Substance Profile for The Challenge [[4-[[2-(4-cyclohexylphenoxy)ethyl]ethylamino]-2-methylphenyl]methylene]-, propanedinitrile CAS No. 54079-53-7

Introduction

The Canadian Environmental Protection Act, 1999 (CEPA 1999) required the Minister of Health and Minister of the Environment to categorize the approximately 23 000 substances on the Domestic Substances List (DSL). Categorization involved identifying those substances on the DSL that are a) considered to be persistent (P) and/or bioaccumulative (B), based on criteria set out in the Persistence and Bioaccumulation Regulations (Government of Canada, 2000), and "inherently toxic" (iT) to humans or other organisms, or b) that present, to individuals in Canada, the greatest potential for exposure (GPE).

Further to this activity, the Act requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that meet the categorization criteria. A screening assessment involves a scientific evaluation of available information for a substance to determine whether the substance meets the criteria set out in section 64 of CEPA 1999. Based on the results of a screening assessment, the Ministers can propose taking no further action with respect to the substance, adding the substance to the Priority Substances List (PSL) for further assessment or recommending the addition of the substance to the List of Toxic Substances in Schedule 1 of CEPA 1999 and, where applicable, the implementation of virtual elimination of releases to the environment.

A number of substances have been identified by the Ministers as high priorities for action based on the information obtained through the categorization process. This includes substances:

- that were found to meet all of the ecological categorization criteria, including persistence, bioaccumulation potential and inherent toxicity to aquatic organisms (PBiT), and that are known to be in commerce in Canada, and/or
- that were found either to meet the categorization criteria for GPE or to present an intermediate potential for exposure (IPE), and were identified as posing a high hazard to human health based on available evidence on carcinogenicity, mutagenicity, developmental toxicity or reproductive toxicity.

Based on a consideration of the ecological and/or human health concerns associated with these substances, and the requirement under section 76.1 of CEPA 1999 for the Ministers to apply a weight of evidence approach and the precautionary principle when conducting and interpreting the results of an assessment, sufficient data are currently available to consider these substances as meeting the criteria under Section 64 of CEPA 1999.

As such, the Ministers have issued a Challenge to industry and other interested stakeholders through publication in Canada Gazette Part I December 9, 2006 to submit, within the timelines stated in the Challenge section of this document, below, specific information that may be used to develop and benchmark best practices for risk management and product stewardship.

The substance [[4-[[2-(4-cyclohexylphenoxy)ethyl]ethylamino]-2-methylphenyl] methylene]-, propanedinitrile was identified as a high priority for action as it was found to be persistent, bioaccumulative and inherently toxic to aquatic organisms and is believed to be in commerce in Canada. The technical human health and ecological information, that formed the basis for concern associated with this substance, is contained in Appendices I and II, respectively.

Substance Identity

For the purposes of this report, this substance will be referred to as "CHPD" ("cyclohexylphenoxy dinitrile"), which has been derived from the inventory name Propanedinitrile, [[4-[[2-(4-cyclohexylphenoxy)ethyl]ethylamino]-2-methylphenyl] methylene]-.

CAS Registry Number	54079-53-7			
Inventory name	Propanedinitrile, [[4-[[2-(4-cyclohexylphenoxy)ethyl]ethylamino]-2-methylphenyl]methylene]-			
Other names	[[4-[[2-(4-cyclohexylphenoxy)ethyl]ethylamino]-2-methylphenyl] methylene] malononitrile; [4-[[2-(4-Cyclohexylphenoxy)ethyl] ethylamino]-2-methylbenzylidene] malononitrile; N-2-[(4-Cyclohexyl) phenoxy]ethyl-N-ethyl-4-(2,2-dicyanoethenyl)-3-methylaniline			
Chemical group	Discrete organics			
Chemical sub-groups	Anilines; tertiary aromatic amines; aliphatic amines			
Chemical formula	$C_{27}H_{31}N_3O$			
Chemical structure (NCBI)	~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~ ~			
SMILES	N#CC(=Cc1c(cc(N(CCOc2ccc(cc2)C2CCCC2)CC)cc1)C)C#N			
Molecular mass (NCBI)	413.555g/mol			

Based on information submitted in response to a legal Notice published under Section 71 of CEPA 1999, up to 1000 kg of the substance were in commerce in Canada in 2000. Potential uses of this chemical include: colourant (pigment/stain/dye/ink); formulation component.

