# Pharmaceutical Water Screening Values Report

Methods and Results of Rapid Assessments for Pharmaceuticals

Minnesota Department *of* Health

Drinking Water Contaminants of Emerging Concern Program

**July 2018 Update**

*The lowest therapeutic doses for two active pharmaceutical Ingredients, Lomefloxacin and Pentoxifylline, were updated. The calculated water screening values were updated as a result of these changes. The changes have been made to the Pharmaceutical Water Screening Values Table available on MDH's Rapid Assessments for Pharmaceuticals webpage. The values have not been updated in this report.*

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Upon request, this material will be made available in an alternative format such as large print, Braille, or audio recording. Printed on recycled paper.

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# Contents

Executive Summary ..... 5
Abbreviations ..... 6
Background ..... 7
Methodology ..... 7
Overview ..... 7
Selection of Pharmaceuticals for Evaluation ..... 8
Selection of API Data for Assessment ..... 8
API Exclusion Criteria ..... 9
Lowest Therapeutic Dose Calculation ..... 10
Toxicity Data Collection to Determine Appropriate Uncertainty and Adjustment Factors ..... 10
Screening Reference Dose Calculation ..... 15
Water Screening Value Calculation ..... 16
Evaluation of the results ..... 16
Results ..... 17
APIs included in the Assessment ..... 17
LTD Calculations ..... 18
Screening Reference Dose Calculations ..... 18
Water Screening Value Calculations ..... 19
Initial and Secondary Review Process ..... 19
Discussion ..... 20
FDA Labels and Data Sources ..... 20
UF and AF Selection and Application ..... 21
Conservativeness of Water Screening Values ..... 22
Reassessment of Screening Values ..... 23
Potential Future Work ..... 23
Recommendations for Use of Screening Values ..... 23
Summary ..... 24
References ..... 26
Table 1. Mean Weights by Age used in LTD Calculations ..... 29
Table 2. Comparison of API Water Screening Values and MDH Health-Based Guidance Values ..... 30
Figure 1. Decision Tree for Applying Uncertainty and Adjustment Factors ..... 31
Appendix A. API Rapid Assessment Values Table ..... 32

# Executive Summary

The Minnesota Department of Health (MDH) developed a method for evaluating the health risks of pharmaceuticals found or likely to be found in drinking water. The project included two key steps:

1. Create rapid assessment methods that could be easily and quickly performed using a limited number of high quality information sources.
2. Use the methods, to assess active pharmaceutical ingredients (APIs) and to evaluate the results.

The rapid assessment methods were designed as a series of decisions to guide the collection of information and the assessment process. US Food and Drug Administration (FDA) approved labels were the primary source of information for the assessment. Additional information sources were used to fill data gaps when an FDA label was not sufficient.

MDH selected 119 active pharmaceutical ingredients (API)s for assessment from a list of the most commonly prescribed pharmaceuticals in the United States, as well as those commonly looked for (monitored) and found in the environment. MDH developed screening reference doses and water screening values for the APIs. For a limited number of APIs, MDH health-based guidance values developed from in-depth analyses of toxicity data and use of well-established risk assessment methods were available. MDH compared the health-based guidance values to the water screening values in order to validate the conservativeness of the screening level methods.

The main outcome was the development of water screening values. A water screening value is a concentration of an API in water that can be consumed daily with no anticipated health risk to humans. The water screening values developed are intended to be lower (have a greater margin of safety) than values that result from an in-depth assessment by MDH. The water screening values are tools that can be used to assist risk assessors, risk managers, and others in determining whether the level of an API in sources of drinking water warrants further evaluation, including monitoring. They are not designed or intended to be used to provide definitive estimates of risk. In addition, water screening values are useful in understanding whether laboratory detection levels are adequate for monitoring.

MDH recommends using the results of the screening level assessments to:

- Identify APIs that occur at environmental concentrations unlikely to pose a human health risk and identify those warranting a more thorough evaluation
- Guide future monitoring efforts
- Inform development or refinement of laboratory analytical techniques

# Abbreviations

ADI – Acceptable Daily Intake

AF – Adjustment Factor

API – Active Pharmaceutical Ingredient

BW – Body weight

DRI – Dietary Reference Intake

EPA – United States Environmental Protection Agency

FDA – United States Food and Drug Administration

HED – Human Equivalent Dose

HSDB – Hazardous Substances Data Bank

IARC – International Agency for Research on Cancer

LOAEL – Lowest Observed Adverse Effect Level

LTD – Lowest Therapeutic Dose

MOA – Mode of Action

MDH - Minnesota Department of Health

MRHD – Maximum Recommended Human Dose

NDA – New Drug Application submitted to the United States Food and Drug Administration

NOAEL – No Observed Adverse Effect Level

NTP – National Toxicology Program

OTC – Over-the-Counter

POD – Point of Departure

RfD – Reference Dose

RSC – Relative Source Contribution

SRD – Screening Reference Dose

UF – Uncertainty Factor

# Background

Pharmaceutical use has grown rapidly and continues to grow as the industry expands and the demand among consumers increases. In the past 25 years, the portion of the population that uses at least one prescription pharmaceutical has risen approximately 10 percent. Currently, nearly half of all Americans take at least one prescription medication (Centers for Disease Control and Prevention - National Center for Health Statistics, 2013).

Pharmaceuticals are detected in drinking water sources throughout the world. They have been detected in many water types including pre- and post-treated wastewater, surface water in rivers and lakes, groundwater, and in drinking water from the tap (Daughton, 2010; Fram, 2011; Kolpin, 2002; Lee, 2011). Concentrations found in Minnesota are usually low (below human therapeutic dose levels). However, pharmaceuticals are formulated for maximum potency directed toward specific biological targets and can have multiple adverse side effects at low doses. Thus, even low environmental levels may be a cause for concern for human populations.

MDH required a rapid assessment method that could be performed efficiently and with limited information sources to assess and prioritize a large number of pharmaceuticals, including commonly prescribed pharmaceuticals not currently included in water monitoring programs.

This report includes a description of the methods MDH developed and used to complete rapid assessments for pharmaceuticals, the results of the assessments, and how to interpret and use the results. The report also describes ways in which MDH's results can be used to help inform risk management decisions.

