Screening Assessment

Twenty-three Substances on the Domestic Substances List Used Primarily as Pharmaceuticals

Chemical Abstracts Service Registry Numbers

50-06-6 (Phenobarbital)	81-81-2 (Warfarin)	7481-89-2 (Zalcitabine)
50-18-0 (Cyclophosphamide)	126-07-8 (Griseofulvin)	13010-47-4 (Lomustine)
55-86-7 (Mechlorethamine)	148-82-3 (Melphalan)	18883-66-4 (Streptozocin)
55-98-1 (Busulfan)	154-93-8 (Carmustine)	20830-81-3 (Daunorubicin)
56-75-7 (Chloramphenicol)	305-03-3 (Chlorambucil)	29767-20-2 (Teniposide)
57-41-0 (Phenytoin)	443-48-1 (Metronidazole)	30516-87-1 (Zidovudine)
68-22-4 (Norethindrone)	446-86-6 (Azathioprine)	51264-14-3 (Amsacrine)
71-58-9 (Medroxyprogesterone)	604-75-1 (Oxazepam)	

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Synopsis

Pursuant to section 68 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment of 23 substances on the *Domestic Substances List* (DSL) that are primarily used as pharmaceuticals. These substances, listed by their Chemical Abstracts Service Registry Number[1] (CAS RN) in the following table, were grouped together in one screening assessment as they were all identified as priorities for assessment based on classifications by other national or international agencies for carcinogenicity or developmental toxicity. A similar screening assessment approach was therefore applied to all of them.

Chemical Abstracts Service Registry Numbers for 23 substances on the DSL used primarily as pharmaceuticals

CAS RN	DSL name	Common pharmaceutical name
50-06-6	2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-ethyl-5-phenyl-	Phenobarbital
50-18-0	2*H*-1,3,2-Oxazaphosphorin-2-amine, *N*,*N*-bis(2-chloroethyl)tetrahydro-, 2-oxide	Cyclophosphamide
55-86-7	Ethanamine, 2-chloro-*N*-(2-chloroethyl)-*N*-methyl-, hydrochloride	Mechlorethamine
55-98-1	1,4-Butanediol, dimethanesulfonate	Busulfan
56-75-7	Acetamide, 2,2-dichloro-*N*-[2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl]-, [*R*-(*R*,*R*)]-	Chloramphenicol
57-41-0	2,4-Imidazolidinedione, 5,5-diphenyl-	Phenytoin
68-22-4	19-Norpregn-4-en-20-yn-3-one, 17-hydroxy-, (17α)-	Norethindrone
71-58-9	Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, (6α)-	Medroxyprogesterone
81-81-2	2*H*-1-Benzopyran-2-one, 4-hydroxy-3-(3-oxo-1-phenylbutyl)-	Warfarin
126-07-8	Spiro[benzofuran-2(3*H*),1′-[2]cyclohexene]-3,4′-dione, 7-chloro-2′,4,6-trimethoxy-6′-methyl-, (1′*S*-*trans*)-	Griseofulvin
148-82-3	L-Phenylalanine, 4-[bis(2-chloroethyl)amino]-	Melphalan
154-93-8	Urea, *N*,*N*′-bis(2-chloroethyl)-*N*-nitroso-	Carmustine
305-03-3	Benzenebutanoic acid, 4-[bis(2-chloroethyl)amino]-	Chlorambucil

[1] The Chemical Abstracts Service Registry Number (CAS RN) is the property of the American Chemical Society; any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the government when the information and the reports are required by law or administrative policy, is not permitted without the prior written permission of the American Chemical Society.

CAS RN	DSL name	Common pharmaceutical name
443-48-1	1*H*-Imidazole-1-ethanol, 2-methyl-5-nitro-	Metronidazole
446-86-6	1*H*-Purine, 6-[(1-methyl-4-nitro-1*H*-imidazol-5-yl)thio]-	Azathioprine
604-75-1	2*H*-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-	Oxazepam
7481-89-2	Cytidine, 2′,3′-dideoxy-	Zalcitabine
13010-47-4	Urea, *N*-(2-chloroethyl)-*N*′-cyclohexyl-*N*-nitroso-	Lomustine
18883-66-4	D-Glucose, 2-deoxy-2-[[(methylnitrosoamino)carbonyl]amino]-	Streptozocin
20830-81-3	5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8*S*,10*S*)-	Daunorubicin
29767-20-2	Furo[3′,4′:6,7]naphtho[2,3-d]-1,3-dioxol-6(5a*H*)-one, 5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-9-[[4,6-*O*-[(*R*)-2-thienylmethylene]-β-D-glucopyranosyl]oxy]-, (5*R*,5a*R*,8a*R*,9*S*)-	Teniposide
30516-87-1	Thymidine, 3′-azido-3′-deoxy-	Zidovudine
51264-14-3	Methanesulfonamide, *N*-[4-(9-acridinylamino)-3-methoxyphenyl]-	Amsacrine

Drugs containing these substances as ingredients were previously assessed under the *Food and Drugs Act* (F&DA) with respect to their safety, effectiveness and quality. This assessment focused on uses and exposures that were not covered as part of the F&DA assessment, specifically the risks posed by the residues resulting from manufacture, formulation and disposal after use.

Entry characterization (how the substances are entering the Canadian environment) was conducted by identifying the potential use of these substances outside of their intended pharmaceutical use. With the exception of warfarin, which is also used as a rodenticide, the only other identified use for these substances was as positive controls in research. Quantities in commerce for the consumption of pharmaceutical products that contain these substances have been estimated using information on amounts purchased by hospitals and pharmacies for 2007, 2011 and 2012.

Given that the main releases of these substances to the environment are through either industrial or down-the-drain consumer releases, the principal potential source of exposure is surface water containing these pharmaceuticals.

In order to estimate exposure in the environment, sales volumes were used as an input into modelling for predicted environmental concentrations (PECs). PECs were generated for water as a result of industrial releases and down-the-drain releases from consumer uses. The PECs from both of these scenarios were then compared with the predicted no-effect concentrations (PNECs), which were based on critical toxicity values

identified during the DSL categorization process. For all substances, the predicted environmental concentration (PEC) in water was below the PNEC calculated for aquatic species.

Measured concentrations in different media, including drinking water, surface water, groundwater and wastewater treatment plant effluent, were identified in the literature for a subset of these substances, either internationally or in Canada. Where available, the measured concentrations were also compared with the PNEC for each substance; the resulting risk quotients were all less than 1, which supports and generates confidence in the modelling results.

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to organisms or the broader integrity of the environment from these substances. It is therefore concluded that the 23 substances do not meet the criteria under paragraph 64(*a*) or 64(*b*) of CEPA 1999, as they are 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.

With regard to potential exposure of the general population, upper-bounding estimated intakes from ingestion of drinking water were very low (< 2.7 ng/kg body weight per day) for all substances. Based on low exposure, risks from exposure to these substances are not expected. To further support this risk characterization, the upper-bounding estimated intakes of the general population were compared with the lowest therapeutic dose identified for each substance. The margins of exposure for these substances were large, ranging from 10 900 to 8×10^{13}.

Based on the adequacy of the margins of exposure, it is concluded that the 23 substances do not meet the criteria under paragraph 64(*c*) of CEPA 1999, as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Conclusion

It is concluded that these 23 substances do not meet any of the criteria set out in section 64 of CEPA 1999.

Table of Contents

1. Introduction

A screening assessment was undertaken on 23 substances on the Domestic Substances List (DSL) that were known or suspected to be used primarily as ingredients in pharmaceuticals and identified during the categorization of substances on the DSL as posing a potential high hazard to human health based on classifications by other national or international agencies for either carcinogenicity or developmental toxicity.

Screening assessments focus on information critical to determining whether a substance meets the criteria as set out in section 64 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999). Screening assessments examine scientific information and develop conclusions by incorporating a weight of evidence approach and precaution.[2]

This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure. Relevant data were identified up to March 2013. Key studies were critically evaluated, along with modelled results, to reach conclusions. When available and relevant, information presented in risk and hazard assessments from other jurisdictions was considered. The screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents the critical studies and lines of evidence most pertinent to the conclusion.

Drugs containing these substances as ingredients are assessed under the *Food and Drugs Act* (F&DA) (Canada 1985) with respect to their safety, effectiveness and quality. This assessment focused on uses and exposures that were not covered as part of the F&DA assessment, specifically the risks posed by the residues resulting from manufacture, formulation and disposal after use.

The 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. Comments on the approach used to assess the substance with respect to human health were received from Warren Foster, McMaster University, Sam Kacew, McLaughlin Centre for Population Health Risk Assessment, and Beate Escher, University of Queensland. While external comments were taken into

[2] A determination of whether one or more of the criteria of section 64 are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs, and the use of consumer products. A conclusion under CEPA 1999 on the substances in the Chemicals Management Plan (CMP) is not relevant to, nor does it preclude, an assessment against the hazard criteria for the *Workplace Hazardous Materials Information System* (WHMIS) that are specified in the *Controlled Products Regulations* for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA 1999 does not preclude actions being taken under other sections of CEPA 1999 or other Acts.

consideration, the final content and outcome of the screening assessment remain the responsibility of Health Canada and Environment Canada.
The critical information and considerations upon which the draft assessment is based are summarized below.

2. Summary of Use Information Used as Basis for this Screening Assessment

Based on the results from categorization of the DSL, the 23 substances listed in this report have all been identified as posing a potential high hazard to human health based on classifications by other national or international agencies for either carcinogenicity or developmental toxicity. The list of substances, along with their hazard classifications and categorization decisions, can be found in Tables A.1, A.2 and A.3 of Appendix A.

For two of these substances, a survey was conducted by issuing a *Notice with respect to selected substances identified as priority for action* pursuant to paragraphs 71(1)(*a*) and 71(1)(*b*) of CEPA 1999. The Notice was published in Part I of the *Canada Gazette* on March 4, 2006 (Canada 2006). The substances surveyed were medroxyprogesterone and oxazepam.

