compound from the unit world is solely a result of reaction.

Table 3. Results of the Level III fugacity modelling (EQC 2003)

	Percentage of substance partitioning into each compartment			
Substance released to:	**Air**	**Water**	**Soil**	**Sediment**
Air (100%)	100.0	0.0	0.0	0.0
Water (100%)	2.0	98.0	0.0	0.0
Soil (100%)	0.0	0.0	100.0	0.0

Tetramethyl-*m*-xylylene diisocyanate is expected to react rapidly in both water and soil, primarily as a result of hydrolysis and also in air, as a result of photo-oxidation, with rapid reactivity with hydroxyl radicals in the atmosphere anticipated. Abiotic reactions are the dominant loss processes in the unit world for releases to air, water and soil for this compound. However, for releases to air, based on this substance's semi-volatility, some losses from atmospheric transport, via advection, are expected.

Persistence and Bioaccumulation Potential

Environmental Persistence

Table 4a presents the empirical degradation data for Tetramethyl-*m*-xylylene diisocyanate.

Table 4a. Empirical data for persistence of tetramethyl-*m*-xylylene diisocyanate

Medium	Fate process	Degradation value	Degradation endpoint (unit)	Reference
Air	Hydrolysis	0.527	Half-life (days)	Cytec Industries 2005
Water	Hydrolysis	13.7	% ThOD (28 days)	Cytec Industries 2005

* ThOD = Theoretical Oxygen Demand

The empirical biodegradation data (Cytec Industries 2005), show 13.7 % biodegradation over 28 days in a ready-biodegradation test (OECD 301 D) for tetramethyl-*m*-xylylene diisocyanate (Table 4a). This indicates that the half-life in water and soil is longer than 182 days (6 months) (Environment Canada 2003), if hydrolysis is not considered. However, when hydrolysis is considered, this substance's half-life in water decreases significantly, as shown by empirical hydrolysis data from Cytec Industries (2005). A robust study summary for this study is presented in Appendix 1. Aliphatic diisocyanates are expected to react with water and form inert and insoluble polyureas under "normal" conditions (Infracor GmbH 2000; Sopac and Boltromejuk 1974). Similarly, aromatic diisocyanates, which are also reactive with water, have been observed to hydrolyze rapidly, forming insoluble polyureas (Pemberton and Tury 2004; Heimbach et al. 1996; Yakabe et al. 1999; Tury et al. 2003). Under certain conditions, particularly those exhibiting high dispersion coupled with low concentrations, there is potential for the formation of diamines as a result of hydrolysis (Sopac and Boltromejuk 1974).

Environment Canada considers hydrolysis to be a primary degradation process for most substances, and therefore is concerned with potential products of hydrolysis within the context of a screening assessment. It is anticipated that in addition to insoluble ureas forming as a result of the hydrolysis of tetramethyl-*m*-xylylene diisocyanate, there is a potential, under certain conditions (i.e., high dispersion and low concentrations), for the formation of tetramethyl-*m*-xylylene diamine; if it is assumed that hydrolysis products

and reactions of tetramethyl-*m*-xylylene diisocyanate will be similar to those of other aliphatic and aromatic diisocyanates (Pemberton and Tury 2004; Heimbach et al. 1996; Yakabe et al. 1999; Tury et al. 2003).

Experimental persistence information was not found for tetramethyl-*m*-xylylene diamine compounds from a literature search and biodegradation modelling was conducted on this compound. The diamine hydrolysis product is not predicted to be persistent in water, with a half-life from the BIOWIN 2000 Ultimate Survey Model estimated at 37.5 days. Using the QSAR-based weight-of-evidence approach, tetramethyl-*m*-xylylene diamine is not expected to be persistent in water.

Table 4b provides the biodegradation predictions for tetramethyl-*m*-xylylene diisocyanate. However, the extent to which these biodegradation models reflect the rapid hydrolysis of this compound and therefore provide meaningful persistence estimations in water, soil and sediment, is uncertain.