# Methodology

## Overview

A number of methodologies have been described in the literature for screening and prioritizing the hazard and risk of pharmaceuticals in the environment (Schwab, 2005; US Environmental Protection Agency, 2008a; WateReuse Research Foundation, 2010; Watts and Crane Associates, 2007). These approaches use various techniques for calculating toxicity values to determine which pharmaceuticals may warrant concern. MDH's rapid assessment implements many concepts of these alternate approaches as well as those of MDH's established risk assessment practices (Minnesota Department of Health, 2008). The values derived in this assessment are referred to as screening reference doses and water screening values. Screening values have many definitions in different areas of risk assessment and site clean-up work. For this evaluation, a water screening value is a concentration of an API in water that can be consumed

daily with no anticipated health risk to humans. This rapid assessment intentionally yields a value that is likely to be more conservative (a lower concentration) than a value developed through a more in-depth consideration of a larger set of toxicity data. These screening values can be used to aid in determining whether a measured level of an API in the environment is unlikely to pose a health concern or warrants additional investigation.

MDH developed a rapid assessment method for active pharmaceutical ingredients (APIs) that could be performed efficiently and with limited information sources. The goal of the project was to develop a rapid process for deriving screening reference doses and water screening values based on the lowest therapeutic dose (LTD) and other readily available information. The rapid assessment was designed to rely upon the most current, reliable, and easily obtained sources that contained the necessary screening information. Literature searches were not conducted for APIs unless issues with data, noted below, required additional effort.

# Selection of Pharmaceuticals for Evaluation

The focus of the assessment was on pharmaceuticals most likely to be found in drinking water sources in Minnesota. Unfortunately, data on the volume of pharmaceuticals prescribed, used, and consumed specifically in Minnesota were not available. Information from PharmacyTimes, which used 2011 and 2012 data provided by IMS Health, contained compiled lists of the top 200 prescribed pharmaceuticals by total number of prescriptions (PharmacyTimes, 2012, 2013). Although these lists were compiled for the United States as a whole, the information was assumed to be representative of the top pharmaceuticals prescribed and used in Minnesota. These top 200 pharmaceuticals became the initial starting point for MDH's assessment. The APIs for each pharmaceutical product were then identified. Duplicate APIs were removed to form a list of unique APIs for the assessment.

In addition to the list of the most commonly prescribed APIs, MDH evaluated APIs that were included on analyte monitoring lists used in Minnesota. The addition of these APIs to the initial list provided a more comprehensive group of pharmaceuticals that could be present in Minnesota's drinking water sources.

# Selection of API Data for Assessment

Each API assessment began by obtaining and examining the most current and appropriate US Food and Drug Administration (FDA) approved labels. These labels were located on DailyMed, a website that provides a searchable database of approved FDA labels (US National Library of Medicine, 2014). An API was often associated with multiple FDA approved labels. MDH selected the most recently updated original packager (when available) label for each API. If a label could not be found for an API in DailyMed, a quick search of the FDA Drugs Database informed whether or not the product was still active in the United States (US Food and Drug Administration, 2015b).

The entire FDA label was searched to find the necessary information to inform the uncertainty factor selection and the dosing calculations (discussed later in the methodology).

Not all FDA labels contained the information necessary to complete a sufficient evaluation, even if the label had been recently updated. To find the necessary information for the evaluation, additional sources were consulted for some APIs. These sources included the National Toxicology Program (NTP), the Hazardous Substances Data Bank (HSDB), the International Agency for Research on Cancer (IARC), and FDA New Drug Application (NDA) data.

# API Exclusion Criteria

While this method was designed to develop screening values for a large number of various APIs, there were some groups of pharmaceuticals for which it may not generate adequately protective values or be well designed to capture the necessary information.

APIs were excluded from assessment (no values were derived) if any of the following criteria were met:

- The primary route of administration of the API was not oral. The bioavailability of an API given orally differs from one given via another route of administration. APIs excluded from assessment included those administered vaginally, dermally, sublingually, via suppository, via injection (intraperitoneally, subcutaneously, or intravenously), and via inhalation.
- The API was a nutritional supplement. The acceptable daily intake (ADI) values and dietary reference intake (DRI) levels for nutrients found in food and pharmaceuticals are available and more appropriate than values developed using this process (Institute of Medicine - Food and Nutrition Board, 1998).
- The API was only supplied as an over-the-counter (OTC) medication. The labels for OTC APIs did not contain the necessary information to perform the rapid assessments.
- The API was an illicit substance. While some illicit substances (such as cocaine) may also be used for therapeutic reasons via prescription, the developed methodology was not appropriate for these APIs.
- The API was identified as a potential genotoxic carcinogen or a potential non-threshold carcinogen. The FDA label often, but not always, had information indicating results of genotoxicity and carcinogenicity testing. If data on the FDA label indicated a potential for a genotoxic mode of action (MOA), the API was excluded from the evaluation. If data present on the FDA label showed evidence of carcinogenicity, additional information sources (previously listed) were consulted to assess whether it was a threshold or non-threshold carcinogen.
- The API has been discontinued for use and sale in the United States for several years. Many discontinued products no longer have active FDA labels with the base level of information for the rapid assessment.

- The API was registered and approved for veterinary uses only. Labels for veterinary APIs are not required to provide the same information as labels for human APIs.

If an appropriate FDA label was found for an API, the Description section of the label was searched for possible exclusion criteria. However, exclusions on the basis of genotoxic or non-threshold carcinogenicity were determined as the uncertainty factor criteria were being assessed and assigned.

## Lowest Therapeutic Dose Calculation

MDH identified or calculated the LTD, the amount of an API that is necessary to produce a clinically effective outcome, from the most appropriate FDA label. The LTD served as the point of departure (POD) for deriving a screening reference dose.

The lowest dose that would be considered for the general population, not including special dosing for individuals with certain conditions requiring lower or limited dosing, was used for the LTD calculation. Doses that were part of a gradual increase towards the target dose over a period of a few days to acclimate the individual to the API were also not considered for use in the LTD calculations.

Doses were most often expressed as milligrams per day (mg/day) on the label. MDH converted the dose to milligrams per kilogram per day (mg/kg-d). The appropriate body weight in kilograms for the conversion was taken from the US Environmental Protection Agency (EPA) Exposure Factors Handbook, which incorporates data from the National Health and Nutrition Examination Survey (US Environmental Protection Agency, 2008b, 2011). The mean weights by age used in the calculations are provided in Table 1. If the label presented the dosing information in mg/kg-d no dosage calculations were necessary.

$$\text{Lowest Therapeutic Dose (LTD) (mg/kg-d)} = \frac{\text{Dose of API (mg/kg)}}{\text{Body Weight based on Age (kg)}}$$

## Toxicity Data Collection to Determine Appropriate Uncertainty and Adjustment Factors

MDH used uncertainty factors (UFs) and adjustment factors (AFs) to account for a range of considerations in calculating the screening reference doses. The factors account for:

(i) uncertainty associated with potential carcinogenic effects;
(ii) variation in the sensitivity among human individuals;
(iii) uncertainty associated with effects seen at therapeutic doses;
(iv) deficiencies in the available data;
(v) uncertainty in extrapolating effects of different lengths of API use and for the potential increase in side effects over time; and
(vi) uncertainty associated with potential endocrine activity.