For five substances, a survey was conducted by issuing a *Notice with respect to inanimate substances (chemicals) on the Domestic Substances List* pursuant to paragraphs 71(1)(*a*) and 71(1)(*b*) of CEPA 1999. The Notice was published in Part I of the *Canada Gazette* on October 3, 2009 (Canada 2009).The five substances surveyed were zalcitabine, warfarin, chloramphenicol, zidovudine and phenobarbital.

In response to both of these notices, there were no reports of activity (import or manufacture) with respect to these seven substances in Canada above the reporting threshold of 100 kg for the specified reporting years. Additional sources of information were also considered to verify the commercial status of these substances in Canada.

For all 23 substances, entry characterization was conducted by searching for information on sources and releases of the substances in relevant databases, particularly to identify potential for exposure of the general population from sources other than pharmaceutical use (Canada [1978]; HSDB 1983– ; Household Products Database 1993– ; LNHPD 2008; DPD 2010; EAFUS 2011; NHPID 2011). Based on notifications submitted under the Cosmetic Regulations to Health Canada, these substances are not used in cosmetic products in Canada (2012 email from the Consumer Product Safety Directorate, Health Canada, to the Existing Substance Risk Assessment Bureau, Health Canada; unreferenced). Information available for all of these substances indicates that their uses are limited to human or veterinary pharmaceuticals and positive controls in research, with the exception of warfarin, which is also used as a rodenticide. This use of warfarin as a rodenticide is regulated by Health Canada under the *Pest Control Products Act* (Canada 2002).

Two of these substances, phenobarbital and oxazepam, are considered to be controlled drugs and are listed under Schedule IV of the *Controlled Drugs and Substances Act.* As controlled substances, these two drugs are subject to the requirements of the *Controlled Drugs and Substances Act* and the *Food and Drug Regulations* (Canada [1978]). The remaining 21 substances are regulated as prescription drugs through the Prescription Drugs List and are subject to the requirements of those regulations (Health Canada

2014; Canada [1978]). Twenty of these substances are listed in the Drug Product Database as active ingredients in products available in Canada for the treatment of a variety of medical conditions (DPD 2014). The other three substances, mechlorethamine, griseofulvin and zalcitabine, were at one time used as active ingredients in prescription pharmaceuticals in Canada. Currently, however, no pharmaceutical products containing these substances as active ingredients are being sold in Canada, as they have been discontinued by the company (DPD 2014). As they are no longer being sold, the use and potential for exposure of or risk to humans or the environment are not further considered in certain aspects of the exposure and risk characterization below.

No information was found regarding additional uses or releases of these substances in Canada based on searches conducted up to March 2013.

When a pharmaceutical is prescribed for use, some of the drug may not be absorbed or metabolized, and even drugs that are metabolized may have active metabolites or may revert to the parent form in environmental media. This may lead to excretion of active drug residues into the wastewater system and release of the wastewater effluent containing these residues into surface water (i.e., lakes, rivers), and this surface water has the potential to be used as drinking water. Therefore, the potential for indirect exposure of the general population to these pharmaceuticals was assessed. Given their potential releases, the main source of indirect exposure to these substances is through water. These pharmaceuticals may be present in water as a result of release from manufacturing or formulation sites and/or release of the substances in feces or urine from consumers directly using these substances. An additional source of the pharmaceuticals in water is from the incorrect disposal of unused drugs into household wastewater. No information was available regarding actual releases of these substances from manufacturing or formulation of the pharmaceuticals. Data, however, were available to estimate the amount of each substance sold to hospitals and pharmacies for prescription across Canada for the years 2007 (McLaughlin and Belknap 2008), 2011 and 2012 (MIDAS 2013) (Appendix B).

3. Ecological Exposure and Risk Characterization from Industrial Releases and Prescription Use

A conservative industrial release scenario was used to determine whether there is a potential ecological risk associated with these 20 substances when released to water via industrial releases (as mentioned above, the three substances no longer registered for use as pharmaceuticals in Canada are not being examined further). This is conducted by comparing the conservative predicted environmental concentration (PEC) in the aquatic environment with a predicted no-effect concentration (PNEC). The result is a risk quotient (RQ) based on an industrial non-site-specific scenario. This simple model represents a point source discharge from an industry, its dilution in a small watercourse and calculation of a risk quotient for that scenario.

A conservative PEC was calculated using the following equation:

$PEC_{aq} = (1000 \times Q \times L) \times (1 - R) / (N \times F \times D)$

where:

PEC_{aq}: Aquatic concentration resulting from industrial releases (mg/L)
1000: Conversion factor (g/kg)
Q: Total substance quantity produced annually at an industrial site (kg/year) (see values for each substance for the most current year, 2012, provided in Appendix B)
L: Loss to wastewater (fraction) (assumed to be 0.5% of total use for pharmaceuticals)
R: Wastewater treatment plant removal rate (fraction) (default = 0%)
N: Number of annual release days (days/year) (assumed to be manufactured in small batches and therefore released 21 days/year)
F: Wastewater treatment plant effluent flow (m^3/day) (default = 3456 m^3/day)
D: Receiving water dilution factor (dimensionless) (default = 10)

This PEC_{aq} value is then used to calculate a risk quotient, as shown in the following equation:

$RQ = PEC_{aq} / (PNEC)$

where:

RQ: Risk quotient (dimensionless)
PEC_{aq}: Aquatic concentration resulting from industrial releases (mg/L)
PNEC: Predicted no-effect concentration (mg/L). The PNECs selected for this assessment were the values identified during the categorization process and are provided in Appendix C; an assessment factor of 100 was used to account for uncertainties in deriving the PNEC.

For two of the substances, daunorubicin and oxazepam, the industrial scenario was further refined to simulate an industrial production site in a large urban area with a wastewater treatment plant flow rate of 285 120 m^3/day and wastewater treatment plant removal rates ranging from 1.9% to 2.5%.

The calculated RQs for all substances were < 1 (see full results in Appendix C). Given that the industrial scenario provides a conservative estimate of exposure, these results indicate a low potential for ecological harm to the aquatic environment resulting from local exposure from a point source industrial release.

A down-the-drain release from pharmaceutical use scenario was employed to estimate the potential concentrations in multiple water bodies receiving wastewater treatment plant effluents to which pharmaceutical products containing the substances may have

been released based on conservative assumptions regarding the amount of chemical used and released by consumers (Environment Canada 2008b). By default, primary and secondary wastewater treatment plant removal rates are assumed to be 0% for these substances, the fraction released during use is assumed to be 100%, the consumer use of the substance is assumed to occur over 365 days/year and the flow rate used for receiving water bodies at all sites is assumed to be the 10th percentile value. These estimates are made for approximately 1000 release sites, which account for most of the major wastewater treatment plants across Canada. Although the default values are recognized to be highly conservative, if indication of risk is low based on these assumptions, further refinement of input values is not required at this time.

In light of uncertainty relating to the identity and environmental stability of the metabolites of these substances, a conservative environmental concentration value was obtained by not considering human metabolism in the derivation of the PECs. RQs were calculated using maximum PECs calculated from down-the-drain releases of these substances from pharmaceutical use and PNECs as identified during the categorization process, derived using an application factor of 100 to account for uncertainties associated with the values. The maximum RQ was < 1 for all of these substances (see full results in Appendix C), indicating a low potential for ecological harm to the aquatic environment resulting from down-the-drain releases from consumer uses.

Measured data for some of these substances were identified for Canada and/or elsewhere in the world and are shown in Appendix D. Concentrations measured in various media, wastewater effluent, surface water, groundwater and drinking water (including bottled water) were examined, and the information available is consistent with the predicted concentrations from the models. The majority of studies did not detect these substances in the media of interest; however, some were measured at concentrations up to 564 ng/L in wastewater effluent. A comparison of the measured values with the PNECs determined for these substances results in RQs that are all < 1, contributing to the weight of evidence indicating that there is no significant potential for ecological harm to the aquatic environment from these substances.

Given the lack of exposure to these substances, no further collection or analysis of information relevant to the persistence, bioaccumulation and inherent toxicity to non-human organisms of these substances has been conducted beyond what was done for categorization. Therefore, the decisions made on the hazard properties during categorization remain unchanged in this assessment. Accordingly, none of the substances are considered to meet the criteria for persistence or for bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations* of CEPA 1999 (Canada 2000).

4. Human Health Exposure and Risk Characterization from Indirect Exposure

Drugs containing these substances as ingredients were previously assessed under the *Food and Drugs Act* (Canada 1985) with respect to their safety, effectiveness and quality. This assessment focused on uses and exposures that were not covered as part of the F&DA assessment, specifically the risks posed by the residues resulting from manufacture, formulation and disposal after use.

Only a portion of pharmaceuticals used would be released into the wastewater system. Drug residues released following prescribed use can be further reduced as a result of wastewater treatment, environmental biodegradation and/or drinking water treatment prior to consumption. The concentration in the water source is also significantly reduced via dilution, as the waste is released into waterways.

Measured data for 18 of these substances were identified for Canada and elsewhere and are shown in Appendix D. Concentrations measured in wastewater effluent, surface water, groundwater and drinking water (including bottled water) were examined. Overall, the studies indicated that the concentration of pharmaceutical measured decreases significantly as the substance moves from the wastewater treatment plant effluent into surface water and then the surface water is treated for drinking water purposes. As there is variability in the use of pharmaceuticals in different countries (due to different population levels, prescription preferences, drug registrations, etc.), the measured concentrations in other countries are not necessarily representative of concentrations in Canadian waters. They can, however, account for releases from all potential sources and for potential reductions in drug concentrations resulting from metabolism, environmental degradation, removal via wastewater treatment, removal via drinking water treatment, etc., depending on the source of the sample. For these reasons, in this case, the measured concentrations are preferable to modelled concentrations, even if measurements were made in other countries. Selection of the most relevant data was based on location of the sampling and the relevance of the media to human exposure. Canadian data were given preference over data from other countries, as they are considered to be most representative of potential exposures of Canadians. Drinking water was considered the most relevant medium, followed by surface water or groundwater, wastewater treatment plant effluent and hospital effluent. If multiple relevant concentrations were available for a particular source (e.g., two measurements in Canadian drinking water), as a conservative approach, the maximum concentration was selected from the measured values identified.