In the atmosphere, modelled data indicate that tetramethyl-*m*-xylylene diisocyanate is rapidly degraded via reactions with hydroxyl radicals (see Table 4b). Information on reaction rates with other oxidative species was not found, although AOPWIN 2000 did not predict this compound to be reactive with ozone (Table 4b). Despite the high reactivity of diisocyanate compounds with water, it has been observed for other diisocyanate compounds, such as toluene diisocyanate, that reaction with atmospheric water was not a significant fate process (Tury et al. 2003). Based on the evidence available, it is believed that tetramethyl-*m*-xylylene diisocyanate should not be considered persistent in the atmosphere based on reactions with photogenerated hydroxyl radicals. In addition, since tetramethyl-*m*-xylylene diisocyanate is not persistent in air, it is not expected to have long-range transport potential (LRTP).

Table 4b. Modelled data for persistence of tetramethyl-*m*-xylylene diisocyanate

Medium	Fate process	Degradation value	Degradation endpoint (unit)	Reference
Air	Atmospheric oxidation	1.056	Half-life (days)	AOPWIN 2000
Air	Ozone reaction	Not reactive	Half-life (days)	AOPWIN 2000
Water	Hydrolysis	< 10	Half-life (minutes)	HYDROWIN 2000
Water	Biodegradation	60	Half-life (days)	BIOWIN 2000, Ultimate survey
Water	Biodegradation	0	Probability	TOPKAT 2004
Water	Biodegradation	0.04	Probability	BIOWIN 2000, MITI Non-linear

Using an extrapolation ratio of 1:1:4 for a water: soil: sediment biodegradation half-life (Boethling et al. 1995), and the biodegradation half-life of 60 days obtained from the Ultimate survey model in BIOWIN (2000), the half-life in soil is also expected to be <182 days and the half-life in sediments <365 days. This indicates that tetramethyl-*m*-xylylene diisocyanate is not expected to be persistent in soil and sediment.

The weight of evidence based on the data described above indicates that tetramethyl-*m*-xylylene diisocyanate does not meet the persistence criteria for air (half-life in air ≥ 2 days) and water or soil (half-life in soil and water ≥ 182 days) or sediments (half-life in sediments ≥ 365 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential for Bioaccumulation

Experimental bioaccumulation values for this chemical were not found. It has been well documented that other aliphatic diisocyanates—as well as aromatic diisocyanates which are expected to be similarly reactive compounds—hydrolyze rapidly in the presence of moisture (Infracor GmbH 2000, Sopac and Boltromejuk 1974, Pemberton and Tury 2004, Heimbach et al. 1996, Yakabe et al. 1999, Tury et al. 2003). Bioaccumulation models cannot take into account the hydrolysis potential of substances. Therefore, modelled values for bioaccumulation offer little supporting evidence for bioaccumulation for substances that undergo near instantaneous reaction in the environment. Also, based on the high reactivity of diisocyanates, should any uptake of the parent compound occur, it is anticipated that it would be hydrolyzed and/or metabolized in the gut at rates significant enough to counter any potential for bioaccumulation.

The high reactivity of tetramethyl-*m*-xylylene diisocyanate with water also makes the determination of an experimental log K_{ow} difficult. As a result, the reliability of log K_{ow} values used as input into the bioaccumulation models is questionable.

Since no experimental bioaccumulation factor (BAF) or bioconcentration factor (BCF) data for tetramethyl-*m*-xylylene diisocyanate were available, a QSAR-based weight-of-evidence approach (Environment Canada 2007b), was applied using the BAF and BCF models shown in Table 5.

Table 5. Modelled bioaccumulation data for tetramethyl-*m*-xylylene diisocyanate

Test organism	Endpoint	Value wet weight (L/kg)	Reference
Fish	BAF	6870	Gobas BAF T2MTL (Arnot and Gobas 2003)
Fish	BCF	2700	Gobas BCF T2LTL (Arnot and Gobas 2003)
Fish	BCF	10 326	OASIS 2005
Fish	BCF	887	BCFWIN 2000

The Modified Gobas BAF middle trophic level model produced a BAF of 6870 L/kg. The results of BCF model calculations seem to indicate that this substance could have a high bioconcentration potential. However, because of the reactive nature of diisocyanates, it is anticipated that both the log K_{ow} predictions, and the bioaccumulation models that depend on them, likely significantly overestimate the lipophilic nature of these compounds.

