Screening Assessment for the Challenge

5H-Dibenz[b,f]azepine-5-propanamine, 3-chloro-10,11-dihydro-N,N-dimethyl-, monohydrochloride (Clomipramine hydrochloride)

Chemical Abstracts Service Registry Number
17321-77-6

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 of 5H-Dibenz[b,f]azepine-5-propanamine, 3-chloro-10,11-dihydro-N,N-dimethyl-, monohydrochloride (Clomipramine hydrochloride), Chemical Abstracts Service Registry Number (CAS RN) 17321-77-6. Clomipramine hydrochloride was identified as a high priority for screening assessment and included in the Challenge because it was initially 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. Few data are available for clomipramine hydrochloride and many of the measured and predicted values used in this screening assessment are for the related compound, clomipramine (CAS RN 303-49-1).

The substance, clomipramine hydrochloride, 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.

Clomipramine hydrochloride is an organic substance that is used as a pharmaceutical product for humans and animals. The substance is not naturally produced in the environment. The available information indicates that, in 2006, clomipramine hydrochloride was not manufactured in Canada in quantities equal to or greater than the reporting threshold of 100 kg; however, one company reported importing the substance in the range of 100 to 1000 kg per year and a second reported importing it in an amount below the threshold quantity of 100 kg. In addition, several Canadian companies identified themselves as having a stakeholder interest in the substance. Overall, it would appear that clomipramine hydrochloride is not present in large quantities in Canadian commerce and, therefore, potential releases of the substance to the Canadian environment are considered to be low. In addition, based on reported use patterns and other information, most of the substance (97%) is expected to be chemically transformed (metabolized) during use, with only a small proportion of the original compound released into wastewaters (2.5%) and soil (0.5%).

Experimental and predicted values of greater than 9 for the acid dissociation constant (pK_a) suggest that ionization of clomipramine hydrochloride is almost complete at typical pH values in the environment, with the ionized form acting as a weak base. Therefore, clomipramine hydrochloride entering the environment is expected to reside predominantly in water, although some partitioning to sediment and/or soil may also occur depending on the compartment of release.

Based on ultimate degradation results from several quantitative structure-activity relationship (QSAR) models, clomipramine hydrochloride meets persistence criteria

(half-life ≥ 182 days in water and soil and > 365 days in sediment) as set out in the *Persistence and Bioaccumulation Regulations*.

Clomipramine hydrochloride was categorized as bioaccumulative based on model predictions for the neutral compound. However, given the evidence for ionization and metabolism, as well as predicted bioaccumulation and bioconcentration factors (BAF/BCF) ranging from 7 to 155 for the ionized form expected to predominate at environmental pH (6 to 9), it is considered unlikely to accumulate to significant levels in organisms and, therefore, does not meet bioaccumulation criteria in the *Persistence and Bioaccumulation Regulations*.

Clomipramine hydrochloride is predicted to have moderate to high aquatic toxicity (acute LC_{50} values for the ionized form range from < 1–10 mg/L) and therefore is considered to be potentially hazardous to aquatic organisms. Experimental data indicate that clomipramine hydrochloride has low mammalian toxicity. A risk quotient analysis, integrating a conservative predicted environmental concentration (PEC) with a predicted no-effect concentration (PNEC) resulted in a risk quotient (PEC/PNEC) value of 0.03, indicating that concentrations of clomipramine hydrochloride in water are unlikely to cause adverse effects to populations of pelagic organisms in Canada.

While clomipramine hydrochloride meets the criteria for persistence and is predicted to be potentially hazardous to aquatic species, given the low quantities in commerce and its dispersive uses, it is considered to have low exposure potential and to present a negligible risk to the Canadian environment.

Therefore, it is concluded that clomipramine hydrochloride 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.

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

Based on the information available, it is concluded that clomipramine hydrochloride does not meet any of the criteria set out in section 64 of CEPA 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 2006), 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 these substances identified as high priorities.

The substance 5H-Dibenz[b,f]azepine-5-propanamine, 3-chloro-10,11-dihydro-N,N-dimethyl-, monohydrochloride was identified as a high priority for assessment of ecological risk as it had initially 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 November 17, 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, submissions of information pertaining to the uses, importation and quantity in commerce of the substance were received.

Although 5H-Dibenz[b,f]azepine-5-propanamine, 3-chloro-10,11-dihydro-N,N-dimethyl-, monohydrochloride 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 was not

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

Screening assessments under CEPA 1999 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 applying a weight-of-evidence approach and precaution as required under CEPA 1999.