For the two substances for which no measured data were identified, conservative assumptions were used when estimating the potential indirect exposure of the general population. For the purposes of modelling, it was assumed for all substances that 100% of the pharmaceutical purchased by hospitals or pharmacies in the most recent year for which data were available (2012) was dispensed, used as prescribed and eventually released into the wastewater system. It was also assumed that none of the pharmaceutical was removed through wastewater treatment or drinking water treatment

processes and that there was no environmental degradation of the substance. It is recognized that these assumptions are highly conservative; however, if indication of risk is low based on these assumptions, further refinement would not be required.

Down-the-drain releases to surface water were modelled using the down-the-drain releases from pharmaceutical use scenario, as described in the ecological exposure section, and maximum PECs can be found in Appendix C. This scenario estimates concentrations in approximately 1000 waterways across Canada. The highest values estimated by this model are typically in small waterways with low dilution capacity, which are unlikely sources of drinking water. As a result, this scenario would be expected to overestimate actual concentrations in drinking water.

The estimated upper-bounding intakes of these pharmaceuticals by the general population were represented by formula-fed infants 0–6 months of age, which is estimated to be the most highly exposed age class, on a body weight basis, of those examined. The equation for deriving the estimated intake is given below:

$$\text{Intake} = (PEC_{aq} \times IR) / bw$$

where:

Intake: Estimated intake of the substance from drinking water (mg/kg bw per day)
PEC_{aq}: Predicted environmental concentration in receiving water from modelled or measured data (mg/L)
IR: Ingestion rate of drinking water for formula-fed infants: 0.8 L/day (Health Canada 1998)
bw: Default body weight for infants 0–6 months of age: 7.5 kg (Health Canada 1998)

The estimated intakes for 18 substances with measured concentrations are presented in Appendix E, and intakes for 2 substances with only modelled concentrations are presented in Appendix F.

Estimated intakes for all substances were low and range from 1.6×10^{-7} to 2.7 ng/kg bw per day. Since the majority of the measurements were based on wastewater treatment plant effluent or surface water, it is expected that these estimates provide conservative upper-bounding estimates of possible exposure and that actual exposures would be significantly lower.

Based on low exposure, risks from exposure to these substances are not expected. This determination is further supported by consideration of two additional lines of evidence for evaluation of the potential for harm to human health.

A comparison was made between the range of estimated intake values for this group of 20 substances and the threshold of toxicological concern (TTC) value of 2.5 ng/kg bw per day originally proposed by Kroes et al. (2004). For all 20 substances, estimated intakes are in the range of or below the TTC. Although the TTC may not be applicable

to every member of this group, it does provide a reference point against which the range of estimated intakes can be compared. TTC values, which are derived using probabilistic approaches, establish generic human exposure threshold values below which it is expected that the probability of adverse effects is low. A TTC value of 0.15 µg/day (equivalent to 2.5 ng/kg bw per day) has been established for potentially carcinogenic substances with structural alerts for genotoxicity. Additional higher TTC values have been established for substances not containing similar structural alerts (Munro et al. 1996a, b; Kroes et al. 2004; EFSA 2012; Dewhurst and Renwick 2013).

A second comparison was also made to evaluate potential risk. The lowest therapeutic dose (LTD) for each substance was identified, and a margin of exposure (MOE) was calculated to determine the ratio between the upper-bounding estimate of intake by the general population and the dose that would be expected to produce a pharmacological effect. This approach is consistent with methodology described elsewhere (Webb et al. 2003; Schwab et al. 2005; Watts et al. 2007; Bull et al. 2011; WHO 2011). The LTD is the lowest concentration that evokes a desired therapeutic effect among target populations and is equivalent to the lowest dose prescribed or recommended, taking into account the number of doses per day (WHO 2011). These values are derived from an assessment of the balance between safety and efficacy. LTDs were identified for each pharmaceutical by examining the dosage and administration guidelines presented in the product monographs submitted to Health Canada as part of the pre-market drug authorization, which are available from the Health Canada Drug Product Database (DPD 2010).

MOEs were derived using the equation below and are presented in Appendix E or F:

$$MOE = LTD/Intake$$

where:

MOE: Margin of exposure (dimensionless)
LTD: Lowest therapeutic dose (mg/kg bw per day)
Intake: Maximum estimated intake for drinking water derived from modelled or measured concentrations (mg/kg bw per day)

MOEs for these substances were large and ranged from 10 900 to 8.0×10^{13}. Given the very conservative nature of the exposure inputs and the use of human data to derive a point of departure for risk characterization, these MOEs support the determination that risks from indirect exposure to these substances are low.

5. Uncertainties

There is uncertainty regarding the estimation of exposure due to the lack of data on concentrations in Canadian surface water or drinking water for many of these substances. However, confidence is high that actual exposures would be lower than the ones presented from the measured data and models used. The uncertainty in both the environmental and human health risk estimates could be reduced by using measured concentration data from Canadian surface water and/or drinking water for these substances. However, it is unlikely that potential exposures were underestimated.

Potential general population exposures to these substances could occur via other sources, such as ingestion of fish or swimming in waters where the pharmaceuticals are present, but these exposures are expected to be much less than the exposure through drinking water and so are not considered in this assessment.

Some of these substances may have additional off-label or veterinary uses that are not considered in this assessment. The quantities of the substances being used for these purposes are unknown, and so estimation of releases is not possible at this time. For the substances which have measured environmental concentrations these releases may be reflected in those measurements,

It is recognized that the LTD represents an exposure level at which a desired pharmacological response is achieved and further that at this exposure level, adverse effects, in addition to intended effects, may occur in some patients. For certain indications and certain classes of drugs, the nature of these unintended effects may be significant. However, the LTD is developed for patients who require treatment for a particular illness and therefore are likely to be more susceptible to potential effects than a healthy individual. Although the use of the LTD provides a tier 1 type of assessment that does not utilize all the toxicity data that may be available for each substance, the highly conservative exposure defaults that have been used lead to significant MOEs between the LTD and the estimated intakes.

6. Conclusion

Considering all available lines of evidence presented in this screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from these 23 substances. It is concluded that these 23 substances do not meet the criteria under paragraphs 64(*a*) or (*b*) of CEPA 1999 as they are 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. Based on the information presented in this screening assessment, it is concluded that these 23 substances do not meet the criteria under paragraph 64(c) of CEPA 1999 as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is concluded that these 23 substances do not meet any of the criteria set out in section 64 of CEPA 1999.

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Appendix A: Substance Identity and Human Health and Ecological Classifications for 23 Pharmaceuticals

Table A.1: List of 23 DSL substances, primarily used as pharmaceuticals, with common pharmaceutical name and drug class

CAS RN	DSL name	Common pharmaceutical name	Drug class
50-06-6	2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-ethyl-5-phenyl-	Phenobarbital	Sedative / hypnotic / anticonvulsant / antihyperbilirubinemic
50-18-0	2*H*-1,3,2-Oxazaphosphorin-2-amine, *N*,*N*-bis(2-chloroethyl)tetrahydro-, 2-oxide	Cyclophosphamide	Antineoplastic
55-86-7[a]	Ethanamine, 2-chloro-*N*-(2-chloroethyl)-*N*-methyl-, hydrochloride	Mechlorethamine	Antineoplastic
55-98-1	1,4-Butanediol, dimethanesulfonate	Busulfan	Antineoplastic
56-75-7	Acetamide, 2,2-dichloro-*N*-[2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl]-, [*R*-(*R*,*R*)]-	Chloramphenicol	Antibiotic
57-41-0	2,4-Imidazolidinedione, 5,5-diphenyl-	Phenytoin	Anticonvulsant
68-22-4	19-Norpregn-4-en-20-yn-3-one, 17-hydroxy-, (17α)-	Norethindrone	Oral contraceptive
71-58-9	Pregn-4-ene-3,20-dione, 17-(acetyloxy)-6-methyl-, (6α)-	Medroxyprogesterone	Oral contraceptive
81-81-2	2*H*-1-Benzopyran-2-one, 4-hydroxy-3-(3-oxo-1-phenylbutyl)-	Warfarin	Anticoagulant
126-07-8[a]	Spiro[benzofuran-2(3*H*),1′-[2]cyclohexene]-3,4′-dione, 7-chloro-2′,4,6-trimethoxy-6′-methyl-, (1′*S*-*trans*)-	Griseofulvin	Antifungal
148-82-3	L-Phenylalanine, 4-[bis(2-chloroethyl)amino]-	Melphalan	Antineoplastic
154-93-8	Urea, *N*,*N*′-bis(2-chloroethyl)-*N*-nitroso-	Carmustine	Antineoplastic
305-03-3	Benzenebutanoic acid, 4-[bis(2-chloroethyl)amino]-	Chlorambucil	Antineoplastic