To the extent that hydrolysis of tetramethyl-*m*-xylylene diisocyanate may form tetramethyl-*m*-xylylene diamine, in addition to insoluble polyureas, it is worthwhile to consider the bioaccumulation potential of the diamine hydrolysis product. An experimental log K_{ow} for tetramethyl-*m*-xylylene diamine was not found, however, an estimated log K_{ow} of 1.89 was predicted by KOWWIN (2000). This indicates that the bioaccumulation potential of this hydrolysis product of tetramethyl-*m*-xylylene diamine is low. Analogous bioaccumulation data from the potential hydrolysis products of similarly reactive aromatic diisocyanates would seem to support the conclusion of low bioaccumulation potential for these substances, with empirical BCFs for toluene diamine for example found to range from <5 to <50 in carp (MITI 1992).

The weight of evidence indicates that the substance tetramethyl-*m*-xylylene diisocyanate does not meet the bioaccumulation criteria (BCF or BAF $\geq$ 5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential to Cause Ecological Harm

Ecological Effects Assessment

In the Aquatic Compartment

There is modelled and experimental evidence that tetramethyl-*m*-xylylene diisocyanate causes harm to aquatic organisms at relatively low concentrations (Tables 6a and 6b).

Table 6a. Empirical data for aquatic toxicity of tetramethyl-*m*-xylylene diisocyanate

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
Algae	Acute (96 hours)	EC_{50}[1]	0.36*	Cytec Industries 2003
Daphnia	Acute (48 hours)	LC_{50}[2]	5.2	Cytec Industries 2005
Daphnia	Acute (48 hours)	NOEC[3]	< 1.0	Cytec Industries 2005
Fish	Acute (96 hours)	LC_{50}[2]	0.67	Cytec Industries 2005
Fish	Acute (96 hours)	NOEC[3]	0.32	Cytec Industries 2005

[1] EC_{50} – The concentration of a substance that is estimated to cause some toxic sublethal effect on 50% of the test organisms.
[2] LC_{50} – The concentration of a substance that is estimated to be lethal to 50% of the test organisms.
[3] NOEC – The no-observed-effect concentration is the highest concentration in a toxicity test not causing a statistically significant effect in comparison to the controls.
* Categorization pivotal iT value

The empirical toxicity data for tetramethyl-*m*-xylylene diisocyanate indicate that this substance is highly hazardous to aquatic organisms, with an LC_{50} to fish (*Pimephales promelas*) of 0.67 mg/L and an observed EC_{50} to algae (biomass) of 0.36 mg/L (Cytec Industries 2005; Cytec Industries 2003). A number of other chronic and acute toxicity

assays also provide evidence of the moderate to high hazard of this substance to aquatic organisms (Cytec Industries 2005). A robust study summary for the 2003 Cytek Industries study is presented in Appendix 1.

Based on the expected rapid hydrolysis of this substance, the role of tetramethyl-*m*-xylylene diisocyanate or that of a product of its hydrolysis in directly exerting these toxic effects, is uncertain. However, the evidence in either case suggests that tetramethyl-*m*-xylylene diisocyanate, its hydrolysis products, or a combination of the two, is highly hazardous to aquatic organisms.

A range of aquatic toxicity predictions were obtained from the various QSAR models considered (Table 6b). These results similarly indicate that the substance is moderately to highly hazardous to aquatic organisms.

Table 6b. Modelled data for aquatic toxicity of tetramethyl-*m*-xylylene diisocyanate

Test organism	Type of test	Endpoint	Value (mg/L)	Model/reference
Fish	Acute (96 hours)	LC_{50}[1]	1.35	ECOSAR 2004
			≤0.6	TIMES 2007 (Canadian-POPs) for Unspecified Reactive Mode
			49.76	AIES 2003-2005
			1.2	TOPKAT 2004
Daphnia	Acute (48 hours)	EC_{50}[2]	1.2	TOPKAT 2004

[1] EC_{50} – The concentration of a substance that is estimated to cause some toxic sublethal effect on 50% of the test organisms.
[2] LC_{50} – The concentration of a substance that is estimated to be lethal to 50% of the test organisms.