THE CHALLENGE

Based on the information presented in Appendix II of this document, it is expected that the screening assessment of this substance will conclude that it satisfies the definition of toxic under section 64 of CEPA 1999 in that it "may enter 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". The substance will then be proposed for addition to the List of Toxic Substances in Schedule I of the Act and proposed for virtual elimination of releases to the environment.

Subsequent risk management activities will be based on the objective of eliminating the release of a measurable quantity of a PBiT substance to the environment. In the absence of further information on existing handling practices for these substances, proposed actions would be based on realistic worst case assumptions. At this time, prohibition is being considering through regulations, of the manufacture, use, sale, offer for sale and import of this substance, except for those activities controlled under the *Pest Control Products Act* and/or the *Food and Drugs Act*.

Opportunity to Submit Information on P, B and iT Properties

Through the categorization exercise, available experimental aquatic toxicity information as well as experimental data on the potential for a substance to persist or bioaccumulate in the environment were collected prior to December 2005. Where acceptable experimental data were not available, Quantitative Structure Activity Relationships (QSARs) or read across data were used to fill the data gaps. Since the categorization outcome on P, B, and iT form the basis for prioritizing this substance for action, and experimental data are preferred, interested parties have an opportunity to provide relevant experimental study information on the persistence, bioaccumulation, and inherent toxicity to aquatic organisms for this substance.

Efforts should focus on providing data for the endpoints for which quality experimental data does not already exist, as demonstrated by the information summarized in Appendix II of this document. As submitted data will be evaluated for completeness and robustness, it is recommended that stakeholders follow the guidance for test protocols and alternative approaches for test data, as described in Section 8 of the "Guidelines for the Notification and Testing of New Substances: Chemicals & Polymers". ¹

Responses to this part of the challenge for this substance should be received at the address provided below by June 5, 2007.

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¹ "Guidelines for the Notification and Testing of New Substances: Chemicals & Polymers (version 2005)", Government of Canada, Available from http://www.ec.gc.ca/substances/nsb/eng/cp_guidance_e.shtml

Opportunity to Submit Additional Information on Current Uses and Existing Control Measures to Inform the Risk Management Approach for this Substance

The Ministers of Health and Environment are inviting the submission of additional information that is deemed beneficial by interested stakeholders, relating to the extent and nature of the management/stewardship of substances listed under the Challenge.

Organizations that may be interested in submitting additional information in response to this invitation include those that manufacture, import, export or use this substance whether alone, in a mixture, in a product or in a manufactured item.

Additional information is being invited in the following areas:

- Import, manufacture and use quantities
- Substance and product use details
- Releases to the environment and spill management
- Current and potential risk management and product stewardship actions
- Existing legislative or regulatory programs controlling/managing the substance
- Information to support the development of a regulatory impact assessment.

A questionnaire is available which provides a detailed template as an example for the submission of this information. Guidance on how to respond to the challenge questionnaire is also available. Interested stakeholders are invited to provide available additional information, recognizing that not all questions in the questionnaire may be relevant to a particular substance, use, or industrial sector.

Copies of the questionnaire and associated guidance are available from the Government of Canada Chemicals Portal (www.chemicalsubstanceschimiques.gc.ca), or from the contact provided below.

Responses to this part of the challenge for this substance should be received at the address provided below by June 5, 2007.

Request for Documents and Submission of Information

Documents and instructions may be requested from the following contact. Information in response to the above Challenge must be submitted to this address.