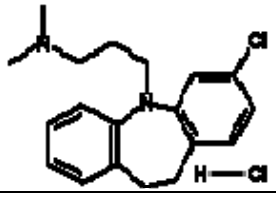
This screening assessment considers any new information on chemical properties, hazards, uses and exposure identified after December 2005, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review documents, stakeholder research reports and from recent literature searches up to May 2009. Key studies were critically evaluated and only results from studies of good quality were used to reach conclusions, although other studies and modelling results may have been considered as part of the weight of evidence. When available and relevant, information presented in hazard assessments from other jurisdictions was also used. The screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents the most critical data 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. This assessment has undergone external written peer review/consultation.. Additionally, a draft of this screening assessment was subject to a 60-day public comment period. While external comments were taken into consideration, the final content and outcome of the screening risk assessment remain the responsibility of Health Canada and Environment Canada. 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 by its common name, clomipramine hydrochloride.

Table 1. Substance identity

Chemical Abstracts Service Registry Number (CAS RN)	**17321-77-6**
Domestic Substances List (DSL) name	**5H-Dibenz[b,f]azepine-5-propanamine, 3-chloro-10,11-dihydro-N,N-dimethyl-, monohydrochloride**
National Chemical Inventories (NCI) names[1]	*5H-Dibenz[b,f]azepine-5-propanamine, 3-chloro-10,11-dihydro-N,N-dimethyl-, monohydrochloride* (ENCS, AICS, ASIA-PAC) *Clomipramine hydrochloride* (EINECS)
Other names	*3-Chloro-5-(3-(dimethylamino)propyl)-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride* *3-Chloroimipramine hydrochloride* *Anafranil* *Anaphranil* *Anatranil* *Chlorimipramine hydrochloride* *Chloroimipramine monohydrochloride*
Chemical group (DSL Stream)	Discrete organics
Major chemical class or use	Dibenzazepine
Major chemical sub-class	Amines
Chemical formula	$C_{19}H_{23}ClN_2 \times HCl$
Chemical structure	
SMILES	c12N(CCCN(C)C)c3cc(Cl)ccc3CCc1cccc2
Molecular mass	351.31 g/mol

[1] National Chemical Inventories (NCI). 2006: AICS (Australian Inventory of Chemical Substances); ASIA-PAC (Asia-Pacific Substances Lists); EINECS (European Inventory of Existing Commercial Chemical Substances); ENCS (Japanese Existing and New Chemical Substances).

Physical and Chemical Properties

Table 2 contains experimental and modelled physical and chemical properties of clomipramine hydrochloride that are relevant to its environmental fate. Very few experimental data are available and most properties have been estimated based on a modelling approach.

It should also be noted that many of the property estimations provided in Table 2 are those of clomipramine (CAS RN 303-49-1). With the exception of the experimental data for melting point, empirical data on physical and chemical properties are not available for the monohydrochloride that is the subject of this assessment. It is likely that the hydrochloride group is added to clomipramine in order to enhance water solubility and thus increase the ease of administration (see section below on Uses). Salts of a drug are often used, as they show better solubility in aqueous media in the physiological pH range. Once in the body, the salt dissolves, releasing the ionized drug as the active ingredient.

Table 2. Physical and chemical properties used for clomipramine hydrochloride

Property	Type	Value	Temperature (°C)	Reference
Melting point (ºC)	Experimental	189–192		Merck Index 2001
	Modelled	151.83 (weighted value)		MPBPWIN 2000
Boiling point (ºC)	Experimental	160–170		Merck Index 2001
	Modelled	400.74 (adapted Stein and Brown method)		MPBPWIN 2000
Density (kg/m^3)	No information available			
Vapour pressure (Pa)	Modelled	2.00×10^{-5} (1.51×10^{-7}mm Hg; modified Grain method)	25	MPBPWIN 2000
Henry's Law constant ($Pa\cdot m^3/mol$)	Modelled	7.58×10^{-4} (7.48×10^{-9} $atm\cdot m^3/mol$; bond estimate)	25	HENRYWIN 2000

Property	Type	Value	Temperature (°C)	Reference
Log K_{ow} (Octanol-water partition coefficient) (dimensionless)	Experimental	5.19		Hansch et al. 1995
		3.32 at pH 7.4[(1)]		Hansch et al. 1995
	Modelled	5.65		KOWWIN 2000
Log K_{oc} (Organic carbon-water partition coefficient) (dimensionless)	Modelled	5.011		PCKOCWIN 2000
Water solubility (mg/L)	Experimental	Freely soluble		Merck Index 2001
	Modelled	0.35 (neutral form) 21.64 (ionized form)	25	WSKOWWIN 2000
Other solubilities (g/L)	Experimental (methanol)	Freely soluble		Merck Index 2001
	Experimental (methylene chloride)	Freely soluble		Merck Index 2001
	Experimental (hexane)	Practically insoluble		Merck Index 2001
	Experimental (ethyl ether)	Practically insoluble		Merck Index 2001
pK_a (Acid dissociation constant) (dimensionless)	Experimental	9.57	20–25	Shalaeva et al. 2008
	Modelled	pK_a 9.46 at pH 7		ACD/pK_aDB 2005