Each UF or AF was assigned values of 1, 3, or 10 based on the available information and established MDH risk assessment practices. A UF or AF of 1 meant no uncertainty factor was needed. A value of 10 was assigned for the Intraspecies UF (applied to all APIs uniformly), values of 1 or 10 were assigned for the Cancer AF, values of 3 or 10 were assigned for the LOAEL to NOAEL UF, and values of 1, 3, or 10 were considered for the Database UF, Duration UF, and Endocrine Activity AF. Efforts were made to ensure that there was no overlap in the application of UFs and AFs assigned to each API. A detailed decision tree for applying the UFs and AFs is presented in Figure 1. The decision criteria used to guide the assignment of a particular UF or AF (values of 3 or 10 only) are outlined below.

For certain APIs, it was necessary to assign UFs and AFs on a pharmaceutical class basis. This occurred when there was a lack of information on the specific FDA label for a particular API, but effects were reported as associated with a class of drugs on labels of similar APIs.

## Cancer AF (AF1)

Many APIs that were assessed were potential carcinogens. MDH accounted for the risk of cancer by applying a cancer AF to API assessments as needed, based on the available information from the FDA label and other sources which have been previously mentioned in this report. The information was evaluated to determine the likelihood that an API was a threshold carcinogen, a carcinogen for which there is sufficient evidence that a level of exposure exists below which there is no cancer risk.

MDH compared the human equivalent dose (HED), the dose in humans that would induce the same effects that were seen in animal studies (calculated by the FDA and presented on the FDA labels and supporting information), to the maximum recommended human dose (MRHD) (presented in FDA approved studies) or the LTD. A cancer AF of 10 was applied if there was sufficient evidence that the HED was near or below the MRHD or LTD. No cancer AF (i.e., AF of 1) was applied when there was sufficient evidence of a threshold well above the MRHD or LTD, the cancer presented on the label was not relevant to humans (species specific), or if the cancer was localized at the site of administration and not relevant to oral administration.

## Intraspecies Variability (UF1)

The difference in how individuals respond to substances, including pharmaceuticals, can vary widely. MDH accounted for this variation by applying an intraspecies variability factor (UF1) of 10 to every API.

## LOAEL-NOAEL UF (UF2)

Although APIs are designed to exert a beneficial effect for those receiving prescription doses, they could have an undesirable effect in those populations that do not need them. Additionally, many APIs have some type of adverse effect (side effect) at the therapeutic dose. The available human clinical studies generally do not test or report effects at doses lower than the minimum therapeutic doses. The LTD is most comparable to a lowest observed adverse effect level

(LOAEL). Due to the lack of information of side effects that occur at lower doses than the LTD, MDH could not identify a no observed adverse effect level (NOAEL). MDH accounted for this uncertainty by applying a LOAEL-NOAEL UF to each API, depending on the severity of the effects outlined on the FDA label, and if necessary, supported by additional sources.

As a default, a UF of 3 was applied. However, based on the data, a UF of 10 was applied when at least one of the following conditions applied:

- The API was labeled Pregnancy Category D or X, or labeled as unsafe for pregnant women.

  The FDA has established categories (A, B, C, D, and X) to indicate potential risks during pregnancy. Category A indicates that there is adequate information in humans that demonstrates there is no risk to the fetus. Category B indicates that animal studies have failed to demonstrate risk to fetus and that there are no well controlled studies in pregnant women. Category C indicates that animal studies have shown adverse effects on the fetus and that there are no adequate studies in humans. However, the potential benefits of taking the API may warrant use in pregnant women despite the potential risk to the fetus. Category D indicates positive evidence of risk to the fetus based on adverse reactions observed in humans, however, the potential benefits may outweigh the risks. Category X indicates studies in animals or humans have demonstrated fetal abnormalities, there is evidence of risk to the fetus, and the risks outweigh the potential benefits (US Food and Drug Administration, 2014a). Categories D and X warrant the use of a more protective UF because these effects for sensitive populations may appear at the LTD.

- The API was labeled Pregnancy Category C and the LTD approximated the dose used in reproductive/development studies that was indicated on the FDA label.
- The API was intended for life threatening conditions.

  The side effects of these APIs can often be severe. In treating a life threatening illness, the potential benefits (i.e., saving a life) may outweigh the potential risk of severe side effects. However, for the general population, the severe side effects are not warranted or worth the risk.

- The API was not clinically tested in children or, if tested in children, had a different safety profile than adults, and the LTD applied only to adults.

  The screening level assessments are meant to be protective of sensitive populations and life stages. As children are often more sensitive to the biological effects of a pharmaceutical, an extra protective factor was warranted.

- The LTD has been linked to serious and/or life threatening adverse effects.

- The FDA label for the API contains a Black Box Warning.

  Certain serious warnings, particularly those that may lead to death or serious injury, are often required to be presented on the label in a black box with bold text marked "Warning". These warnings are usually based on clinical data, but can be based on animal toxicity data and reporting of adverse effects (US Food and Drug Administration, 2014a).

  Warnings for which MDH assigned a UF of 10 were serious, life threatening effects not related to the condition or illness that the API was treating. Examples of black box warnings that did warrant the UF of 10 included statements concerning specific organ system risks (increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke; increased risk of serous gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach; increased risk of tendon rupture in all ages). Examples of black box warnings that did not warrant this UF of 10 included statements concerning drug abuse or overdose, increased suicide from antidepressants, and those related to specific genetic polymorphisms (potential vulnerability due to genetic polymorphism was addressed via the intraspecies UF).

## Database UF (UF3)

A database UF was applied to APIs that had less extensive toxicity testing, presented on both the FDA label and in a search of additional sources (previously listed),or that might lack availability of certain types of studies relevant to sensitive populations.

A UF of 3 was applied to APIs that might have extensive toxicity testing but appeared to be missing an important study. For example, multigenerational reproductive/developmental studies or suitable equivalent studies evaluating effects in offspring through adulthood could not be located for many APIs, either on the label or in additional sources.

A UF of 10 was applied to APIs with no animal toxicity testing or studies that tested very limited endpoints. Some of these APIs may actually have adequate animal testing in FDA files but those files were relatively inaccessible. In this case, retrieving or requesting such data from FDA was not feasible for rapid assessment purposes. If information was not described on the labels or additional sources (previously listed), then a database UF 10 was generally applied.