DSL Surveys Coordinator Place Vincent Massey, 20th Floor 351 Saint Joseph Boulevard Gatineau QC K1A 0H3

Tel: 1-888-228-0530/819-956-9313 Fax: 1-800-410-4314 / 819-953-4936

Email: DSL.surveyco@ec.gc.ca

Appendix I Human Health Information to Support The Challenge for [[4-[[2-(4-cyclohexylphenoxy)ethyl]ethylamino]-2methylphenyl]methylene]-, propanedinitrile (CHPD) CAS No. 54079-53-7

Introduction

Under the *Canadian Environmental Protection Act, 1999* (CEPA, 1999), Health Canada undertook to categorize all substances on the Domestic Substances List (DSL) to identify those representing the greatest potential for human exposure (GPE) and those among a subset of substances considered persistant (P) and/or bioaccumulative (B) that are also considered to be "inherently toxic" to humans.

In order to efficiently identify substances that represent the highest priorities for screening assessment, Health Canada developed and applied a Simple Exposure Tool (SimET) to the DSL to identify those substances that meet the criteria for GPE, Intermediate Potential for Exposure (IPE) or Low Potential for Exposure (LPE), and a Simple Hazard Tool (SimHaz) to identify those substances that pose a high or low hazard.

CHPD is considered to meet the criteria for LPE under SimET and does not meet the criteria for high hazard under SimHaz. This document summarizes the currently available information on which the SimET and SimHaz results are based.

Exposure Information from Health Related Components of DSL Categorization

As mentioned above, SimET was developed and used to identify substances on the DSL considered to represent GPE. This approach was based on three lines of evidence: 1) the quantity in commerce in Canada, 2) the number of companies involved in commercial activities in Canada (i.e., number of notifiers), and 3) the consideration by experts of the potential for human exposure based on various use codes. The proposed approach was released for public comment in November 2003 and also enabled designation of substances as presenting an IPE or LPE, based on criteria for quantity and nature of use (Health Canada, 2003).

Results of the Application of SimET

CHPD has been determined to be LPE based on a consideration of the DSL nomination information listed below.

Nomination Information for DSL

Quantity in Commerce

The quantity reported to be manufactured, imported or in commerce in Canada during the calendar year 1986 was 1100 kg.

Number of Notifiers

The number of notifiers for the calendar years 1984-1986 was < 4.

Use Codes and Description

The following DSL use codes have been identified for the substance:

- Colourant pigment/stain/dye/ink
 Formulation component
 Pigment, Dye and Printing Ink
- 86 Plastics

Hazard Information from Health Related Components of DSL Categorization

Simple Hazard Tool (SimHaz)

SimHaz is a tool that has been used to identify, among all of the approximately 23 000 substances on the DSL, those considered to present either high or low hazard to human health based on formalized weight of evidence criteria and/or peer review/consensus of experts. This tool has been developed through extensive compilation of hazard classifications of Health Canada and other agencies and consideration of their robustness based on availability of transparent documentation of both process and criteria (Health Canada, 2005).

Results of the Application of SimHaz

CHPD has not been classified for hazard by any of the agencies considered under the SimHaz tool and therefore does not meet the criteria for high hazard under SimHaz.

Uncertainties

SimET and SimHaz have been developed as robust tools for effectively identifying substances from the DSL considered to be human health related priorities for further consideration. It is recognized that they do not include a number of elements normally

considered in a human health risk assessment such as a comprehensive characterization of exposure and hazard, a comparison of exposure metrics to hazard metrics, and a detailed analysis of uncertainties.

References

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Health Canada. 2005. Proposed Integrated Framework for the Health-Related Components of Categorization of the Domestic Substances List under CEPA 1999. http://www.hc-sc.gc.ca/ewh-semt/alt-formats/hecs-sesc/pdf/contaminants/existsub/framework-int-cadre-e.pdf

Appendix II

Ecological Information to Support The Challenge for

[[4-[[2-(4-cyclohexylphenoxy)ethyl]ethylamino]-2-methylphenyl]methylene]-, propanedinitrile (CHPD) CAS No. 54079-53-7

Introduction

The information in this document will form the basis of a screening assessment under section 74 of CEPA, 1999. Data relevant to an ecological screening assessment were identified in original literature, review documents, commercial and government databases prior to December 2005. Properties and characteristics may also have been estimated using Quantitative Structure Activity Relationship (QSAR) models. In addition, an industry survey was conducted for the year 2000 through a Canada Gazette Notice issued pursuant to section 71 of CEPA 1999 (Environment Canada, 2001). This Notice requested data on the Canadian manufacture, import, uses and releases of the substance.