[1] Value represents apparent distribution coefficient (log D) as substance is significantly ionized at pH 7.4 (Hansch et al. 1987)

Experimental and predicted values of greater than 9 for the acid dissociation constant (pK_a) suggest that clomipramine will exist primarily as a protonated cation at ambient pH in the environment, acting as a weak base. Hansch et al. (1987, 1995) reported an octanol-water partition coefficient (log K_{ow}) of 5.19 for the neutral clomipramine compound, but a lower distribution coefficient (log D) of 3.32 at pH 7.4, due to substantial ionization of the substance at this pH.

The characteristic of ionization influences both the water solubility and the partitioning behaviour of clomipramine. Clomipramine in the neutral form is predicted to have low vapour pressure (2.00×10^{-5} Pa at 25°C; MPBPWIN 2000), low water solubility (0.35

mg/L at 25°C; WSKOWWIN 2000), a high octanol-water partition coefficient (log K_{ow} 5.65; KOWWIN 2000) and very high organic carbon-water partition coefficient (log K_{oc} 5.011; PCKOCWIN 2000). The ionized form, however, is expected to have greater water solubility and therefore less tendency to reside in lipophilic materials such as the organic fraction of soil and sediment and the fatty tissues of organisms. When the log D value of 3.32 derived by Hansch et al. (1987, 1995) is used to estimate water solubility for the ionized form of clomipramine, the resulting value of 21.64 mg/L (WSKOWWIN 2000) is much higher than that of 0.35 mg/L estimated for the neutral form of the substance (see Table 2). Clomipramine hydrochloride itself is expected to dissociate in water at ambient pH, releasing the positively charged (protonated) form of clomipramine.

The Merck Index (2001) does not provide information on the water solubility of clomipramine, but specifies that chlomipramine hydrochloride is freely soluble in water. This information supports the supposition that the hydrochloride group is added to clomipramine in order to facilitate water solubility.

Overall, clomipramine hydrochloride is expected to predominantly reside in water, although some partitioning to soil and/or sediment may also occur, depending on the compartment of release.

Sources

There is no reference in the published literature to the natural occurrence of clomipramine hydrochloride in the environment.

Based on a survey conducted under section 71 of CEPA 1999, in 2006, no clomipramine hydrochloride was manufactured in Canada at quantities greater than or equal to the reporting threshold of 100 kg; however, one company reported importing the substance in the range of 100 to 1000 kg per year and a second reported importing the substance in an amount below the threshold quantity of 100 kg (Environment Canada 2007a). The substance was imported into Canada in bulk pharmaceutical tablet form, for repackaging and distribution. In addition, four Canadian companies identified themselves as having a stakeholder interest in the substance.

Clomipramine (CAS RN 303-49-1) is not specified on either the Domestic Substances List (DSL) or Non-Domestic Substances List (NDSL) and it is therefore considered that only the hydrochloride form (i.e., CAS RN 17321-77-6) is present in Canadian commerce.

Uses

Reported uses of clomipramine hydrochloride in Canada are as a pharmaceutical product for human and animal use. Information obtained from the section 71 survey conducted for the year 2006 (Environment Canada 2007a) indicated that approximately 85% of the total quantity of clomipramine hydrochloride imported into Canada in that year was destined for human use, with the remaining 15% intended for veterinary applications.

Additional information on potential uses of clomipramine hydrochloride was identified through searches of the available scientific and technical literature. Clomipramine hydrochloride is described as a tricyclic antidepressant that can be used to treat depressive illness, panic disorder, obsessive-compulsive behaviour, alcoholism, obesity and bulimia (Martin et al. 1996; Chemindustry.com Inc. 2005). It may also be applied as an analgesic, and recent studies (e.g., Parker and Pilkington 2006) suggest that it may find application in the treatment of some malignancies. The substance also has some veterinary use, for example in the treatment of separation anxiety in dogs (Novartis Animal Health US, Inc. 2005).

Health Canada includes clomipramine and its salts on the list of drugs currently regulated as new drugs in Canada (Health Canada 1999), and the substance (as the hydrochloride) appears on the World Health Organization (WHO) Model List of Essential Medicines (WHO 2007). WHO defines essential medicines as those drugs that satisfy the health care needs of the majority of the population and should therefore be available at all times in adequate amounts and in appropriate dosage forms, at a price the community can afford.