CAS RN	DSL name	Common pharmaceutical name	Drug class
443-48-1	1*H*-Imidazole-1-ethanol, 2-methyl-5-nitro-	Metronidazole	Antibiotic
446-86-6	1*H*-Purine, 6-[(1-methyl-4-nitro-1*H*-imidazol-5-yl)thio]-	Azathioprine	Immunosuppressant
604-75-1	2*H*-1,4-Benzodiazepin-2-one, 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-	Oxazepam	Anxiolytic sedative
7481-89-2[a]	Cytidine, 2′,3′-dideoxy-	Zalcitabine	Antiretroviral
13010-47-4	Urea, *N*-(2-chloroethyl)-*N*′-cyclohexyl-*N*-nitroso-	Lomustine	Antineoplastic
18883-66-4	D-Glucose, 2-deoxy-2-[[(methylnitrosoamino)carbonyl]amino]-	Streptozocin	Antineoplastic
20830-81-3	5,12-Naphthacenedione, 8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-, (8*S*,10*S*)-	Daunorubicin	Antimitotic / antibiotic
29767-20-2	Furo[3′,4′:6,7]naphtho[2,3-d]-1,3-dioxol-6(5a*H*)-one, 5,8,8a,9-tetrahydro-5-(4-hydroxy-3,5-dimethoxyphenyl)-9-[[4,6-*O*-[(*R*)-2-thienylmethylene]-β-D-glucopyranosyl]oxy]-, (5*R*,5a*R*,8a*R*,9*S*)-	Teniposide	Antineoplastic
30516-87-1	Thymidine, 3′-azido-3′-deoxy-	Zidovudine	Antiretroviral
51264-14-3	Methanesulfonamide, N-[4-(9-acridinylamino)-3-methoxyphenyl]-	Amsacrine	Antineoplastic

Abbreviations: CAS RN, Chemical Abstracts Service Registry Number; DSL, Domestic Substances List

[a] Substance that has been discontinued by the company post-market and is no longer registered as a pharmaceutical available for sale in Canada (DPD 2010).

Table A.2: Human health classifications for the 23 substances

CAS RN	Common pharmaceutical name	Classification for human health	Reference for classification
50-06-6	Phenobarbital	Possibly carcinogenic to humans	IARC 1977
50-18-0	Cyclophosphamide	Carcinogenic to humans	IARC 2012

CAS RN	Common pharmaceutical name	Classification for human health	Reference for classification
50-18-0	Cyclophosphamide	Known human carcinogen	NTP 2011
55-86-7	Mechlorethamine	Reasonably anticipated human carcinogen	NTP 2011
55-98-1	Busulfan	Carcinogenic to humans	IARC 2012
55-98-1	Busulfan	Known human carcinogen	NTP 2011
56-75-7	Chloramphenicol	Probably carcinogenic to humans	IARC 1990
57-41-0	Phenytoin	Possibly carcinogenic to humans	IARC 1996
57-41-0	Phenytoin	Reasonably anticipated human carcinogen	NTP 2011
68-22-4	Norethindrone	Reasonably anticipated human carcinogen	NTP 2011
71-58-9	Medroxyprogesterone	Possibly carcinogenic to humans	IARC 2012
81-81-2	Warfarin	Known to cause developmental toxicity in humans	ESIS ©1995–2012
126-07-8	Griseofulvin	Possibly carcinogenic to humans	IARC 2001
148-82-3	Melphalan	Carcinogenic to humans	IARC 2012
148-82-3	Melphalan	Known human carcinogen	NTP 2011
154-93-8	Carmustine	Probably carcinogenic to humans	IARC 1987
154-93-8	Carmustine	Reasonably anticipated human carcinogen	NTP 2011
305-03-3	Chlorambucil	Carcinogenic to humans	IARC 2012
305-03-3	Chlorambucil	Known human carcinogen	NTP 2011
443-48-1	Metronidazole	Possibly carcinogenic to humans	IARC 1987
443-48-1	Metronidazole	Reasonably anticipated human carcinogen	NTP 2011
446-86-6	Azathioprine	Carcinogenic to humans	IARC 2012
446-86-6	Azathioprine	Known human carcinogen	NTP 2011
604-75-1	Oxazepam	Possibly carcinogenic to humans	IARC 1996
7481-89-2	Zalcitabine	Possibly carcinogenic to humans	IARC 2000
13010-47-4	Lomustine	Probably carcinogenic to humans	IARC 1987
13010-47-4	Lomustine	Reasonably anticipated human	NTP 2011

CAS RN	Common pharmaceutical name	Classification for human health	Reference for classification
		carcinogen	
18883-66-4	Streptozocin	Possibly carcinogenic to humans	IARC 1978
18883-66-4	Streptozocin	Reasonably anticipated human carcinogen	NTP 2011
20830-81-3	Daunorubicin	Possibly carcinogenic to humans	IARC 1976
29767-20-2	Teniposide	Probably carcinogenic to humans	IARC 2000
30516-87-1	Zidovudine	Possibly carcinogenic to humans	IARC 2000
51264-14-3	Amsacrine	Possibly carcinogenic to humans	IARC 2000

Abbreviation: CAS RN, Chemical Abstracts Service Registry Number

Table A.3: Ecological categorization outcomes for the 23 substances

CAS RN	Common pharmaceutical name	P status[a]	B status[a]	iTeco status[a]
50-06-6	Phenobarbital	No	No	No
50-18-0	Cyclophosphamide	No	No	No
55-86-7	Mechlorethamine	No	No	No
55-98-1	Busulfan	No	No	No
56-75-7	Chloramphenicol	No	No	No
57-41-0	Phenytoin	No	No	No
68-22-4	Norethindrone	No	No	No
71-58-9	Medroxyprogesterone	No	No	No
81-81-2	Warfarin	No	No	No
126-07-8	Griseofulvin	No	No	Yes
148-82-3	Melphalan	No	No	No
154-93-8	Carmustine	No	No	No
305-03-3	Chlorambucil	No	No	No
443-48-1	Metronidazole	No	No	No
446-86-6	Azathioprine	No	No	No
604-75-1	Oxazepam	No	No	Yes
7481-89-2	Zalcitabine	No	No	No
13010-47-4	Lomustine	No	No	No
18883-66-4	Streptozocin	No	No	No
20830-81-3	Daunorubicin	No	No	Yes
29767-20-2	Teniposide	No	No	No
30516-87-1	Zidovudine	No	No	No
51264-14-3	Amsacrine	No	No	No

Abbreviations: B, bioaccumulation; CAS RN, Chemical Abstracts Service Registry Number; iTeco, inherently toxic to non-human organisms; P, persistence

[a] Environment Canada (2006).

Appendix B: Estimated Quantities of 23 Pharmaceuticals Used in Canada for the Years 2007, 2011 and 2012

Table B.1: Estimated quantities of 23 pharmaceuticals used in Canada for the years 2007, 2011 and 2012

CAS RN	Common pharmaceutical name	Estimated quantity of drug used in Canada in 2007 (kg)[a]	Estimated quantity of drug used in Canada in 2011 (kg)[b]	Estimated quantity of drug used in Canada in 2012 (kg)[b]
50-06-6	Phenobarbital	894	766	874
50-18-0	Cyclophosphamide	134	92	88
55-86-7	Mechlorethamine	1	N/A	N/A
55-98-1	Busulfan	1	1	1
56-75-7	Chloramphenicol	4	7	2
57-41-0	Phenytoin	10 442	9 080	8 457
68-22-4	Norethindrone	17	113	110
71-58-9	Medroxyprogesterone	461	172	172
81-81-2	Warfarin	735	733	699
126-07-8	Griseofulvin	1	N/A	N/A
148-82-3	Melphalan	1	1	1
154-93-8	Carmustine	1	1	1
305-03-3	Chlorambucil	2	2	1
443-48-1	Metronidazole	13 352	8 546	8 672
446-86-6	Azathioprine	1 077	1 534	1 661
604-75-1	Oxazepam	2 532	1 497	1 425
7481-89-2	Zalcitabine	1	N/A	N/A
13010-47-4	Lomustine	1	1	1
18883-66-4	Streptozocin	2	0.04	< 0.000 001
20830-81-3	Daunorubicin	1	1	1
29767-20-2	Teniposide	1	0.03	0.05
30516-87-1	Zidovudine	1 138	471	410
51264-14-3	Amsacrine	1	1	0.1

Abbreviations: CAS RN, Chemical Abstracts Service Registry Number; N/A, not available

[a] McLaughlin and Belknap (2008).

[b] IMS (2013).

Appendix C: Results from Environmental Exposure Modelling for 20 Pharmaceuticals Using Quantity Data from 2012

Table C.1: Results from environmental exposure modelling for 20 pharmaceuticals using quantity data from 2012

CAS RN	Common pharmaceutical name	PNEC: iTeco value identified during categorization / 100 (mg/L)[a]	Estimated PEC for industrial releases[b] (mg/L)	Estimated RQ for industrial releases[b]	Estimated maximum PEC for consumer releases[c] (mg/L)	Estimated maximum RQ for consumer releases[c]
50-06-6	Phenobarbital	4.84	0.0060	1.2×10^{-3}	1.3×10^{-3}	2.7×10^{-4}
50-18-0	Cyclophosphamide	48.1	0.0006	1.2×10^{-5}	1.3×10^{-4}	2.7×10^{-6}
55-98-1	Busulfan	18.75	< 0.0001	5.3×10^{-6}	1.5×10^{-6}	8.0×10^{-8}
56-75-7	Chloramphenicol	542.5	< 0.0001	1.8×10^{-7}	3.1×10^{-6}	5.7×10^{-9}
57-41-0	Phenytoin	0.088	0.0583	0.66	1.3×10^{-2}	0.15
68-22-4	Norethindrone	6.9	0.0008	1.2×10^{-4}	1.7×10^{-4}	2.5×10^{-5}
71-58-9	Medroxyprogesterone	0.0145	0.0012	0.083	2.6×10^{-4}	1.8×10^{-2}
81-81-2	Warfarin	34.3	0.0048	1.4×10^{-4}	1.1×10^{-3}	3.2×10^{-5}
148-82-3	Melphalan	3900	< 0.0001	2.6×10^{-8}	1.5×10^{-6}	3.9×10^{-10}
154-93-8	Carmustine	134	< 0.0001	7.5×10^{-7}	1.5×10^{-6}	1.1×10^{-8}
305-03-3	Chlorambucil	189.4	< 0.0001	5.3×10^{-7}	1.5×10^{-6}	7.9×10^{-9}
443-48-1	Metronidazole	0.125	0.0597	0.48	1.3×10^{-2}	0.1
446-86-6	Azathioprine	61.8	0.0114	1.8×10^{-4}	2.5×10^{-3}	$4. \times 10^{-5}$
604-75-1	Oxazepam	0.95	0.0001	1.1×10^{-4}	2.2×10^{-3}	2.3×10^{-3}
13010-47-4	Lomustine	15.6	< 0.0001	6.4×10^{-6}	1.5×10^{-6}	9.6×10^{-8}
18883-66-4	Streptozocin	1627	< 0.0001	6.2×10^{-8}	1.5×10^{-12}	9.2×10^{-16}
20830-81-3	Daunorubicin	4.9×10^{-7}	$2. 0 \times 10^{-8}$	0.04	3.5×10^{-7}	0.7
29767-20-2	Teniposide	207.4	< 0.0001	4.8×10^{-7}	7.6×10^{-8}	3.7×10^{-10}
30516-87-1	Zidovudine	732.5	0.0028	3.8×10^{-6}	6.3×10^{-4}	8.6×10^{-7}
51264-14-3	Amsacrine	4.8	< 0.0001	2.1×10^{-5}	1.5×10^{-7}	3.1×10^{-8}