In Other Environmental Compartments

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

Ecological Exposure Assessment

No data concerning concentrations of tetramethyl-*m*-xylylene diisocyanate in environmental media (air, water, soil, sediment) in Canada have been identified. Environmental concentrations are, therefore, estimated from available information, including estimated substance quantities, release rates, and receiving water bodies.

Environment Canada's Industrial Generic Exposure Tool – Aquatic (IGETA) was employed to estimate the substance concentration (reasonable worst-case) in a generic water course receiving industrial effluents (Environment Canada 2008a). The generic scenario is designed to provide these estimates based on conservative assumptions regarding the amount of chemical processed and released, the number of processing days, the sewage treatment plant removal rate, and the size of the receiving watercourse. The

tool models an industrial-release scenario based on loading data from sources such as industrial surveys and knowledge of the distribution of industrial discharges in the country, and calculates a predicted environmental concentration (PEC). The equation and inputs used to calculate the PEC in the receiving water course are described in Environment Canada (2008b). Assuming a use quantity of 100 kg (which is the threshold reporting value for the 2005 section 71 notice, but which was not reached by any facility in Canada), the predicted environmental concentration in water (PEC) was 0.0006 mg/L.

Characterization of Ecological Risk

A conservative predicted no-effect concentration (PNEC) was estimated based on the NOEC to fish. The 96-hour NOEC for tetramethyl-*m*-xylylene diisocyanate was 0.32 mg/L. A factor of 100 was then applied to account for uncertainty in extrapolating acute to chronic (long-term) toxicity and from laboratory results to the field. The resulting PNEC is 0.0032 mg/L. When compared to the conservative PEC calculated above for industrial releases to water, the resulting risk quotient (PEC/PNEC) is 0.0006/0.0032 = 0.19. Therefore, it is estimated that concentrations of tetramethyl-*m*-xylylene diisocyanate in surface waters in Canada resulting from point source releases appear unlikely to cause adverse effects on populations of aquatic organisms. There is a five-fold margin of safety afforded by the conservative risk quotient to account for uncertainty associated with calculation of the PEC and PNEC.

Based on the available information, tetramethyl-*m*-xylylene diisocyanate does not persist in the environment and is not bioaccumulative based on criteria defined in the *Persistence and Bioaccumulation Regulations* (Canada 2000). Furthermore, in water this substance is expected to undergo relatively rapid hydrolysis, forming insoluble polyureas and diamines. Information on concentrations of tetramethyl-*m*-xylylene diisocyanate in the environment has not been identified at this time. However, the experimental ecotoxicological data indicate that tetramethyl-*m*-xylylene diisocyanate, and its hydrolysis products, could cause harm to aquatic organisms at relatively low concentrations in the water. Risk quotients for aquatic exposures indicate that tetramethyl-*m*-xylylene diisocyanate concentrations likely do not exceed concentrations associated with effects, even when using conservative scenarios and assumptions. Therefore tetramethyl-*m*-xylylene diisocyanate is unlikely to be causing harm to populations of aquatic organisms in Canada.

Uncertainties in Evaluation of Ecological Risk

Information on concentrations of tetramethyl-*m*-xylylene diisocyanate in the Canadian environment is currently lacking. However, the lack of importation or manufacture of tetramethyl-*m*-xylylene diisocyanate in Canada at significant volumes suggests very low releases of this chemical into the Canadian environment.

Significant uncertainties are also associated with the evaluation of physical and chemical properties and aquatic toxicity. Water solubility and log K_{ow} are principle considerations

in determining the fate and bioavailability of a substance and estimating its aquatic toxicity. Experimentally derived values for these properties were not available for tetramethyl-*m*-xylylene diisocyanate, as the rapid hydrolysis of aliphatic diisocyanates prevents the measurement of these properties. Similarly, due to the reactivity of this compound in the presence of moisture, the reliability of the predictions of these properties is questionable. This also has implications for the estimated bioaccumulation potential, as that endpoint is estimated from log K_{ow}.