Releases to the Environment

Based on comparatively small total import volumes (see Sources section above), releases to the Canadian environment are estimated to be low.

As a pharmaceutical product, releases of clomipramine hydrochloride to the Canadian environment from human use are expected to be diffuse in nature and primarily to wastewater. Release to the soil compartment could occur through the application of sewage sludge as biosolids to agricultural and pasture lands. In addition, there may be some release to soil through use of the substance as a veterinary product. The total quantity released to soil is not expected to be large, given the low total import volume and proportionately higher losses through other mechanisms (i.e., chemical transformation and release to sewer; see below).

Mass Flow Tool

To estimate potential releases of the substance to the environment at different stages of its life cycle, a mass flow tool was developed (Environment Canada 2008a). Empirical data concerning releases of specific substances to the environment are seldom available.

Therefore, for each identified type of use of the substance, the proportion and quantity of release to the different environmental media are estimated, as is the proportion of the substance chemically transformed or sent for waste disposal. Unless specific information on the rate or potential for release of the substance from landfills and incinerators is available, the Mass Flow Tool does not quantitatively account for releases to the environment from disposal.

Assumptions and input parameters used in making the release estimates are based on information obtained from a variety of sources including responses to regulatory surveys, Statistics Canada, manufacturers' websites, technical databases and documents. Of particular relevance are emission factors, which are generally expressed as the fraction of a substance released to the environment, particularly during its manufacture, processing, and use associated with industrial processes. Sources of such information include emission scenario documents, often developed under the auspices of the Organisation for Economic Co-operation and Development (OECD), and default assumptions used by different international chemical regulatory agencies. It is noted that the level of uncertainty in the mass of substance and quantity released to the environment generally increases further down the life cycle.

Table 3. Estimated releases and losses of clomipramine hydrochloride to environmental media, chemical transformation and transfer to waste disposal sites, based on the Mass Flow Tool

Fate	Proportion of the mass (%)	Major life cycle stage involved
Releases to receiving media:		
Soil	0.5	Consumer use
Air	0.0	–
Sewer[b]	2.5	Consumer use
Chemically transformed	97[a]	Consumer use
Transferred to waste disposal sites (e.g., landfill, incineration)	0.0	–

[a] A metabolism rate of 97% was estimated from Oryx Pharmaceuticals Inc.(2002). Specific assumptions used in derivation of these estimates are summarized in Environment Canada 2008b. For the purposes of calculating a conservative environmental concentration, metabolism was not considered in the derivation of a Predicted Environmental Concentration (see Ecological Exposure Assessment section).

[b] Wastewater before any form of treatment.

Most clomipramine hydrochloride (97%) is expected to be chemically transformed (metabolized) during use,with only a small proportion of the original compound being released to sewer (2.5%) or soil (0.5%).

Environmental Fate

Based on its physical and chemical properties (Table 2) and compartments to which it is released, clomipramine hydrochloride is expected to predominantly reside in water, although some partitioning to soil and/or sediment may also occur, depending on the compartment of release.

The ionization dissociation constant (pK_a) of 9.5 indicates that clomipramine hydrochloride will occur primarily as the ionized form when the substance is present in aquatic systems at the environmentally relevant pH range of 6 to 9. The ionized form has higher water solubility and a lower octanol/water partition coefficient (log K_{ow}) than the neutral form, suggesting that it will be less likely to partition into the lipid fraction of organisms and therefore will have lower bioaccumulation potential than the neutral form.

Based on the measured log K_{ow} of 3.32 at pH 7.4, clomipramine hydrochloride will likely adsorb to some extent to sediment and soil particles. The higher water solubility of the substance suggests that some leaching from soil is also possible; however, because it is ionized in solution, it is unlikely to volatilize from the soil surface.

The low volatility of clomipramine hydrochloride suggests that if released to air, the substance will be removed from this compartment to soil or surface water through wet or dry deposition processes.

Persistence and Bioaccumulation Potential

Environmental Persistence

The above analysis of environmental fate indicates partitioning of this substance mainly into water, although some partitioning into soil and sediment may also occur.

No experimental degradation data for clomipramine hydrochloride have been identified. Given the ecological importance of the water compartment, the fact that most of the available models apply to water and the fact that clomipramine hydrochloride is expected to be released mainly to this compartment, persistence in water was primarily examined using predictive QSAR models for biodegradation. Clomipramine hydrochloride does not contain functional groups expected to undergo hydrolysis.

Table 4 summarizes the results of available QSAR models for degradation in various environmental media.