Abbreviations: CAS RN, Chemical Abstracts Service Registry Number; iTeco, inherently toxic to non-human organisms; PEC, predicted environmental concentration; PNEC, predicted no-effect concentration; RQ, risk quotient

[a] Selected PNEC values were the iTeco values identified during the categorization process divided by 100 to account for uncertainty in the data. For references or further details, see the results of categorization (Environment Canada 2006).
[b] PECs calculated using Environment Canada's Industrial Generic Exposure Tool – Aquatic (Environment Canada 2008a).
[c] PECs calculated using Environment Canada's Mega Flush Consumer Release Scenario Tool (Environment Canada 2008b).

Appendix D: Measured Concentrations of 18 Pharmaceuticals in Wastewater Treatment Plant Influent and Effluent, Surface Water, Groundwater and Drinking Water

Table D.1: Measured concentrations of 18 pharmaceuticals in wastewater treatment plant influent and effluent, surface water, groundwater and drinking water

CAS RN	Common pharmaceutical name	Sampling location	Media measured	Range of values[a] (ng/L) (mean)	Detection limit[a] (ng/L)	Reference
50-06-6	Phenobarbital	Back River WWTP, Baltimore, MD, USA	WWTP influent	110	4	Yu et al. 2012
50-06-6	Phenobarbital	Back River WWTP, Baltimore, MD, USA	WWTP effluent	ND	4	Yu et al. 2012
50-06-6	Phenobarbital	Northern Italy	WWTP influent	110–270 (210)	3	Verlicchi et al. 2012
50-06-6	Phenobarbital	Northern Italy	WWTP effluent	110–170 (140)	2	Verlicchi et al. 2012
50-06-6	Phenobarbital	Northeastern Spain	Surface water	25.6–29.7	LOQ = 10	Boleda et al. 2011
50-06-6	Phenobarbital	Northeastern Spain	Drinking water	< LOD–25.1*	LOQ = 10	Boleda et al. 2011
50-06-6	Phenobarbital	Catalonia and Ebro River Basin, Spain	Surface water	ND	0.3	Gros et al. 2009
50-06-6	Phenobarbital	Catalonia and Ebro River Basin, Spain	WWTP effluent	ND	0.7	Gros et al. 2009
50-06-6	Phenobarbital	Germany and Croatia	Surface water	ND	1	Peschka et al. 2006
50-06-6	Phenobarbital	Germany and Croatia	WWTP effluent	ND	10	Peschka et al. 2006
50-18-0	Cyclophosphamide	Six WWTPs	WWTP effluent	ND–18.5	RL = 2.72–71.5	Smyth and Teslic 2013

CAS RN	Common pharmaceutical name	Sampling location	Media measured	Range of values[a] (ng/L) (mean)	Detection limit[a] (ng/L)	Reference
		across Canada				
50-18-0	Cyclophosphamide	Six WWTPs across Canada	WWTP effluent	ND–149	RL = 2.72 – 71.5	Smyth and Teslic 2013
50-18-0	Cyclophosphamide	Montréal, St. Lawrence River, Canada	WWTP effluent	ND	10–59	Garcia-Ac et al. 2009a
50-18-0	Cyclophosphamide	Montréal, St. Lawrence River, Canada	Surface water	ND	10–59	Garcia-Ac et al. 2009a
50-18-0	Cyclophosphamide	Montréal, Canada	Surface water	ND	1	Garcia-Ac et al. 2009b
50-18-0	Cyclophosphamide	Montréal, Canada	Drinking water	ND	1*	Garcia-Ac et al. 2009b
50-18-0	Cyclophosphamide	Little River WWTP and Detroit River, Canada	WWTP effluent	2.5–4	0.8–1.2	Hua et al. 2006
50-18-0	Cyclophosphamide	Little River WWTP and Detroit River, Canada	Surface water	ND	0.2–0.4	Hua et al. 2006
50-18-0	Cyclophosphamide	Atlantic Canada	WWTP effluent	ND	20	Brun et al. 2006
50-18-0	Cyclophosphamide	Fourteen WWTPs across Canada	WWTP effluent	ND	500	Metcalfe et al. 2003
50-18-0	Cyclophosphamide	Fourteen WWTPs across Canada	WWTP influent	ND	100	Metcalfe et al. 2003

CAS RN	Common pharmaceutical name	Sampling location	Media measured	Range of values[a] (ng/L) (mean)	Detection limit[a] (ng/L)	Reference
50-18-0	Cyclophosphamide	Germany	Surface water	4	NA	Kümmerer and Al-Ahmad 2010
50-18-0	Cyclophosphamide	Germany	WWTP effluent	(20)	10	Ternes 1998
50-18-0	Cyclophosphamide	Germany	Surface water	ND	10	Ternes 1998
50-18-0	Cyclophosphamide	Stockholm, Sweden	WWTP effluent	< 15 – < 20	15	Lundström et al. 2010
50-18-0	Cyclophosphamide	Canton of Zurich, Switzerland	WWTP effluent	2–10	0.03	Buerge et al. 2006
50-18-0	Cyclophosphamide	Canton of Zurich, Switzerland	Surface water	0.05–0.17	0.02–0.1	Buerge et al. 2006
50-18-0	Cyclophosphamide	Italy	WWTP effluent	ND	< 1	Castiglioni et al. 2006
50-18-0	Cyclophosphamide	Italy	WWTP effluent	ND–9.0	1.9	Castiglioni et al. 2005
50-18-0	Cyclophosphamide	Italy	Drinking water	ND	0.2	Zuccato et al. 2000
50-18-0	Cyclophosphamide	Italy	Surface water	2.2–10.1	0.2	Zuccato et al. 2000
50-18-0	Cyclophosphamide	Five rivers in the Madrid region, Spain	Surface water	ND	3	Valcarcel et al. 2011
50-18-0	Cyclophosphamide	Five rivers in the Madrid region, Spain	Drinking water	ND	3	Valcarcel et al. 2011
50-18-0	Cyclophosphamide	France	Bottled mineral water	ND	0.001	Dévier et al. 2013
50-18-0	Cyclophosphamide	France	Drinking water	ND	1.5	Mompelat et al. 2011
50-18-0	Cyclophospham	France	Surface	ND	1.5	Mompelat et

CAS RN	Common pharmaceutical name	Sampling location	Media measured	Range of values[a] (ng/L) (mean)	Detection limit[a] (ng/L)	Reference
	ide		water			al. 2011
50-18-0	Cyclophosphamide	France	WWTP effluent	300	30	Catastini et al. 2008
50-18-0	Cyclophosphamide	Perth, Australia	WWTP effluent	ND	5–100	Busetti et al. 2009
50-18-0	Cyclophosphamide	Perth, Australia	WWTP effluent	ND	50	Rodriguez et al. 2007
55-98-1	Busulfan	Six WWTPs across Canada	WWTP influent	ND	RL = 37.9 –274	Smyth and Teslic 2013
55-98-1	Busulfan	Six WWTPs across Canada	WWTP effluent	ND	RL = 37.9*–274	Smyth and Teslic 2013
56-75-7	Chloramphenicol	Six WWTPs across Canada	WWTP effluent	ND	RL = 1300– 110 000	Smyth and Teslic 2013
56-75-7	Chloramphenicol	Six WWTPs across Canada	WWTP influent	ND	RL = 1300– 110 000	Smyth and Teslic 2013
56-75-7	Chloramphenicol	Seventeen drinking water systems across Ontario, Canada	Raw water	ND	2	Kleywegt et al. 2011
56-75-7	Chloramphenicol	Seventeen drinking water systems across Ontario, Canada	Drinking water	ND	2*	Kleywegt et al. 2011
56-75-7	Chloramphenicol	France	Bottled mineral water	ND	0.005	Dévier et al. 2013
56-75-7	Chloramphenicol	Northern Italy	WWTP influent	13–24 (19)	9	Verlicchi et al. 2012

CAS RN	Common pharmaceutical name	Sampling location	Media measured	Range of values[a] (ng/L) (mean)	Detection limit[a] (ng/L)	Reference
56-75-7	Chloramphenicol	Northern Italy	WWTP effluent	ND	7	Verlicchi et al. 2012
56-75-7	Chloramphenicol	Catalonia and Ebro River Basin, Spain	WWTP effluent	ND	NA	Gros et al. 2009
56-75-7	Chloramphenicol	Catalonia and Ebro River Basin, Spain	Surface water	ND–0.4 (0.2)	NA	Gros et al. 2009
56-75-7	Chloramphenicol	Wales, United Kingdom; Poland	Surface water	< MQL	2.5; MQL = 10	Kasprzyk-Hordern et al. 2007
56-75-7	Chloramphenicol	North Han River, Korea	Surface water	ND	NA	Choi et al. 2008
56-75-7	Chloramphenicol	South Han River, Korea	Surface water, low flow	(27.1)	NA	Choi et al. 2008
56-75-7	Chloramphenicol	South Han River, Korea	Surface water, high flow	ND	NA	Choi et al. 2008
56-75-7	Chloramphenicol	Kyung-Ahn stream, Korea	WWTP effluent, low flow	75[b] (51)	NA	Choi et al. 2008
56-75-7	Chloramphenicol	Kyung-Ahn stream, Korea	WWTP effluent, high flow	ND	NA	Choi et al. 2008
56-75-7	Chloramphenicol	Kyung-Ahn stream, Korea	Surface water, high flow	ND	NA	Choi et al. 2008
56-75-7	Chloramphenicol	Kyung-Ahn stream, Korea	Surface water, low flow	30	NA	Choi et al. 2008
56-75-7	Chloramphenico	Mainstrea	WWTP	ND	NA	Choi et al.