## Duration UF (UF4)

A duration UF was applied to account for uncertainty based on length of API use, limited chronic testing, or the potential for increased severity of effects over time.

A duration AF of 3 was applied when at least one of the following conditions applied:

- The API was intended for chronic use with no expected increase in severity of adverse effects over time based on extensive time of human use, but had no or limited accessible chronic animal studies.
- The API was intended for chronic use and had sufficient chronic studies in animals, but had some evidence of increased or new risk of adverse effects in humans associated with longer durations of use, including increased risk of dependence on the API.
- The API was intended for chronic use and had sufficient chronic studies in animals, but was relatively new to market, and there was still uncertainty about possible duration-related effects due to a relatively short history of human use.

A duration AF of 10 was applied when at least one of the following conditions applied:

- The API was intended for short-term use only.
- The API was intended for subchronic use and had no or limited chronic studies in animals. This included APIs not intended to treat chronic or lifetime conditions.
- The API was intended for chronic and/or lifetime use with no or limited chronic studies in animals, and there was some evidence for an increased severity of adverse effects with a longer duration of use.

## Endocrine Activity AF (AF2)

MDH accounted for potential adverse effects relating to endocrine activity by applying an endocrine activity AF. The AF was applied for endocrine activity and effects that were either the intended effect or side effects of the API. Concerns that the established LOAEL-NOAEL UF was not adequate to be protective of the very low level potencies or account for potential non-monotonic thresholds of concern for potential endocrine active APIs warranted the use of this AF.

For these assessments, endocrine activity was defined using the EPA definition and included effects seen in the female reproductive system, the male reproductive system, the pituitary gland, the adrenal gland, changes in hormones (estrogen, testosterone, androgen), hormonal changes related to the nervous system, blood sugar changes, and metabolism effects (US Environmental Protection Agency, 2014b).

When an apparent endocrine effect was aggravated by, but not caused by the API (e.g., aggravation of diabetes symptoms in patients who were already diabetic), an endocrine AF was not applied unless an endocrine mode-of-action was apparent. Additionally, APIs that masked signs of endocrine disease by controlling symptoms (e.g., controlling for arrhythmias caused by hyperthyroidism) were not assigned an endocrine AF. Also, endocrine effects described on the label as rare adverse events that were not causally associated with treatment were not included.

An endocrine activity AF of 3 was applied when at least one of the following conditions applied:

- There were clear hormonal effects in animals but testing in humans was performed and no effects were observed.
- There were small but clinically insignificant changes in hormone levels seen in studies.
- Endocrine effects were frequent in post-market surveillance in humans, however, there were negative endocrine effects reported in animal studies (in which endocrine effects were evaluated), and no other precautions for endocrine effects were provided on the FDA label.
- There were infrequent endocrine effects in post market surveillance or clinical trials in humans and there were no animal studies to support the observed endocrine effects.

An endocrine activity AF of 10 was applied when one or more of the following conditions applied:

- The endocrine effects observed were the intended effect of the API.
- The endocrine effects were described in the "Warnings/Precautions" or "Pharmacodynamics" sections of the FDA label.
- The endocrine effects were described in the "Adverse Reactions" section of the FDA label as leading to discontinuation of treatment.
- There are hormonal lab tests that are required or recommended as part of treatment/monitoring for individuals taking the API.
- The endocrine effects are described as frequent adverse reactions in post-marketing surveillance or clinical trials and/or there are animal data indicating positive hormonal effects that are relevant to humans.

# Screening Reference Dose Calculation

The calculated LTDs, along with UF and AF assignments, were used to derive screening reference doses (SRD) for each API. Similar to calculations for a reference dose (RfD), a daily oral dose that is not likely to have appreciable risk or adverse effects, the SRD is calculated by dividing the LTD by the overall total UF (US Environmental Protection Agency, 2014a).

The overall total UF was calculated by multiplying all applicable UFs and AFs. Consistent with established MDH risk assessment methods, the total UFs are considered log or half log values, and the combination of two half log values is 10 (e.g. 3x3=10) (Minnesota Department of Health, 2008).

Application of both AFs (cancer and endocrine activity) was found to be overly conservative based on comparisons performed by MDH (described in detail in the results and discussion sections).

$$\text{Screening Reference Dose (SRD) (mg/kg-d)} = \frac{\text{LTD (mg/kg-d)}}{\text{UF1 * UF2 * UF3 * UF4 * (AF1 or AF2)}}$$

# Water Screening Value Calculation

A water screening value was derived using the previously calculated SRD, a relative source contribution (RSC) factor, a unit conversion factor, and a drinking water intake rate. MDH's standard non-cancer assessment algorithm for calculating short-term water guidance values was used as the template to ensure that the resulting water screening values were protective of the most highly exposed populations (Minnesota Department of Health, 2008).

The RSC is a factor that allocates a portion of the reference dose to exposure from ingestion of water and the rest to other exposure pathways and sources (Minnesota Department of Health, 2008). MDH uses the US EPA Exposure Decision Tree to select appropriate RSCs, which range from 0.2 to 0.8 (US Environmental Protection Agency, 2000). Water screening values were calculated using an RSC of 0.8 for the majority of the APIs included in this evaluation. This was based on the assumption that individuals who were not taking a prescription medication would receive most, if not all, of their exposure to the API from contaminated drinking water. For those individuals who take medication, the additional drinking water exposure will be negligible.

Some prescription APIs may also be present in multiple OTC products. Two of these APIs, acetaminophen and ibuprofen, are also widely used in pharmaceutical products specifically intended for infants and children. Given the common and significant potential non-water sources of exposure to acetaminophen and ibuprofen from multiple products available for infants and children and the concerns about frequency of unintended overdoses in infants and children, an RSC of 0.2 was applied to be protective for additional exposure from drinking water (Ryan, 2008; Schille, 2009).

$$\text{Water Screening Value (ug/L)} = \frac{\text{SRD (mg/kg-d)} * \text{RSC} * \text{Unit Conversion Factor (ug/mg)}}{\text{Infant Water Intake Rate (L/kg-d)}}$$

$$\text{Water Screening Value (ug/L)} = \frac{\text{SRD (mg/kg-d)} * 0.8^{a} * 1000 \text{ ug/mg}}{0.289 \text{ (L/kg-d)}}$$

[a] In this assessment, an RSC of 0.2 was used for ibuprofen and for acetaminophen, which was used as a comparison between water screening values and MDH health-based guidance values.