Table 4. Modelled data for degradation of clomipramine hydrochloride

Fate Process	Model and model basis	Model Result and Prediction	Extrapolated Half-life (days)
AIR			
Atmospheric oxidation	AOPWIN 2000	$t_{1/2}$ = 0.04 day	< 2
Ozone reaction	AOPWIN 2000	n/a[1]	n/a
WATER			
Hydrolysis	HYDROWIN 2000	n/a[1]	n/a
Biodegradation (aerobic)	BIOWIN 2000 Sub-model 3: Expert Survey (ultimate biodegradation)	1.64[2] "recalcitrant"	> 182[4]
Biodegradation (aerobic)	BIOWIN 2000 Sub-model 4: Expert Survey (primary biodegradation)	2.52[2] "weeks-months"	< 182[4]
Biodegradation (aerobic)	BIOWIN 2000 Sub-model 5: MITI linear probability	-0.29[3] "does not biodegrade fast"	> 182[4]
Biodegradation (aerobic)	BIOWIN 2000 Sub-model 6: MITI non-linear probability	0.0[3] "does not biodegrade fast"	> 182[4]
Biodegradation (aerobic)	CATABOL 2004-2008 % BOD (biological oxygen demand)	% BOD = 10 "biodegrades slowly"	> 182[4]

[1] Model does not provide an estimate for this type of structure.
[2] Output is a numerical score
[3] Output is a probability score
[4] Expected half-lives for BIOWIN and CATABOL models are determined based on Environment Canada 2009.

In air, a predicted atmospheric oxidation half-life value of 0.04 day (see Table 4 above) demonstrates that this substance is likely to be rapidly oxidized. There is no estimate for the reaction half-life of this substance with other photo-oxidative species in the atmosphere, such as ozone. However, it is expected that reactions with hydroxyl radicals will be the most important fate process in the atmosphere for clomipramine hydrochloride. With a half-life of 0.04 day via reactions with hydroxyl radicals, clomipramine hydrochloride is considered not persistent in air.

Clomipramine hydrochloride does not contain functional groups that are likely to undergo hydrolysis, and no hydrolysis rate constant could be estimated for the substance. The biodegradation models predict that clomipramine hydrochloride will undergo primary biodegradation in a period of weeks to months, but that ultimate biodegradation (i.e., complete mineralization) will occur only slowly and the substance may therefore be recalcitrant in the environment. The results of biodegradation modelling indicate that the half-life for ultimate biodegradation of clomipramine hydrochloride in water is > 182 days.

The available empirical information on metabolism indicates that clomipramine hydrochloride is largely chemically transformed (97%) upon ingestion (Oryx Pharmaceuticals Inc. 2002; see Bioaccumulation section below) and this suggests there is potential for primary microbial degradation of the substance in the environment. This is

consistent with the BIOWIN 4 primary survey model half-life result of "weeks to months", suggesting comparatively fast primary degradation. Although no experimental information is available on the stability of the compound itself or its metabolites in surface waters, modelled ultimate degradation results suggest that the metabolites are likely to be relatively stable.

Therefore, in the absence of measured environmental biodegradation data, such as ready-biodegradation data, and in light of the unanimity of the model predictions particularly relating to ultimate degradation, clomipramine hydrochloride will be considered to meet the persistence criteria (i.e., half-life in water is ≥ 182 days).

Using an extrapolation ratio of 1:1:4 for a water: soil: sediment biodegradation half-life (Boethling et al. 1995), the biodegradation half-life in soil is also ≥ 182 days and the half-life in sediments is > 365 days.

Based on the modelled data presented in Table 4 above, clomipramine hydrochloride meets the persistence criteria in water, soil and sediment (half-lives in soil and water ≥ 182 days and half-life in sediment ≥ 365 days), but does not meet the criterion for air (half-life criterion of ≥ 2 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential for Bioaccumulation

Experimental and modelled log K_{ow} values for the neutral form of clomipramine suggest that this chemical may have the potential to bioaccumulate (see Table 2 above).

Since no experimental bioaccumulation factor (BAF) and/or bioconcentration factor (BCF) data for clomipramine hydrochloride were available, a predictive approach was applied using available BAF and BCF models as shown in Tables 5a and 5b below. According to the *Persistence and Bioaccumulation Regulations* (Canada 2000), a substance is bioaccumulative if the BAF or BCF is $\geq$ 5000. Measures of BAF are the preferred metric for assessing the bioaccumulation potential of substances. This is because the BCF may not adequately account for the bioaccumulation potential of substances via the diet, which predominates for substances with log K_{ow} > ~4.0 (Arnot and Gobas 2003).