CAS RN	Common pharmaceutical name	Sampling location	Media measured	Range of values[a] (ng/L) (mean)	Detection limit[a] (ng/L)	Reference
	l	m Han River, Korea	effluent, high flow			2008
56-75-7	Chloramphenicol	Mainstream Han River, Korea	WWTP effluent, low flow	44[b] (36.9)	NA	Choi et al. 2008
56-75-7	Chloramphenicol	Mainstream Han River, Korea	Surface water, high flow	53.8	NA	Choi et al. 2008
56-75-7	Chloramphenicol	Mainstream Han River, Korea	Surface water, low flow	42.9[b] (31.3)	NA	Choi et al. 2008
56-75-7	Chloramphenicol	Beijing, China	WWTP effluent	16.9	1	Sui et al. 2009
56-75-7	Chloramphenicol	Guanghou, China	Primary effluent	ND	MQL = 80	Peng et al. 2008
56-75-7	Chloramphenicol	Guanghou, China	Final effluent	ND	MQL = 80	Peng et al. 2008
56-75-7	Chloramphenicol	Guanghou, China	Primary effluent	146–173	10	Peng et al. 2006
56-75-7	Chloramphenicol	Guanghou, China	Final effluent	ND	20	Peng et al. 2006
56-75-7	Chloramphenicol	Pearl River Delta, China	Surface water, high flow	11–266	5	Xu et al. 2007a
56-75-7	Chloramphenicol	Pearl River Delta, China	Surface water, low flow	54–187	5	Xu et al. 2007a
56-75-7	Chloramphenicol	Pearl River Delta, China	WWTP effluent	ND–17	5	Xu et al. 2007b
57-41-0	Phenytoin	Various WWTPs in southern Ontario	Final effluent	42–299	20	Lee and Peart 2007
57-41-0	Phenytoin	Various	Primary	35–313	20	Lee and

CAS RN	Common pharmaceutical name	Sampling location	Media measured	Range of values[a] (ng/L) (mean)	Detection limit[a] (ng/L)	Reference
		WWTPs in southern Ontario	effluent			Peart 2007
57-41-0	Phenytoin	Back River WWTP, Baltimore, MD, USA	WWTP influent	410	5	Yu et al. 2012
57-41-0	Phenytoin	Back River WWTP, Baltimore, MD, USA	WWTP effluent	120	5	Yu et al. 2012
57-41-0	Phenytoin	Nineteen water utilities, USA	Source water	ND	0.5	Benotti et al. 2009
57-41-0	Phenytoin	Nineteen water utilities, USA	Drinking water	ND	0.5	Benotti et al. 2009
57-41-0	Phenytoin	Las Vegas, NV, USA	WWTP effluent	200	10	Wert et al. 2009
57-41-0	Phenytoin	Rocky Mountains, CO, USA	WWTP effluent	430	10	Wert et al. 2009
57-41-0	Phenytoin	Pinellas County, FL, USA	WWTP effluent	310	10	Wert et al. 2009
57-41-0	Phenytoin	Colorado River, USA	Source water	89	1	Snyder et al. 2006
57-41-0	Phenytoin	Colorado River, USA	WWTP effluent	176	1	Snyder et al. 2006
57-41-0	Phenytoin	Various water systems, NV, USA	Effluent	106	0.332	Trenholm et al. 2006
57-41-0	Phenytoin	Various water systems, NV, USA	Effluent	ND–16	0.332	Trenholm et al. 2006

CAS RN	Common pharmaceutical name	Sampling location	Media measured	Range of values[a] (ng/L) (mean)	Detection limit[a] (ng/L)	Reference
57-41-0	Phenytoin	Las Vegas, NV, USA	WWTP effluent	287	1	Vanderford and Snyder 2006
57-41-0	Phenytoin	Las Vegas, NV, USA	Las Vegas wash	170	1	Vanderford and Snyder 2006
57-41-0	Phenytoin	Las Vegas, NV, USA	Drinking water	1.3–6.2*	1	Vanderford and Snyder 2006
57-41-0	Phenytoin	Baltimore, MD, USA	WWTP effluent	250	NA	Yu et al. 2006
57-41-0	Phenytoin	Llobrega River, northeastern Spain	Finished water	10[b] (9)	LOQ = 0.02	Huerta-Fontela et al. 2011
57-41-0	Phenytoin	Llobrega River, northeastern Spain	Raw water	140[b] (56)	LOQ = 0.02	Huerta-Fontela et al. 2011
57-41-0	Phenytoin	Six WWTPs, northern Spain	Effluent	ND–170	0.2	Huerta-Fontela et al. 2010
57-41-0	Phenytoin	Perth, Australia	WWTP effluent	71	55	Busetti et al. 2009
57-41-0	Phenytoin	Perth, Australia	Secondary WWTP effluent	ND	5	Busetti et al. 2009
57-41-0	Phenytoin	Perth, Australia	WWTP effluent	ND	20	Rodriguez et al. 2007
57-41-0	Phenytoin	Han River, Seoul, South Korea	River	1.8–17 (9.5)	NA	Yoon et al. 2010
57-41-0	Phenytoin	Han River, Seoul, South Korea	Creek (effluent dominated)	21–54 (37)	NA	Yoon et al. 2010
68-22-4	Norethindrone	Six WWTPs across Canada	WWTP effluent	ND	RL = 113–8660	Smyth and Teslic 2013

CAS RN	Common pharmaceutical name	Sampling location	Media measured	Range of values[a] (ng/L) (mean)	Detection limit[a] (ng/L)	Reference
68-22-4	Norethindrone	Six WWTPs across Canada	WWTP influent	ND	RL = 113–8660	Smyth and Teslic 2013
68-22-4	Norethindrone	Five WWTPs, western Canada	WWTP effluent	ND–159	32–45 (38)	Fernandez et al. 2007
68-22-4	Norethindrone	Various locations in Alberta, Canada	WWTP effluent	ND	0.07–0.3	Sosiak and Hebben 2005
68-22-4	Norethindrone	Various locations in Alberta, Canada	Surface water	ND–0.77*	0.07–0.3	Sosiak and Hebben 2005
68-22-4	Norethindrone	Catalonia, Spain	WWTP effluent	ND	Not specified	Fernandez et al. 2009
68-22-4	Norethindrone	Llobregat River tributaries, Spain	Surface water	ND	NA	Solé et al. 2000
68-22-4	Norethindrone	Bern, Switzerland	WWTP effluent	ND	5	Baig et al. 2008
68-22-4	Norethindrone	France	Bottled mineral water	ND	0.05	Dévier et al. 2013
68-22-4	Norethindrone	Eight DWTPs in France	Raw water	ND–5.6	LOQ = 0.02	Vulliet et al. 2011
68-22-4	Norethindrone	Eight DWTPs in France	Drinking water	ND–6.8	LOQ = 0.02	Vulliet et al. 2011
68-22-4	Norethindrone	Rhône-Alpes, France	Surface water	2.7–2.8	0.01	Vulliet et al 2008
68-22-4	Norethindrone	Rhône-Alpes, France	Groundwater	4.2–5.6	0.01	Vulliet et al 2008
68-22-4	Norethindrone	Seine River	WWTP effluent	< 6.5	1–8	Labadie and Budzinski

CAS RN	Common pharmaceutical name	Sampling location	Media measured	Range of values[a] (ng/L) (mean)	Detection limit[a] (ng/L)	Reference
		estuary, France				2005a
68-22-4	Norethindrone	Seine River estuary, France	Surface water	ND	1–8	Labadie and Budzinski 2005a
68-22-4	Norethindrone	Bordeaux and Jalle d'Eysines River, France	WWTP effluent	< 1.0 – < 5.0	0.4–3.0	Labadie and Budzinski 2005b
68-22-4	Norethindrone	Prague, Czech Republic	Surface water	ND	NA	Morteani et al. 2006
68-22-4	Norethindrone	Prague, Czech Republic	WWTP effluent	ND	NA	Morteani et al. 2006
68-22-4	Norethindrone	Prague, Czech Republic	Drinking water	ND	NA	Morteani et al. 2006
68-22-4	Norethindrone	Beijing, Tonghui River and Quing River, China	WWTP effluent	ND	1.2, 0.4, 0.3	Chang et al. 2011
68-22-4	Norethindrone	Beijing, Tonghui River and Quing River, China	Surface water	ND	1.2, 0.4, 0.3	Chang et al. 2011
68-22-4	Norethindrone	Beijing, China	Tap water	ND	0.5–3.4	Sun et al. 2009
68-22-4	Norethindrone	Beijing, China	WWTP effluent	ND	0.5–3.4	Sun et al. 2009
68-22-4	Norethindrone	Beijing, China	Surface water	ND	0.5–3.4	Sun et al. 2009
68-22-4	Norethindrone	Saitama, Japan	WWTP effluent	ND	0.6, 0.3	Chang et al. 2008
68-22-4	Norethindrone	Saitama, Japan	Surface water	ND	0.6, 0.3	Chang et al. 2008