# Evaluation of the results

Following the collection of data to inform all UF and AF assignments and the calculation of the screening reference doses and water screening values, MDH evaluated the calculated values and the decisions selected that informed the value calculations. A secondary review of all

decisions relating to UF and AF selections was performed to check for thoroughness of the initial assessment as well as to determine if there needed to be any changes or further description added to the methodology. Following the secondary reviews, some of the criteria for UF and AF selection were refined to be more explicit and clear. The conservativeness of the water screening values was also evaluated by comparing the water screening values to MDH derived health-based guidance values.

# Results

A total of 119 unique APIs were included in this assessment. The full list of APIs that were evaluated, along with the corresponding UF and AF designations, screening reference doses, and water screening values is located in Appendix A of this report.

## APIs included in the Assessment

Of the 119 APIs assessed, 80 were from the original list of the most prescribed pharmaceuticals in the US, and 39 were taken from monitoring/analytical lists used in Minnesota.

The original list of 200 most prescribed pharmaceuticals contained a total of 121 APIs. There were fewer APIs than prescribed pharmaceuticals because the list contained multiple products that contained the same APIs. Of the 121 unique APIs, 41 were excluded for the following reasons:

- 15 had non-oral routes of administration
- 8 were nutritional supplements
- 11 were identified as potential genotoxic carcinogens
- 3 had insufficient information to assess whether they were threshold or non-threshold and were excluded
- 1 was excluded because it is currently being assessed for development of MDH health-based guidance.
- 3 were excluded from the final count of 119 as they were used to compare the water screening values to MDH health-based guidance values. While water screening values were still calculated, they are not included in the final count of 119 or presented in Appendix A. Instead they are presented in Table 2.

The additional 39 APIs were selected from analyte lists used in monitoring studies in Minnesota as well as reports of detections in the literature, to enhance the list of 80 APIs from the most prescribed list.

# LTD Calculations

Of the calculated LTDs, 106 were based on adult dosing presented on the label along with an adult body weight, and 13 were based on child and adolescent dosing and body weights. The breakdown of age ranges and corresponding weights used in LTD calculation are below:

- 106 were calculated using dosing recommendations for adults (<18 years of age) with a body weight of 80 kg
- 7 were calculated using dosing recommendations for 12-17 years of age (Mean weight for 17 years of age used – 68 kg)
- 1 was calculated using dosing recommendations for 6-14 years of age (Mean weight for 14 years of age used – 61.5 kg)
- 1 was calculated using dosing recommendations for 8-13 years of age (Mean weight for 13 years of age used – 56.9 kg)
- 1 was calculated using dosing recommendations for 6-12 years of age (Mean weight for 12 years of age used – 50.3 kg)
- 3 were calculated using body weight dosing information directly from the corresponding label for any <18 years of age, no separate calculations

The LTD calculations ranged from 0.0013 mg/kg-d to 25 mg/kg-d, spanning four orders of magnitude.

# Screening Reference Dose Calculations

The overall total UF applied to the 119 APIs ranged from 100 to 30,000. UFs and AFs were applied with the following frequencies:

- The Cancer AF (AF1) of 10 was applied to 9/119 (8 percent) of APIs.
- The Intraspecies UF (UF1) was applied to 119/119 (100 percent) of APIs.
- The LOAEL-NOAEL UF (UF2) of 10 was applied to 102/119 (86 percent) and the LOAEL-NOAEL UF (UF2) of 3 was applied to 17/119 (14 percent) of APIs.
- The Database UF (UF3) of 10 was applied to 2/119 (2 percent) and the Database UF (UF3) of 3 was applied to 101/119 (85 percent) of APIs.
- The Duration AF (AF2) of 10 was applied to 42/119 (35 percent) and the Duration AF (AF2) of 3 was applied to 50/119 (42 percent) of APIs.
- The Endocrine Activity AF (AF3) of 10 was applied to 41/119 (34 percent) and the Endocrine Activity AF (AF3) of 3 was applied to 4/119 (3 percent) of APIs.
- The overall Cancer or Endocrine Activity AF of 10 was applied to 46/119 (39 percent) and the overall Cancer or Endocrine Activity AF of 3 was applied to 4/119 (3 percent) according to the recommendations for calculating the overall UF for deriving the screening reference dose

Three classes of APIs were assessed together in regards to assigning the cancer and endocrine activity AFs. This occurred when there was a lack of information on the specific FDA label for a particular API, but effects were reported as associated with a class of drugs on labels of similar APIs. APIs in the statin drug class were assessed together in regards to assigning an endocrine activity AF, of which all were assigned an AF of 10. This included Atorvastatin, Lovastatin, Pravastatin, Rosuvastatin, and Simvastatin. APIs in the sulfonamide drug class were assessed together in regards to assigning an endocrine activity AF, of which all were assigned an AF of 10. This included Sulfadiazine, Sulfamethizole, and Sulfamethoxazole. APIs in the tetracycline drug class were assessed together in regards to assigning a cancer AF and an endocrine activity AF, of which all received AFs of 1 and 10, respectively. This included Demeclocycline, Doxycycline, Minocycline, Oxytetracycline, and Tetracycline.

The screening reference doses ranged from 0.00000016 mg/kg-d to 0.13 mg/kg-d, spanning six orders of magnitude.

## Water Screening Value Calculations

The water screening values ranged from 0.0004 ug/L to 400 ug/L, spanning six orders of magnitude. All calculations used the API specific screening reference doses, the same water intake rate of 0.289 L/kg-d, and an RSC of 0.8, except for ibuprofen which used an RSC of 0.2.

The water screening values for four APIs were compared with MDH derived health-based guidance values for the same four APIs. The four APIs compared were Acetaminophen, Carbamazepine, Sulfamethoxazole, and Venlafaxine. The water screening values and MDH health-based guidance values, along with the comparison of the level of conservativeness, are located in Table 2. The water screening values for these APIs were 4-250x more conservative than the MDH non-cancer guidance values. None of the four exceeded the health-based guidance values.

## Initial and Secondary Review Process

The assessment process was relatively rapid. Multiple assessments were completed per day. The initial assessment was enhanced by the secondary reviews of the assessments. Secondary assessments were performed to evaluate whether other individuals came to the same conclusions regarding LTD selection and UF/AF assessment using the developed criteria. Most secondary reviews came to the same conclusions. When secondary reviews resulted in differences the primary assessments were reviewed with extra scrutiny, methods refined, and consensus reached quickly.

# Discussion

## FDA Labels and Data Sources

Selection of an appropriate FDA label was key to completing a rapid assessment. For each API, it is vital to find the most current, active FDA label. Ideally, labels that were from the original packager and brand names and no more than two to three years old were used in this assessment. When original packager labels were not available, repackagers and generic labels were used. When the most recent label was more than two years old, the FDA Drugs Database was consulted to see if that product was indeed the most current label available (US Food and Drug Administration, 2015b).