Physical and Chemical Properties

Experimental data on physico-chemical properties of CHPD are not available. Table 1 contains modelled data which are relevant to the environmental fate of this chemical.

Table 1: Modelled physico-chemical properties for CHPD

Property	Value/Units	Reference
Melting point (MP)	243.76 °C	MPBPWIN v.1.41
Boiling point (BP)	566.71 °C	MPBPWIN v.1.41
Henry's Law constant (HLC)	$3.69 \times 10^{-12} \text{ atm-m}^3/\text{mole}$	HenryWin v3.10
log Koc	6.282	PCKOCWIN v.1.66
log Kow	7.88	Kowwin v.1.67
Vapour pressure (VP)	$3.066 \times 10^{-10} \text{ Pa}; 2.3 \times 10^{-12} \text{ mm Hg}$	EPIWIN v3.12
Water solubility (WS)	0.0002544 mg/L	WSKOW v.1.41

Manufacture, Importation, and Uses

Manufacture and Importation

A survey conducted pursuant to section 71 of the CEPA 1999 indicated that during the year 2000, CHPD (CAS No. 54079-53-7) was not manufactured in Canada in a quantity meeting the 100kg reporting threshold. In addition, no companies reported that they

manufactured or imported CHPD, in a mixture or product at a concentration less than 10 grams per kilogram (< 1% w/w) in the year 2000 (Environment Canada, 2001).

One company reported importing between 100 and 1000 kg of CHPD into Canada in 2000 (Environment Canada, 2001).

Elsewhere, CHPD was used in the USA. According to the information provided by the US EPA, in the years 1994, 1998, and 2002, import/usage quantities were in the range of 4.5-225 tonnes/year.

According to the Substances in Preparations in Nordic Countries database (SPIN), this chemical was used in Sweden and Denmark in the years 1999-2004. However, information on exact use quantities and use patterns is not open to the public.

Uses

For uses reported in the calendar year 1986, refer to Appendix I. Information on use received through the S. 71 survey (Environment Canada, 2001) has been claimed as confidential business information (ESB, 2003).

Releases, Fate, and Presence in the Environment

Releases

The substance CHPD is not naturally produced in the environment.

The company importing this substance did not report a release of this chemical to the environment. Considering that the Section 71 survey did not gather release information from users of the substance, and given that based on available information, use of the chemical could be dispersive, it is expected that CHPD is being released into the Canadian environment, although the quantities of the releases are unknown.

Fate

The very high log K_{oc} value of ~6.3 (Table 1) indicates that if released into water, this chemical is expected to strongly adsorb to suspended solids and sediments. Volatilization from water surfaces is not expected based upon an estimated Henry's Law constant of 3.69×10^{-12} atm-m³/mole (Table 1). Thus, if water is a receiving medium, CHPD is expected to mainly partition into sediments, which can be illustrated by the results of Level III Fugacity modelling (Table 2).

Table 2: Results of the Level III fugacity modelling (EPIWIN V3.12) for CHPD

Receiving media	% in Air	% in Water	% in Soil	% in Sediment
Air (100%)	0.03	0.19	85.2	14.6
Water (100%)	0.00	1.26	0.00	98.7
Soil (100%)	0.00	0.00	99.8	0.19
Air, water, soil (33.3% each)	0.00	0.71	44	55.2

If released to soil, CHPD is expected to have extremely high adsorptivity to soil, i.e. expected to have very low mobility in this environmental compartment, based upon an estimated log K_{oc} of ~ 6.3 (Table 1). Volatilization from moist soil surfaces seems to be an unimportant fate process based upon an extremely low Henry's Law constant of 3.7×10^{-12} atm-m³/mol. This chemical will not volatilize from dry soil surfaces based upon estimated vapor pressure of 3×10^{-10} Pa. Therefore, if soil is a receiving medium, CHPD is expected to remain almost exclusively in soil, as indicated by the results of Level III Fugacity modelling (Table 2).

An extremely low value of a vapour pressure of 3×10^{-10} Pa (Table 1) indicates that CHPD is a non-volatile chemical, and it is expected to exist solely in the particulate phase in the ambient atmosphere.