CAS RN	Common pharmaceutical name	Sampling location	Media measured	Range of values[a] (ng/L) (mean)	Detection limit[a] (ng/L)	Reference
71-58-9	Medroxyprogesterone	Six WWTPs across Canada	WWTP effluent	ND	RL = 6.95*–352	Smyth and Teslic 2013
71-58-9	Medroxyprogesterone	Six WWTPs across Canada	WWTP influent	ND	RL = 6.95 –352	Smyth and Teslic 2013
71-58-9	Medroxyprogesterone	Beijing, China	WWTP effluent	ND–1.1	0.03	Chang et al. 2011
71-58-9	Medroxyprogesterone	Beijing, China	Surface water	0.04–34	0.008–0.5	Chang et al. 2009
71-58-9	Medroxyprogesterone	Saitama, Japan (two WWTPs)	WWTP effluent	(0.03), (0.42)	0.16, 0.04	Chang et al. 2008
71-58-9	Medroxyprogesterone	Saitama, Japan (two WWTPs)	Surface water	ND	0.01	Chang et al. 2008
81-81-2	Warfarin	Seventeen drinking water systems across Ontario, Canada	Drinking water	ND	5*	Kleywegt et al. 2011
81-81-2	Warfarin	Ontario, Canada	Surface water	ND–3.87	0.5	Chan et al. 2014
81-81-2	Warfarin	British Columbia, Canada	Surface water	ND–6.9	0.5	Chan et al. 2011
81-81-2	Warfarin	Montana, USA	Groundwater	ND	NA	Godfrey et al. 2007
81-81-2	Warfarin	France	Surface water	ND–1.8	1.5	Mompelat et al. 2011
81-81-2	Warfarin	France	Drinking water	ND	1.5	Mompelat et al. 2011
81-81-2	Warfarin	Llobrega River, northeastern Spain	Raw water	3[b] (1)	LOQ = 0.1	Huerta-Fontela et al. 2011

CAS RN	Common pharmaceutical name	Sampling location	Media measured	Range of values[a] (ng/L) (mean)	Detection limit[a] (ng/L)	Reference
81-81-2	Warfarin	Llobrega River, northeastern Spain	Finished water	ND	LOQ = 0.1	Huerta-Fontela et al. 2011
81-81-2	Warfarin	Six WWTPs, northern Spain	WWTP effluent	ND	0.02	Huerta-Fontela et al. 2010
81-81-2	Warfarin	Perth, Australia	WWTP effluent	ND	15, 5	Busetti et al. 2009
148-82-3	Melphalan	Six WWTPs across Canada	WWTP effluent	ND	RL = 120*–3570	Smyth and Teslic 2013
148-82-3	Melphalan	Six WWTPs across Canada	WWTP influent	ND	RL = 120 –3570	Smyth and Teslic 2013
154-93-8	Carmustine	Six WWTPs across Canada	WWTP effluent	ND	RL = 126*–1150	Smyth and Teslic 2013
154-93-8	Carmustine	Six WWTPs across Canada	WWTP influent	ND	RL = 126 –1150	Smyth and Teslic 2013
443-48-1	Metronidazole	Six WWTPs across Canada	WWTP influent	ND–560	RL = 6.32–76	Smyth and Teslic 2013
443-48-1	Metronidazole	Six WWTPs across Canada	WWTP effluent	ND–360	RL = 6.32–76	Smyth and Teslic 2013
443-48-1	Metronidazole	France	Bottled mineral water	ND	0.0004	Dévier et al. 2013
443-48-1	Metronidazole	Eight DWTPs in France	Raw water	ND–0.1	5	Vulliet et al. 2011
443-48-1	Metronidazole	Eight DWTPs in	Drinking water	ND	5*	Vulliet et al. 2011

CAS RN	Common pharmaceutical name	Sampling location	Media measured	Range of values[a] (ng/L) (mean)	Detection limit[a] (ng/L)	Reference
		France				
443-48-1	Metronidazole	Northern Italy	WWTP influent	28–56 (42)	4, 1	Verlicchi et al. 2012
443-48-1	Metronidazole	Northern Italy	WWTP effluent	13–41 (28)	4, 1	Verlicchi et al. 2012
443-48-1	Metronidazole	Tagus River, central Spain	Surface water	ND–19	LOQ = 3	Valcarcel et al. 2013
443-48-1	Metronidazole	Spain	Mineral bottled water	ND	3	Gonzalez Alonso et al. 2012
443-48-1	Metronidazole	Madrid, Spain	WWTP effluent	ND–127 (55)	3	Rosal et al. 2010
443-48-1	Metronidazole	Catalonia and Ebro River Basin, Spain	WWTP effluent	ND–295 (164)	0.7	Gros et al. 2009
443-48-1	Metronidazole	Catalonia and Ebro River Basin, Spain	Surface water	6–45 (21)	0.3	Gros et al. 2009
443-48-1	Metronidazole	Wales, United Kingdom; Poland	Surface water	< MQL	0.5; MQL = 1.5	Kasprzyk-Hordern et al. 2007
443-48-1	Metronidazole	Umeå, Stockholm, Floda Gothenburg, Kalmar, Sweden	WWTP effluent	ND	33	Lindberg et al. 2005
443-48-1	Metronidazole	Sweden	WWTP effluent	15–80	NA	Wennmalm and Gunnarsson 2005
443-48-1	Metronidazole	Sweden	Surface water	ND–43	NA	Wennmalm and Gunnarsson 2005

CAS RN	Common pharmaceutical name	Sampling location	Media measured	Range of values[a] (ng/L) (mean)	Detection limit[a] (ng/L)	Reference
446-86-6	Azathioprine	Six WWTPs across Canada	WWTP effluent	ND	RL = 12.6*–100	Smyth and Teslic 2013
446-86-6	Azathioprine	Six WWTPs across Canada	WWTP influent	ND	RL = 12.6 –100	Smyth and Teslic 2013
604-75-1	Oxazepam	Six WWTPs across Canada	WWTP influent	180–1090	RL = 25.3–289	Smyth and Teslic 2013
604-75-1	Oxazepam	Six WWTPs across Canada	WWTP effluent	49–465	RL = 25.3–289	Smyth and Teslic 2013
604-75-1	Oxazepam	Five WWTPs in the Netherlands	WWTP effluent	237–994	NA	Bijlsma et al. 2012
604-75-1	Oxazepam	Five WWTPs in the Netherlands	WWTP influent	177–915	NA	Bijlsma et al. 2012
604-75-1	Oxazepam	France	Surface water	ND–68.7	0.3	Mompelat et al. 2011
604-75-1	Oxazepam	France	Drinking water	ND–12.2*	0.3	Mompelat et al. 2011
604-75-1	Oxazepam	Eight DWTPs in France	Raw water	ND–57	LOQ = 10	Vulliet et al. 2011
604-75-1	Oxazepam	Eight DWTPs in France	Drinking water	ND–2.5	LOQ = 10	Vulliet et al. 2011
604-75-1	Oxazepam	Llobrega River, northeastern Spain	Raw water	46[b] (20)	LOQ = 0.01	Huerta-Fontela et al. 2011
604-75-1	Oxazepam	Llobrega River,	Drinking water	ND	LOQ = 0.01	Huerta-Fontela et

CAS RN	Common pharmaceutical name	Sampling location	Media measured	Range of values[a] (ng/L) (mean)	Detection limit[a] (ng/L)	Reference
		northeastern Spain				al. 2011
604-75-1	Oxazepam	Madrid, Spain	WWTP effluent	< MQL–129	10	Gonzalez Alonso et al. 2010
604-75-1	Oxazepam	Madrid, Spain	Surface water	< MQL	10	Gonzalez Alonso et al. 2010
604-75-1	Oxazepam	Stockholm, Sweden	WWTP effluent	47–540	NA	Lundström et al. 2010
604-75-1	Oxazepam	Slovenia	Surface water	ND–31	3	Kosjek et al. 2012
604-75-1	Oxazepam	Berlin, Germany	WWTP effluent	(250)	NA	Herberer 2002
13010-47-4	Lomustine	Six WWTPs across Canada	WWTP effluent	ND–108*	RL = 75.9–1700	Smyth and Teslic 2013
13010-47-4	Lomustine	Six WWTPs across Canada	WWTP influent	ND	RL = 75.9–1700	Smyth and Teslic 2013
20830-81-3	Daunorubicin	Six WWTPs across Canada	WWTP effluent	ND	RL = 25.3*–541	Smyth and Teslic 2013
20830-81-3	Daunorubicin	Six WWTPs across Canada	WWTP influent	ND	RL = 25.3 –541	Smyth and Teslic 2013
20830-81-3	Daunorubicin	France	Bottled mineral water	ND	0.002	Dévier et al. 2013
29767-20-2	Teniposide	Six WWTPs across Canada	WWTP effluent	ND	RL = 12.6*–160	Smyth and Teslic 2013
29767-20-2	Teniposide	Six WWTPs across Canada	WWTP influent	ND	RL = 12.6 –160	Smyth and Teslic 2013
30516-	Zidovudine	Six WWTP	WWTP	ND	RL =	Smyth and