It was important to be aware and stay up to date on new and changing FDA labeling requirements. Changes to labeling requirements could impact these assessments as information may be presented differently or be found in different sections of an FDA label. For example, the FDA published a final rule in 2014 that changed how pregnancy and lactation data are to be presented on the label (US Food and Drug Administration, 2014b). This new rule removes the use of pregnancy letter categories (A, B, C, D, and X) to classify risks of the API during pregnancy, and replaces it with three subsections labeled Pregnancy, Lactation, and Females and Males of Reproductive Potential. These changes will be gradually phased in for existing products and will immediately impact ones new to the market. These changes may affect the search for information necessary to inform UF and AF application in the future.

Changes to FDA labels occur frequently as new safety data are added, and it was important to be aware and stay up to date on APIs that were being evaluated as the label information could change. When there is updated safety information for an API, the FDA generally directs that all relevant active labels be updated to reflect these changes. However, not all labels in DailyMed for an API were always updated. Sometimes this was because the product containing the API was no longer manufactured or the packager had changed as the formulation was acquired by different companies as products become generic. DailyMed does not appear to have a process to archive these labels unless a new label is issued by the same manufacturer to replace an old one. When searching DailyMed for a label containing an API, it also became evident that labels returned via a search are not prioritized or listed by the date of label. While DailyMed was an excellent source of information, these issues with label updates did add more time to the rapid assessment process. When selecting a label that appeared to be older when no recent (0-3 years old) labels could be found, the FDA Medical Product Safety Information pages were consulted to see if there had been any safety updates for the product containing the API being assessed (US Food and Drug Administration, 2015a). Overall, locating the most recent label for an API provided the most up-to-date information for selected APIs, but sometimes multiple sources needed to be consulted.

MDH originally attempted to use only the FDA label as a source of information to perform these screening level assessments. However, not all labels contained the same level of information necessary to assess all UF and AF criteria decisions. While some labels contained very thorough descriptions of clinical studies and all toxicity tests evaluated for the API, many did not contain adequate information to assess all concerns, especially carcinogenicity or reproductive concerns. For this reason, as well as those issues presented previously with labels, additional sources were necessary to complete the assessments.

# UF and AF Selection and Application

While uncertainty factors for duration, database deficiencies, LOAEL-NOAEL extrapolation, and intraspecies differences are commonly used in established risk assessment practices, adjustment factors for cancer and endocrine activity potential are not. MDH chose to include adjustment factors for cancer potential and endocrine activity in the rapid assessment method to add extra protection to the derived screening water values.

While these adjustment factors are not typically used, there was precedence in other published reports looking at evaluating pharmaceuticals in water, for applying them in this process. A report on the Australian Guidelines for Water Recycling developed surrogate acceptable daily intakes for pharmaceuticals. This report applied a 10-fold safety factor to hormonally active steroids on the grounds that the potential effects on normal hormonal function and fertility is unwanted in those not being treated.(Australian Environmental Protection and Heritage Council; National Health and Medical Research Council; Natural Resource Management Ministerial Council, 2008). This is similar to the endocrine activity AF applied in this assessment. Another report, by the WateReuse Foundation, focused on identifying hormonally active compounds for health concerns from water. While no values were calculated, a methodology for evaluating these compounds was developed and incorporated an uncertainty factor of 10 to be applied to an API that was a non-genotoxic carcinogen or an endocrine disrupting compound(WateReuse Research Foundation, 2010). Both of these reports helped to inform the use of both a cancer and endocrine activity adjustment factor.

MDH felt that these additional adjustment factors were warranted and provided an extra level of protection that may not always be provided by other uncertainty factors. In regards to endocrine activity, APIs that disrupt the endocrine system or hormone function, whether intentionally or not, warranted an additional safety (adjustment) factor. The LOAEL-NOAEL UF may not be protective of endocrine effects due to the low level potencies and potential non-monotonic threshold dose responses for these APIs. Specifically, the AF of 10 that MDH applied to APIs that have the intended effect of endocrine activity was meant to protect non-target populations (those not needing the intended therapeutic effect) from effects that may not be desirable. Also, endocrine active APIs can have side effects related to the endocrine system in addition to the intended endocrine effect (e.g., contraceptives). In regards to the cancer AF,

there were also concerns that the LOAEL-NOAEL UF may not be sufficiently protective at a screening level for these effects.

## Conservativeness of Water Screening Values

The rapid assessment methodology was designed to develop screening reference doses and water screening values that were appropriately conservative (i.e. protective) for a screening level assessment. There are several reasons why the resulting values were likely to be more conservative than values generated using established MDH risk assessment methodology.

MDH used an adult body weight of 80 kg in LTD calculations. In most risk assessment methodologies, the average adult body weight used for intake calculations is 70 kg. However, according to the EPA, the average adult body weight has shifted and that 80 kg is more representative of the population (US Environmental Protection Agency, 2011). Dividing the dose recommendations (mg/day) by a higher body weight results in a lower LTD (mg/kg-d). This is true for all LTDs that are based on adult dosing. The lower LTD results in lower, and therefore more conservative, screening reference doses and water screening values.

Along with the use of an adult body weight for LTD calculations, the use of the intake rate of 0.289 L/kg-d, based on bottle-fed infants resulted in conservative values. Bottle-fed infants have the highest intake of water on a per body weight basis than any other life-stage, and thus, are more likely to be exposed to contaminants in drinking water at higher mg/kg-d doses than adults. This intake rate should be protective of other sensitive populations as well as infants. The same intake rate and reasoning was used in MDH's Pesticide Rapid Assessment Report, which produced rapid assessments for pesticides (Minnesota Department of Health, 2014). By using an increased water intake rate, the calculated water screening values are lower than if an adult intake rate or an intake rate used for chronic exposure durations.

Another conservative decision was how MDH applied UFs and used additional AFs. According to established MDH risk assessment methods, a maximum UF of 3,000 is applied in the development of health-based guidance values. Any chemical with a UF over this is deemed to have insufficient information to derive a value. However in this assessment, there was no maximum UF, as overall UF ranged from 100 to 30,000. MDH took this step in order to utilize as many APIs as possible, including those with relatively little data on the label, and in order to maintain a consistent level of conservatism. No data were available to MDH to determine if more appropriate choices could have been made to limit the combination of multiple UFs. Also, as described previously, MDH applied additional AFs for cancer and endocrine activity potential. These are not standard safety factors in risk assessment methodologies, but did contribute to an increased safety margin in calculating the water screening values.