Therefore, it can be concluded that when this chemical is released to the environment, soil and sediment are expected to be the major media of concern.

Presence in the Environment

No monitoring data relating to the presence of this substance in environmental media (air, water, soil, sediment) have been identified.

Evaluation of P, B, and iT Properties

Environmental Persistence

For air, no experimental persistence data are available for CHPD. QSAR predictions show that once released into the environment, this chemical seems to be rapidly oxidized, as indicated by an atmospheric oxidation half-life value of 0.04 days (Table 3), assuming an average atmospheric hydroxyl-radical concentration of 1.5×10^6 molecule/cm³.

Ozone-reaction half-life is quite long: 218 days (Table 3). This compound is not expected to react appreciably with other photo-oxidative species in the atmosphere such as NO₃, nor is it 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 CHPD, and with a half-life of 0.04 days via reactions with hydroxyl radical, this chemical is not persistent in air.

Table 3: Predicted persistence values for CHPD

Medium	Fate Process	Degradation Value	Degradation Endpoint	Reference
Air	Atm. oxidation	0.0414	Half-life (days)	EPIWIN v3.12
Air	Ozone reaction	218	Half-life (days)	EPIWIN v3.12
Water/Soil	Biodegradation	182	Half-life (days)	BIOWIN v4.01, Ultimate survey
Water/Soil	Biodegradation	0.0106	Probability	BIOWIN v4.01, MITI Non-linear Probability
Water/Soil	Biodegradation	0.0782	Probability	BIOWIN v4.01, MITI Linear Probability
Water/Soil	Biodegradation	0	Probability	Topkat v.6.1

For estimating biodegradation in water, a QSAR-based weight-of-evidence approach (ESD, 2006a) was applied using the models shown in Table 3. Based on these results, the estimated timeframe for biodegradation indicates that CHPD can be considered as persistent in water.

To extrapolate half-life in water to half-lives in soils and sediments, an approach has been developed using Boethling's extrapolation factors ($t_{1/2 \text{ water}}$: $t_{1/2 \text{ soil}}$: $t_{1/2 \text{ sediment}} = 1$: 1: 4, BIOWIN v4.01). Estimated timeframe for biological degradation of CHPD indicates that this chemical is expected to be persistent in soil and sediments.

The long-range transport potential (LRTP) of Propanedinitrile, CHPD is estimated to be low according to the model prediction presented in Table 4. The TaPL3 model was used to estimate of Characteristic Travel Distance (CTD), defined as the maximum distance traveled by 63% of the substance or, in other words, the distance that 37% of the substance may travel beyond the CTD. Beyer *et al.* (2000) have proposed CTD of >2000 km as representing high LRTP, 700-2000 km as moderate, and <700 km as low. Based on result of the TaPL3 model, CHPD has low LRTP (i.e. this substance is expected to remain primarily in the areas close to its emission sources).

Table 4: Model-predicted Characteristic Travel Distances for CHPD

Characteristic Travel Distance	Reference	
467 km	TaPL3 (CEMC, 2003)	

Therefore, the empirical and modelled data indicate that CHPD meets the persistence criteria (half-lives in soil and water \geq 182 days, in sediments \geq 365 days) as set out in the Persistence and Bioaccumulation Regulations (Government of Canada, 2000).

Potential for Bioaccumulation

Experimental data for the octanol-water partition coefficient, as well as experimental bioaccumulation and bioconcentration factors are not available for CHPD. Modelled log

 K_{ow} value of 7.88 (Table 5) indicates that this chemical could potentially bioaccumulate in organisms.

Table 5: Predicted bioaccumulation values for CHPD

Test Organism	Endpoint	Value (wet weight, L/kg)	Reference
Fish	BAF	3626306	Gobas BAF T2MTL (Arnot & Gobas, 2003)
Fish	BCF	12700	Modified Gobas BCF 5% T2LTL (Arnot & Gobas, 2003)
Fish	BCF	15198	OASIS
Fish	BCF	3999	BCFWIN v2.15

The Modified Gobas middle-trophic-level BAF model produced a BAF of approximately 3,600,000 L/kg, demonstrating that CHPD has the potential to be highly bioaccumulative. Three BCF models provide a weight-of-evidence of high bioconcentration potential of this substance (~4,000 to ~15,000 L/kg, Table 5), which supports the conclusion that this substance can accumulate in the tissues of aquatic organisms and may biomagnify in the food web. It should be noted however, that metabolism information for this substance was not available and was not, therefore, used in the BAF and BCF models.