Kinetic mass-balance modelling is in principle considered to provide the most reliable prediction method for determining bioaccumulation potential because it allows for metabolism correction as long as the log K_{ow} of the substance is within the log K_{ow} domain of the model. A kinetic mass-balance model developed by Arnot and Gobas (2003) and corrected for metabolism potential using a molecular fragment approach was used to estimate the bioaccumulation potential of clomipramine hydrochloride. Because metabolic potential can be related to body weight and temperature (e.g., Hu and Layton 2001, Nichols et al. 2007), the metabolic rate constant (k_M) was normalized to 15^{o}C and a 10 g fish (Arnot et al. 2008).

Table 5a. Fish BAF and BCF predictions for the neutral and ionized forms of clomipramine using the Arnot-Gobas kinetic model (2003) corrected for metabolic rate

Metabolic rate constant k_M (/day)	LogK_{ow} Used	BCF (L/kg)	BAF (L/kg)	Half-life (days)	Reference
6.659	5.19	59.73	60.38	0.10	Middle Trophic Level (Arnot and Gobas 2003; BCFBAF 2008)
0	5.19	10 000	56 234	31.26	Middle Trophic Level (Arnot and Gobas 2003; BCFBAF 2008)
0	3.32	145	155	0.53	Middle Trophic Level (Arnot and Gobas 2003; BCFBAF 2008)

Additional model predictions were used to evaluate the potential for bioaccumulation in aquatic species (Table 5b).

Table 5b: Additional modelled fish bioaccumulation data for clomipramine

LogK_{ow} Used	Endpoint	Value wet weight (L/kg)	Reference
5.4	BCF	7.1	Baseline BCF Model (Dimitrov et al. 2005; BBM 2008)
5.19	BCF	1978	BCFWIN 2000
5.19	BCF	1234	BCFBAF 2008 Regression-based estimate
3.32	BCF	7.1	Baseline BCF Model (Dimitrov et al. 2005; BBM 2008)
3.32	BCF	71.85	BCFWIN 2000
3.32	BCF	72.03	BCFBAF 2008 Regression-based estimate

Model estimates derived based on the neutral form of the substance (i.e., log K_{ow} 5.19) and without consideration of metabolism predict that clomipramine will have the potential to bioaccumulate in fish and biomagnify in food webs, and this formed the basis of the categorization decision to consider the substance potentially bioaccumulative as defined in the *Persistence and Bioaccumulation Regulations* (Canada 2000) .

However, the available information suggests that clomipramine hydrochloride is likely to be significantly ionized in the environmentally relevant pH range of 6–9 (see Fate section above). In addition, the published literature indicates that clomipramine hydrochloride will be extensively metabolized by organisms (97%; Oryx Pharmaceuticals Inc. 2002). Faigle and Dieterle (1973) examined the metabolism and pharmacokinetics of clomipramine (as the commercial product Anafranil) in mice, rats, dogs and humans using radiolabelling to track movement of the substance through the body. Clomipramine

passed readily across lipid membranes following oral administration, with nearly complete absorption from the gastrointestinal tract. This was followed by rapid and nearly complete metabolism of the drug, and the formation of hydrophilic polar metabolites. An N-desmethyl-metabolite was detected, evidence that demethylation at the N,N-dimethlamino- group is one route of biotransformation of clomipramine in mammals. In addition, the total radioactivity measured exceeded the sum of the unchanged compound plus N-desmethyl-metabolite, indicating that other metabolites were also present. The researchers proposed that demethylation of clomipramine in mammals is accompanied or followed by further processes, such as hydroxylation and conjugation, yielding water-soluble metabolites which can then be easily and rapidly eliminated in the urine and feces. For example, the unchanged drug and N-desmethyl metabolite accounted for only about 2% and 0.5%, respectively, of total radioactivity in the urine of two study volunteers, with the remainder present as a mixture of hydrophilic, polar metabolites.

When both ionization and metabolism are considered in the models, such as with the Baseline BCF Model (Dimitrov et al. 2005; BBM 2008), the resulting BCF value of 7.1 L/kg indicates a low bioaccumulation potential. When metabolism is considered for the neutral compound (i.e., log K_{ow} 5.19; BCFBAF 2008), the resulting BAF and BCF values of 60.38 and 59.73, respectively, also indicate a low potential to bioaccumulate.

Therefore, while the neutral form of clomipramine is predicted to have high bioaccumulation potential, the ionized form most likely to predominate in the environment has a low potential to bioaccumulate. Additionally, there is evidence for extensive metabolism of clomipramine hydrochloride in mammals. When both ionization and metabolism are considered, clomipramine hydrochloride does not meet the bioaccumulation criteria (BAF or BCF > 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

No experimental data for aquatic toxicity were found for this substance, therefore, modelled data were used to estimate the potential for aquatic toxicity. Table 6 contains predicted ecotoxicity values that were considered reliable and were used in the QSAR weight-of-evidence approach for aquatic toxicity (Environment Canada 2007b).