MDH compared the water screening values to MDH derived health-based guidance values of four APIs (previously discussed in methods and results) to check whether these conservative measures resulted in lower values than those that would result from an in-depth risk

assessment. The comparisons showed that the resulting water screening values were lower than the health-based guidance.

## Reassessment of Screening Values

Currently, MDH has established expiration dates of five years for health-based guidance values derived using established MDH risk assessments. Upon expiration, a review is conducted to determine if there is new information that would alter the value upon reassessment. MDH recommends a five year reassessment timeline for the resulting API water screening values as well.

## Potential Future Work

OTCs, genotoxic and non-threshold carcinogens, and APIs with non-oral routes of administration were all excluded from this assessment. These groups of APIs were excluded because the rapid assessment method was not suitable. Alternative approaches would need to be developed to perform the assessments of these types of APIs.

OTCs were set aside because the data necessary to complete the rapid assessment is not readily available. FDA labels for OTC medications are not required to contain the same level of detail as prescription products. MDH would need to consult alternate sources for information than used for prescription APIs. Different decision criteria may also need to be developed based on these alternate sources.

Genotoxic and non-threshold carcinogens were also excluded. After investigation at the secondary review level, it was decided that even an additional cancer AF may not be protective for genotoxic carcinogens and non-threshold carcinogens due to potential low level potencies and genotoxic MOAs. Due to this uncertainty, these carcinogens were excluded from this assessment.

APIs with non-oral routes of administration were set aside because the rapid assessment methodology is not applicable. Conversions to the dosing information and effect levels seen in studies to account for the differences in bioavailability were not accounted for in this methodology. MDH would need to develop new methods to assess these APIs. While there is currently no plan to revisit these API groups, there is the potential that this work may be done in the future depending on staff availability.

## Recommendations for Use of Screening Values

The water screening values developed through the rapid assessment method can be compared to levels of APIs detected during monitoring studies. For example, if concentrations of APIs detected in water are below the water screening value, it can be assumed that no significant risk is likely to occur for humans drinking the water.

The results of the rapid assessments will be used by MDH, and are recommend to be used by others, for the following:

- To set priorities for the derivation of new health-based guidance values. In situations where water screening values are particularly low and/or water detection values exceed the water screening value, MDH may choose to develop risk assessment guidance for the API using additional data and more refined risk assessment techniques.
- To set priorities for new or improved laboratory analytical methods. In situations where water screening values for an API are particularly low and there are no detection data available for comparison, MDH may recommend that an analytical method be developed. The water screening values provide a target for improved detection limits for specific APIs if the values are lower than established limits of current analytical techniques.
- To select APIs for future monitoring efforts. In cases where water screening values are particularly low and an analytical method exists for the API, MDH may recommend that the API be included in future monitoring studies to assess its risk in selected water sources.
- To assist in evaluating water quality. Comparing the monitoring results of water sources to the water screening values can provide an indication of whether the measured environmental level is unlikely to pose a health concern or warrant additional investigation.

The water screening values are not designed or intended to be used to provide definitive estimates of risk. MDH recommends using the water screening values to make certain risk management decisions. For example, if monitoring data are lower than the water screening value for an API, MDH is confident that the water is safe for human consumption. When monitoring results exceed a water screening value, MDH recommends refining the assessment (examining exposure assumptions, finding additional toxicity data, considering the population exposed) before using the information for risk communication or risk management.

# Summary

MDH created a methodology that guides the assessment of a large number of APIs in a relatively rapid manner. Rapid assessments were performed for 119 APIs that are commonly prescribed and/or are commonly monitored for in the environment. FDA approved labels and limited additional sources were consulted to search for API specific data. The data was used to inform the selection of an LTD to calculate screening reference doses and the selection of UFs and AFs to calculate water screening values. MDH ensured the methods were applied consistently by having a second risk assessor review each assessment, and by analyzing the use of uncertainty and adjustment factors. MDH evaluated the conservativeness of the values by

comparing water screening values to MDH health-based guidance values available for specific APIs.

The resulting water screening values provide a risk context for APIs detected in drinking water sources. In addition, these results can be used to prioritize future monitoring efforts and analytical method development, set priorities for derivation of health-based guidance values, and evaluate the quality of environmental drinking water sources.

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# Table 1. Mean Weights by Age used in LTD Calculations

| Age (years) | Mean Weight (kg) |
|---|---|
| 6-7 | 22.5 |
| 7-8 | 27.4 |
| 8-9 | 31.3 |
| 9-10 | 36.2 |
| 10-11 | 39.5 |
| 11-12 | 44.6 |
| 12-13 | 50.3 |
| 13-14 | 56.9 |
| 14-15 | 61.5 |
| 15-16 | 65.9 |
| 16-17 | 68.0 |
| 17-18 | 66.6 |
| ≥18[1] | 80[1] |

[1]The mean weight (kg) for Adults 18+ years of age was taken from the EPA Exposure Factors Handbook 2011 Edition, comprising 1999-2006 data. This mean weight of 80 kg differs from the default 70 kg that is used for adult mean weight in most traditional risk assessments. This increased weight not only reflects the higher average weight of an adult in the United States today, but also adds another level of conservativeness to the calculations.

All data, except age 18 and older, was taken from the EPA Child Specific Exposure Handbook 2008, which uses NHANES IV 1999-2002 data.

If a specific body weight range is described in the FDA label (e.g. 12-17 years of age), the LTD calculations were performed on each age range separately (12-13, 13-14, etc.) to determine the LTD. However, in these instances, the age group with the highest mean weight would usually produce the LTD.

If doses were reported in the FDA label with regards to body weight (e.g. 4 mg/kg instead of as 4 mg once per day), the dosing from the label was used directly and no further calculations with mean body weights were performed.

For ages under 6 years, the dosing is usually reported as mg/kg. This dosing information was used directly, with no further calculations.