There is also some uncertainty associated with the products of hydrolysis, as the assumptions regarding these products are based on observations and information from other aliphatic and aromatic diisocyanates (Infracor GmbH 2000, Sopac and Boltromejuk 1974, Pemberton and Tury 2004, Heimbach et al. 1996, Yakabe et al. 1999, Tury et al. 2003). However, information from Cytec Industries (2005) for tetramethyl-*m*-xylylene diisocyanate indicates that the reaction of this compound with water does result in the formation of insoluble polyureas.

The aquatic toxicity assessment for this substance has some uncertainty as it is not known if the aquatic toxicity empirically observed is a result of toxic effects exerted by tetramethyl-*m*-xylylene diisocyanate directly (e.g., as unreacted material), its hydrolysis products, or a combination of the two. The inherent toxicity for aquatic organisms may have an additional source of uncertainty in some situations, e.g., where these concentrations exceed the solubility of the chemical in water (either experimental or predicted). Given that concentrations for both the toxicity and water solubility often vary considerably (up to several orders of magnitude), it is acknowledged that these uncertainties exist.

For the exposure assessment, the predicted environmental concentration (PEC) accounts for concentrations in water only, so exposure through soils, suspended solids and sediments is not considered. However, given the current release scenarios and quantities used in Canada, exposure is not likely to be significant at this time. Potential releases from products that could contain this substance were not considered in the exposure scenario, adding uncertainty to the exposure characterization.

Conclusion

Based on the information presented in this screening assessment, it is concluded that tetramethyl-*m*-xylylene diisocyanate is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.

It is therefore concluded that tetramethyl-*m*-xylylene diisocyanate does not meet the definition of toxic as set out in section 64 of CEPA 1999. Additionally, tetramethyl-*m*-xylylene diisocyanate does not meet the criteria for persistence and bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

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Appendix I - Robust Study Summaries

ROBUST STUDY SUMMARY - Persistence

Item	Yes	No
***Reference*:** Cytec Industries. 2005. Test plan for TMXDI® (meta) aliphatic isocyanate: Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9 [Internet]. Washington (DC): US Environmental Protection Agency, High Production Volume (HPV) Challenge Program. [cited 2008 Aug]. Available from : http://www.epa.gov/hpv/pubs/summaries/isocyani/c13996rt2.pdf Details on the study taken from IUCLID Dataset (201-15835), Cytek Industries, 21-01-2005 Available from : http://www.epa.gov/HPV/pubs/summaries/isocyani/c13996rr3.pdf		
Test Substance CAS # and name: **2778-42-9; Isocyanic acid, m-phenylenediiso-propylidene**		
Substance purity reported? (Y/N **and** specify) **99.29%**	**X**	
Method		
References (Y/N)	**X**	
OECD, EU, national, or other standard method? (Y/N) OECD Guide-line 111 "Hydrolysis as a Function of pH"	**X**	
If not a standard method, justification of the method/protocol provided? (Y/N)	**n/a**	
Test design / conditions		
Study type (e.g., hydrolysis, biodegradation, etc.): hydrolysis		
Conditions type (aerobic or anaerobic): n/a		
Test medium (air, water, soil, or sediment): water		
Information on stability of the substance in the media of concern available? No		
Information on controls (Y/N **and** specify, positive or negative) **positive & negative**		**X**
Number of replicates (Y/N **and** specify)		**X**
Temperature (Y/N **and** specify) **25C**	**X**	
Test duration (Y/N **and** specify) **24 hours**	**X**	
Analytical method / technique used (Y/N)	**X**	
For photodegradation only		
Reactants of gas-phase reactions		
Light source (Y/N **and** specify)		
Light spectrum and/or relative intensity based on sunlight intensity (Y/N)		
For hydrolysis only		
Measured concentrations reported? (Y/N)		**X**
pH values reported? (Y/N **and** specify)	**X**	
For biodegradation only		
Ready or inherent biodegradation? ready		
Substance concentration (Y/N)		
Inoculum source (Y/N)		
Inoculum concentration ***or*** number of microorganisms (Y/N)		
Results		
Endpoints / values / units: t1/2 pH4: 0.4 h; t1/2 pH7: 0.4 h; t1/2 pH9: 0.3 h		
Information on breakdown products available? No		
Overall score: **7/10= 70%**		
***EC Reliability code*:** 2		