CAS RN	Common pharmaceutical name	Sampling location	Media measured	Range of values[a] (ng/L) (mean)	Detection limit[a] (ng/L)	Reference
87-1		across Canada	effluent		75.9*–1450	Teslic 2013
30516-87-1	Zidovudine	Six WWTP across Canada	WWTP influent	ND–378	RL = 75.9–1450	Smyth and Teslic 2013
30516-87-1	Zidovudine	France	Bottled mineral water	ND	0.002	Dévier et al. 2013
30516-87-1	Zidovudine	Germany	WWTP 1	(98.2)	5	Prasse et al. 2010
30516-87-1	Zidovudine	Germany	WWTP 2	(564)	5	Prasse et al. 2010
30516-87-1	Zidovudine	Germany	Surface water	1.2–170	2.5	Prasse et al. 2010
51264-14-3	Amsacrine	Six WWTPs across Canada	WWTP effluent	ND	RL = 1.26*–15.8	Smyth and Teslic 2013
51264-14-3	Amsacrine	Six WWTPs across Canada	WWTP influent	ND	RL = 1.26–15.8	Smyth and Teslic 2013

Abbreviations: CAS RN, Chemical Abstracts Service Registry Number; DWTP, drinking water treatment plant; LOD, limit of detection; LOQ, limit of quantification; NA, not available; ND, not detected; MQL, method quantification limit;RL, reporting limit; WWTP, wastewater treatment plant

[a]Values marked with an asterisk (*) are values selected for comparison with lowest therapeutic dose (LTD). Selection of the most relevant data was based on location of the sampling and the relevance of the medium to human exposure. Canadian data were given preference over data from other countries, as they are considered to be most representative of potential exposures of Canadians. Drinking water was considered most relevant, followed, in order, by surface water/groundwater and WWTP effluent. Wastewater treatment influent was not considered relevant for the calculation of intake estimates. If multiple relevant concentrations were available, the maximum concentration was selected from the measured values identified.

[b] Maximum reported value (range not provided)

Appendix E: Intake Estimates, Lowest Therapeutic Doses and Calculated Margins of Exposure for 18 Pharmaceuticals with Measured Concentrations

Table E.1: Intake estimates, lowest therapeutic doses and calculated margins of exposure for 18 pharmaceuticals with measured concentrations

CAS RN	Common pharmaceutical name	Maximum measured concentration (mg/L) in most relevant medium[a]	Upper-bounding intake estimate[b] (mg/kg bw per day)	LTD[c] (mg/kg bw per day)	MOE[d,e]
50-06-6	Phenobarbital	2.51×10^{-5} (Boleda et al. 2011)	2.68×10^{-6}	0.42 (PendoPharm 2013)	157 000
50-18-0	Cyclophosphamide	1×10^{-6} (Garcia-Ac et al. 2009b)	1.07×10^{-7}	1 (Baxter Corporation 2012)	9 370 000
55-98-1	Busulfan	3.79×10^{-5} (Smyth and Teslic 2013)	4.04×10^{-7}	0.06 (Triton Pharma Inc. 2010d)	148 000
56-75-7	Chloramphenicol	2×10^{-6} (Kleywegt et al. 2011)	2.13×10^{-7}	25 (Erfa Canada Inc. 2005b)	117 000 000
57-41-0	Phenytoin	6.2×10^{-6} (Vanderford and Snyder 2006)	6.61×10^{-7}	4 (Erfa Canada Inc. 2011)	6 048 000
68-22-4	Norethindrone	7.7×10^{-7} (Sosiak and Hebben 2005)	8.21×10^{-8}	0.005 (Janssen-Ortho Inc. 2012)	60 800
71-58-9	Medroxyprogesterone	6.95×10^{-6} (Smyth and Teslic 2013)	7.41×10^{-8}	0.035 (Pfizer Canada Inc. 2010)	472 000
81-81-2	Warfarin	5×10^{-6} (Kleywegt et al. 2011)	5.33×10^{-7}	0.028 (Novopharm Limited 2005; Bristol-Myers Squibb Canada 2011a; Mylan Pharmaceutica	52 500

CAS RN	Common pharmaceutical name	Maximum measured concentration (mg/L) in most relevant medium[a]	Upper-bounding intake estimate[b] (mg/kg bw per day)	LTD[c] (mg/kg bw per day)	MOE[d,e]
				ls ULC 2011)	
148-82-3	Melphalan	1.20×10^{-4} (Smyth and Teslic 2013)	1.28×10^{-6}	0.014 (Triton Pharma Inc. 2010a)	10 900
154-93-8	Carmustine	1.26×10^{-4} (Smyth and Teslic 2013)	1.34×10^{-6}	0.87 (Eisai Limited 2012)	647 000
443-48-1	Metronidazole	5×10^{-6} (Vulliet et al. 2011)	5.33×10^{-7}	7.05 (Sanofi-aventis Canada Inc. 2011)	13 200 000
446-86-6	Azathioprine	1.26×10^{-5} (Smyth and Teslic 2013)	1.35×10^{-7}	1 (Apotex Inc. 2009; Mylan Pharmaceuticals ULC 2009; Sanis Health Inc. 2010; Teva Canada Limited 2010; Triton Pharma Inc. 2010b)	7 440 000
604-75-1	Oxazepam	1.22×10^{-5} (Mompelat et al. 2011)	1.30×10^{-6}	0.07 (Valeant Canada Limited 2005; Laboratoire Riva Inc. 2006)	53 700
13010-47-4	Lomustine	1.08×10^{-4} (Smyth and Teslic 2013)	1.15×10^{-6}	3.34 (Bristol-Myers Squibb 2010)	2 890 000
20830-81-3	Daunorubicin	2.53×10^{-5} (Smyth and Teslic 2013)	2.69×10^{-7}	1 (Erfa Canada Inc. 2002)	3 700 000
29767-20-2	Teniposide	1.26×10^{-5} (Smyth and Teslic 2013)	1.34×10^{-7}	0.771 (Bristol-Myers Squibb Canada. 2011b)	5 730 000
30516-87-1	Zidovudine	7.59×10^{-5} (Smyth and Teslic 2013)	8.09×10^{-7}	8.46 (Apotex Inc. 2004; Novopharm Limited 2004;	10 400 000

CAS RN	Common pharmaceutical name	Maximum measured concentration (mg/L) in most relevant medium[a]	Upper-bounding intake estimate[b] (mg/kg bw per day)	LTD[c] (mg/kg bw per day)	MOE[d,e]
				ViiV Healthcare Shire Canada 2012)	
51264-14-3	Amsacrine	1.26×10^{-6} (Smyth and Teslic 2013)	1.34×10^{-8}	4.81 (Erfa Canada Inc. 2005a)	357 000 000

Abbreviations: CAS RN, Chemical Abstracts Service Registry Number; LTD, lowest therapeutic dose; MOE, margin of exposure

[a] Selection of the most relevant data was based on location of the sampling and the relevance of the medium to human exposure. Canadian data were given preference over data from other countries, as they are considered to be most representative of potential exposures of Canadians. Drinking water was considered most relevant, followed in order by surface water/groundwater and WWTP effluent. Wastewater treatment influent was not considered relevant for the calculation of intake estimates. If multiple relevant concentrations were available, the maximum concentration was selected from the measured values identified in Appendix C.

[b] Maximum intake estimates were calculated based on the measured concentrations for formula-fed infants aged 0–6 months, as this was the most sensitive age group. Calculations were based on an assumed body weight of 7.5 kg and ingestion of 0.8 L of water per day (Health Canada 1998). When effluent concentrations were used to calculate intake estimates, a default 10-fold dilution factor was applied to account for release of the effluent into a waterway prior to consumption.

[c] The LTD was selected after reviewing product monographs available on the Health Canada Drug Product Database, or elsewhere as necessary. The dose selected was the lowest dose recommended for treatment of regular patients. The dose was converted from milligrams per day or milligrams per square metre using a body weight of 70.9 kg (Health Canada 1998) and a body surface area of 1.82 m^2 for adults (Health Canada 1995), as required. Recommended doses for children were considered if available, but in all cases were higher on a milligram per kilogram body weight basis than the adult dose.

[d] MOE calculated as the LTD divided by the maximum intake estimate.

[e] Numbers may not calculate exactly as shown in the table due to rounding error.

Appendix F: Intake Estimates, Lowest Therapeutic Doses and Calculated Margins of Exposure for Two Substances Based on Modelled Concentrations in Surface Water

Table F.1: Intake estimates, lowest therapeutic doses and calculated margins of exposure for two substances based on modelled concentrations in surface water

CAS RN	Common pharmaceutical name	Maximum PEC estimated[a] (mg/L)	Upper-bounding intake estimate[b] (mg/kg bw per day)	LTD[c] (mg/kg bw per day)	MOE[d]
305-03-3	Chlorambucil	1.50×10^{-6}	1.6×10^{-7}	0.1 (Triton Pharma Inc. 2010c)	625 000
18883-66-4	Streptozocin	1.50×10^{-12}	1.6×10^{-13}	12.85 (Pfizer Canada Inc. 2009)	8.0×10^{13}

Abbreviations: CAS RN, Chemical Abstracts Service Registry Number; LTD, lowest therapeutic dose; MOE, margin of exposure

[a] PECs calculated using Environment Canada's Mega Flush Consumer Release Scenario Tool (Environment Canada 2008b).

[b] Maximum intake estimates were calculated based on the measured concentrations for formula-fed infants aged 0–6 months, as this was the most sensitive age group. Calculations were based on an assumed body weight of 7.5 kg and ingestion of 0.8 L of water per day (Health Canada 1998).

[c] The LTD was selected after reviewing product monographs available on the Health Canada Drug Product Database, or elsewhere as necessary. The dose selected was the lowest dose recommended for treatment of regular patients. The dose was converted from milligrams per day or milligrams per square metre using a body weight of 70.9 kg (Health Canada 1998) and a body surface area of 1.82 m^2 for adults (Health Canada 1995), as required. Recommended doses for children were considered if available, but were higher on a milligram per kilogram body weight basis than the adult dose.

[d] MOE calculated as the LTD divided by the maximum intake estimate.