Table 6. Modelled data for aquatic toxicity

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
Fish	Acute (96 hours)	LC_{50}[1]	0.351[2] 8.886[3]	ECOSAR 2008
			0.38[2]	OASIS Forecast 2005
			0.032[2]*	TOPKAT 2004
			4.67435[2]	AIES 2003–2005
Daphnid	Acute (48 hours)	LC_{50}	1.177[3]	ECOSAR 2008
			0.11[2]	OASIS Forecast 2005
Green algae	Acute (96 hours)	EC_{50}[4]	0.102 – 0.340[2] 0.756 – 9.293[3]	ECOSAR 2008
Mysid shrimp	Acute (96 hours)	LC_{50}	0.065[2] 1.084[3]	ECOSAR 2008

[1] LC_{50} – The concentration of a substance that is estimated to be lethal to 50% of the test organisms.
[2] Predicted toxicity value based on neutral form of substance.
[3] Predicted toxicity value based on ionized form of substance.
[4] EC_{50} – The concentration of a substance that is estimated to cause some toxic sublethal effect on 50% of the test organisms.
*Categorization pivotal iT value.

A range of aquatic toxicity predictions were obtained from the various QSAR models considered. The results suggest that clomipramine will have moderate to high toxicity to aquatic species and that the ionized form (corresponding to a measured log K_{ow} of 3.32), which is likely to predominate at environmental pH 6–9, will be less toxic than the neutral compound. The ionized form of clomipramine is predicted to cause acute effects to aquatic species at concentrations ranging from <1 mg/L to about 10 mg/L. Based on this model evidence, clomipramine hydrochloride has the potential to be acutely toxic to aquatic organisms at relatively low concentrations (acute LC/EC_{50} values < 1.0 mg/L).

B - In Other Environmental Compartments

Clomipramine hydrochloride has exhibited low oral toxicity in laboratory studies conducted using terrestrial mammalian species, with acute oral median lethal dose (LD_{50}) values ranging from 575 (guinea pig) to 1450 mg/kg-bw (rat) and a chronic lowest-observed-adverse-effect level (LOAEL) of 100 mg/kg-bw (rat, dog; Oryx Pharmaceuticals Inc. 2002).

Ecological Exposure Assessment

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

As releases of clomipramine hydrochloride are expected to be primarily to wastewater (see Table 3), a modelling approach was used to estimate potential exposure concentrations in the Canadian aquatic environment. Environmental concentrations were derived using Mega Flush, an Environment Canada modelling tool that uses information

such as estimated substance quantities, release rates, and receiving water bodies to estimate down-the-drain releases from consumer use (Environment Canada 2008a). The Mega Flush tool estimates potential substance concentrations in multiple water bodies receiving sewage treatment plant effluents to which consumer products containing the substance may have been released. Mega Flush is designed to provide these estimates based on assumptions regarding the amount of chemical used and released by consumers and sewage treatment plant removal rates. The equation and inputs used to calculate the predicted environmental concentration (PEC) in the receiving water bodies are described in Environment Canada (2008b). In light of uncertainty relating to the environmental stability of the metabolites of clomipramine hydrochloride, a conservative environmental concentration value was obtained by not considering metabolism in the derivation of the PEC. Assuming a total Canadian use quantity in the range of 100 to 1000 kg in consumer products (the actual amount is confidential business information), derived using import quantities reported for the year 2006 (see Sources section above), the maximum PEC for clomipramine hydrochloride estimated by the Mega Flush tool is 0.00024 mg/L (when using the estimated 10th percentile flow value for receiving water bodies).

Characterization of Ecological Risk

The approach taken in this ecological screening assessment was to examine available scientific information and develop conclusions based on a weight-of-evidence approach and precaution as required under CEPA 1999.

A risk quotient analysis, integrating a PEC with potential adverse effects (PNEC) was conducted and the resulting risk quotient (PEC/PNEC) was used in the estimation of potential risk to the environment. The highest PEC value of 0.00024 mg/L determined using Mega Flush (see section on Ecological Exposure Assessment above) provides a conservative exposure concentration. To derive a PNEC, the lowest toxicity value for the ionic form of the substance of 0.756 mg/L (96-hour EC_{50} for green algae predicted by ECOSAR 2008; see Table 6 above) was divided by an assessment factor of 100 (10 to account for interspecies and intraspecies variability in sensitivity and 10 to estimate a long-term no-effects concentration from a short-term LC_{50}) to give a PNEC of 0.00756 mg/L. The risk quotient, PEC/PNEC, is then 0.00024/0.00756 = 0.03. The results indicate that concentrations of clomipramine hydrochloride in water are unlikely to cause adverse effects to populations of pelagic organisms in Canada.