Therefore, the weight of evidence indicates that CHPD meets the bioaccumulation criteria (BAF \geq 5000, BCF \geq 5000) as set out in the Persistence and Bioaccumulation Regulations (Government of Canada, 2000).

Ecological Effects

In the Aquatic Compartment

There are no experimental aquatic ecotoxicity data available in the literature on this substance. However, modelled data provide evidence that the substance causes harm to aquatic organisms at relatively low concentrations. Table 6 contains those predictions that were considered as reliable and were used in the QSAR weight-of-evidence approach for aquatic toxicity (ESD, 2006a). These results indicate that CHPD is highly hazardous to aquatic organisms, considering very low acute LC50 values (4×10⁻⁵ and 4×10⁻³ mg/L).

Table 6: Modelled aquatic toxicity values for CHPD

Organism	Test type	Endpoint	Value	Reference
Fish	Acute	LC50	0.000042 mg/L	ECOSAR Neutral Org. SAR
Fish	Acute	LC50	0.004 mg/L	ECOSAR v.0.99g Fish

In Other Media

No effects studies for non-aquatic non-mammalian organisms were found for this compound.

Potential to Cause Ecological Harm

Evidence that a substance is highly persistent and bioaccumulative as defined in the Persistence and Bioaccumulation Regulations of CEPA 1999 (Government of Canada, 2000) together with evidence of commercial activity provides a significant indication of its potential to be entering the environment under conditions that may have harmful long term ecological effects (ESD, 2006b). 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. 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 both highly persistent and bioaccumulative, when taken together with other information (such as evidence of toxicity at relatively low concentrations, and evidence of uses and releases) may therefore be sufficient to indicate that the substance has the potential to cause ecological harm.

Importation volumes of CHPD into Canada along with its potential dispersive uses indicate a potential for releases of this chemical into the Canadian environment. Once released into the environment, because of its resistance to degradation it will remain in water, sediment and soil for long times. As it persists in the environment, and because of its lipophyllic character, it will likely bioaccumulate and may be biomagnified in trophic food chains. It has also demonstrated relatively high toxicity. This information suggests that CHPD has the potential affect to cause ecological harm in Canada.

Uncertainties

Based on information collected, there is some uncertainty about the precise use pattern of CHPD imported into Canada. In addition, also some releases are likely, information on concentrations in the Canadian environment is currently lacking.

Neither experimental data for the key physico-chemical properties (e.g. K_{ow} , water solubility, Henry's Law constant), nor experimental data on ecotoxicity, degradation, and bioaccumulation are currently available for CHPD. Therefore, uncertainties exist in the conclusions reached in this document because P, B, and iT evaluations are based on model data.

Regarding toxicity, based on the predicted partitioning behaviour of this chemical, the significance of soil and sediments as important media of exposure cannot be appropriately addressed because no ecotoxicological data are available for these two environmental compartments.

The experimental or predicted concentrations, associated with 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.

There is also uncertainty associated with basing the overall conclusion that CHPD may be causing ecological harm, solely on information relating to its persistence, bioaccumulation, relative toxicity, and use pattern. Typically quantitative risk estimates (i.e., risk quotients or probabilistic analyses) are important lines of evidence when evaluating a substances potential to cause environmental harm. However when risks for persistent and bioaccumulative substances such as CHPD are estimated using such quantitative methods, they are highly uncertain and are likely to be underestimated (ESD, 2006b). Given that long term risks associated with persistent and bioaccumulative substances cannot at present be reliably predicted, quantitative risk estimates have limited relevance. Furthermore, since accumulations of such substances may be widespread and are difficult to reverse, a conservative response to uncertainty (that avoids underestimation of risks) is justified.

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