Reliability category *(high, satisfactory, low)*: **Satisfactory**
Comments:

ROBUST STUDY SUMMARY - Inherent Toxicity

Item	Yes	No
Reference: Cytec Industries. 2003. Isocyanic acid, m-phenylenediiso-propylidene, CAS# 2778-42-9 [report on the Internet]..Washington (DC): US Environmental Protection Agency, High Production Volume (HPV) Challenge Program. [cited 2008 Aug]. Available from: http://www.epa.gov/hpv/pubs/summaries/isocyani/c13996rr.pdf		
Test Substance: CAS 2778-42-9 and name: **2778-42-9; Isocyanic acid, m-phenylenediiso-propylidene**		
* **Substance purity reported?** (Y/N **and** specify) 98-99%	**X**	
Persistence/stability of test substance in aquatic solution reported? (Y/N)		**X**
Method		
References (Y/N)	**X**	
***OECD, EU, national, or other standard method**? (Y/N) **Based on methods outlined in the Committee on Methods for Toxicity Test with Aquatic Organisms, USEPA 660/3-75009. ABC Laboratories Protocol 7601.**	**X**	
If not a standard method, justification of the method/protocol provided? (Y/N)	**n/a**	
***GLP (Good Laboratory Practice)** (Y/N)	**X**	
Test organisms (specify common and/or Latin names) **(***Pimephales promelas*, Fathead minnow)		
Latin or both Latin and common names reported? (Y/N)	**X**	
Life cycle age / stage of test organism (Y/N)		**X**
Sex (Y/N)		**X**
Length and/or weight of test organisms (Y/N)	**X**	
Number of test organisms per replicate (Y/N) **10**	**X**	
Food type / feeding periods (acclimation/during test) (Y/N)	**X**	
Test design / conditions		
Test type – acute or chronic: acute		
Experiment type (laboratory or field) specified? (Y/N)	**X**	
System type (static, semi-static, flow-through) (Y/N) **static**	**X**	
Negative or positive controls? (Y/N **and** specify) **negative**	**X**	
Number of replicates (including controls) and concentrations (Y/N) **10 per test concentration**	**X**	
Exposure pathways (food, water, both) (Y/N)	**X**	
Exposure duration (Y/N **and** specify) **96h**	**X**	
***Measured concentrations reported?** (Y/N)		**X**
Exposure media conditions (temperature, pH, electrical conductivity, hardness, TOC, DOC, DO, major cations and anions; other) (Y/N)	**X**	
Was pH within 6-9 range? yes		
Was temperature within 5-28 °C range? yes		
Photoperiod and light intensity (Y/N)		**X**
Stock and test solution preparation (Y/N)	**X**	
Information on emulsifiers used for poorly soluble / unstable substances (Y/N)	**n/a**	
Analytical monitoring intervals (Y/N) **daily fish observation and water quality**	**X**	

parameters of temperature, dissolved oxygen and pH were measured throughout the test		
Statistical methods used (Y/N)	**X**	
Results		
Toxicity endpoints / values / units **96h NOEC 0.32 mg/L**		
Other endpoints reported (e.g. BCF/BAF, LOEC/NOEC, etc.) LC50 (96h) 0.67 mg/L		
***Was toxicity value below the chemical's water solubility**? (Y/N) **water solubility unknown**	**n/a**	
Other adverse effects (carcinogenicity, mutagenicity, etc)	n/a	
Score: major items – 3 / 4; overall score: 18/23=78%		
***EC Reliability code*:** 2		
Reliability category *(high, satisfactory, low)*: satisfactory		
Comments: Water solubility was not reported; nominal concentrations were used.		