Overall, it would appear that clomipramine hydrochloride is not present in large quantities in Canadian commerce and, therefore, potential sources and releases of the substance to the Canadian environment are likely to be low.

Based on modelled physical and chemical properties, clomipramine hydrochloride is predicted to not degrade quickly in the environment and is expected to be persistent in water, soil and sediment, based on its estimated ultimate biodegradation half-life. Given the evidence for ionization and metabolism, it is considered not to accumulate in organisms and, therefore, not to meet bioaccumulation criteria. Clomipramine hydrochloride has the potential to be acutely toxic to aquatic organisms at relatively low

concentrations (LC_{50} s < 1.0 mg/L). Experimental data indicate that it has low mammalian toxicity.

While predicted data indicate a potential for persistence in the environment and a hazard to aquatic organisms, based on the low quantities in commerce and their disperse pattern of use by consumers it is concluded that clomipramine hydrochloride does not pose a risk to the Canadian environment.

Uncertainties in Evaluation of Ecological Risk

There is uncertainty regarding the physical and chemical properties of clomipramine hydrochloride, and this influences the estimation of environmental behaviour, fate, and potential toxicity. Gaps in the experimental database were filled through the use of QSARs. However, the extent to which the modelled data reflect the actual properties of clomipramine hydrochloride (and clomipramine) is unclear, given indications that the substance will ionize at environmental pH and metabolize in organisms. In the absence of adequate measured data, estimations based on modelled data and professional judgement have been used to provide a conservative assessment of potential risk to the environment.

Regarding ecotoxicity, based on the predicted partitioning behaviour of this chemical, the significance of soil and sediment as potential media of exposure is not well addressed by the effects data available. Modelled effects data are available for pelagic aquatic species; however, the water column may not be the only medium of concern based on partitioning estimates. In addition, while there is empirical evidence of substantial metabolism and low toxicity in mammals, the extent to which this applies to non-mammalian species is unknown. There is also a lack of data respecting the behaviour and fate of metabolic transformation products in the environment, which was addressed by conservatively ignoring transformation in the modelled aquatic exposure scenario.

Conclusion

Based on the information presented in this screening assessment, it is concluded that clomipramine hydrochloride 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 clomipramine hydrochloride does not meet the definition of toxic as set out in section 64 of CEPA 1999. Additionally, clomipramine hydrochloride meets the criteria for persistence but does not meet the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

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Appendix I – PBT Model Inputs Summary Table

	Phys-Chem/Fate	**Fate**	**Fate**	**PBT Profiling**	**Ecotoxicity**
Model Input Parameters	EPIWIN Suite (all models, including: AOPWIN, KOCWIN, BCFWIN BIOWIN and ECOSAR)	EQC (required inputs are different if Type I vs. Type II chemical)	Arnot-Gobas BCF/BAF Model	Canadian-POPs (including: Catabol, BCF Mitigating Factors Model, OASIS Toxicity Model)	Artificial Intelligence Expert System (AIES)/ TOPKAT/ ASTER
SMILES Code	xc12N(CCCN(C)C)c3cc(Cl)ccc3CCc1cccc2			c12N(CCCN(C)C)c3cc(Cl)ccc3CCc1cccc2	c12N(CCCN(C)C)c3cc(Cl)ccc3CCc1cccc2
Molecular weight (g/mol)		351.31 (II)			
Data temperature (ºC)		20 (II)			
Air-water partition coefficient (dimensionless)		3.06×10^{-7} (II)			
Log K_{ow} (Octanol-water partition coefficient; dimensionless)	3.32, 5.19		3.32, 5.19		
Soil-water partition coefficient (L/kg)[1]		2060 (II)			
Sediment-water partition coefficient (L/kg)[1]		4120 (II)			
Suspended particles-water partition coefficient (L/kg)[1]		20600 (II)			
Fish-water partition coefficient (L/kg)[2]		6510 (II)			

Aerosol-water partition coefficient; dimensionless[3]		100 (II)			
Half-life in air (days)		0.0364 (II)			
Half-life in water (days)		180 (II)			
Half-life in sediment (days)		720 (II)			
Half-life in soil (days)		180 (II)			
Metabolic rate constant (1/days)			0, 6.659		

[1] derived from $\log K_{oc}$
[2] derived from BCF data
[3] default value