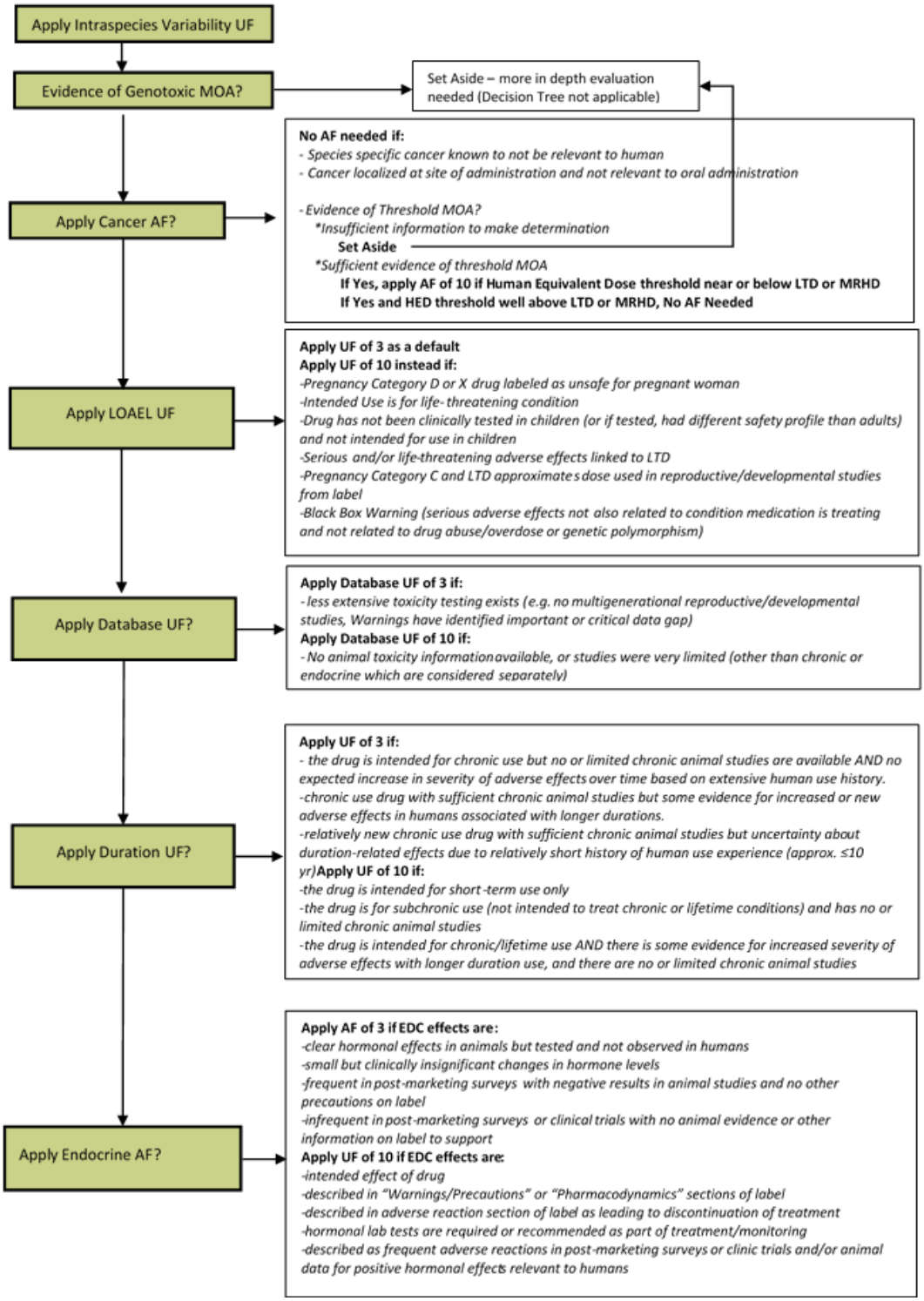
# Table 2. Comparison of API Water Screening Values and MDH Health-Based Guidance Values

| Active Pharmaceutical Ingredient (API) | Water Screening Value (ug/L) | MDH Health-Based Guidance Value (ug/L) | [1]Level of Conservativeness |
|---|---|---|---|
| Acetaminophen | 9-50[2] | 200 ($HBV_{11}$) | 4-22x |
| Carbamazapine | 0.9 | 40 ($HRL_{13}$) | 44x |
| Sulfamethoxazole | 0.4 | 100 ($RAA_{13}$) | 250x |
| Venlafaxine | 0.3 | 10 ($HBV_{15}$) | 33x |

[1] Level of conservativeness refers to how much lower the water screening value derived using the pharmaceutical rapid assessment process is than the MDH health-based guidance value derived using established MDH risk assessment methods.

[2] The water screening value range presented here represents the range in dosing that is recommended for acetaminophen use. The lower value is based on an individual taking one tablet per day while the higher value is based on an individual taking six tablets per day (one every four hours). Both of these dosing regimens are therapeutically relevant, but because acetaminophen is such a common API, both in OTC and prescription products, a range of LTDs was used in the calculation of the water screening values. It should also be noted that an RSC of 0.2 was used in the calculations. The lower value based on only one tablet per day may actually not be relevant to drinking water exposure because if a single tablet dose is compared to an equivalent amount in drinking water consumed over an entire day, the total daily dose and the amount consumed at any given time during the day would actually be far below a therapeutic level and likely be overly conservative.

# Figure 1. Decision Tree for Applying Uncertainty and Adjustment Factors



# Appendix A. API Rapid Assessment Values Table

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Albuterol | 18559-94-9 | 0.075 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF – | 1<br>10<br>3<br>1<br>3<br>1 | 100 | 0.00075 | 2 | Dava Pharmaceuticals, 01/2013 |
| Alendronate | 66376-36-1 | 0.063 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF – | 1<br>10<br>10<br>1<br>3<br>1 | 300 | 0.00021 | 0.6 | Apotex Corp., 10/2014 |
| Allopurinol | 315-30-0 | 2.50 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF – | 1<br>10<br>3<br>1<br>3<br>1 | 100 | 0.025 | 70 | Mylan, 02/2013 |
| Alprazolam | 28981-97-7 | 0.0094 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF – | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.0000094 | 0.03 | Sandoz, 11/2011 |
| Amitriptyline | 50-48-6 | 0.74[a] | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF – | 1<br>10<br>10<br>3<br>3<br>10 | 10000 | 0.000074 | 0.2 | Mylan, 12/2014 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Amlodipine | 88150-42-9 | 0.037[a] | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF – | 1<br>10<br>3<br>1<br>3<br>1 | 100 | 0.00037 | 1 | Macleods Pharmaceuticals, 02/2015 |
| Amoxicillin | 26787-78-0 | 12.5 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>1<br>1 | 1000 | 0.013 | 40 | Teva, 02/2015 |
| Amphetamines (4 base salt equivalents) | - | 0.039 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>1<br>10 | 3000 | 0.000013 | 0.04 | Barr (Adderall), 12/2013 |
| Ampicillin | 69-53-4 | 12.5 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.0042 | 10 | Sandoz, 01/2012 |
| Atenolol | 29122-68-7 | 0.63 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.00063 | 2 | Mylan, 01/2013 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Atorvastatin | 134523-00-5 | 0.13 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>1<br>10[f] | 3000 | 0.000043 | 0.1 | Parke-Davis, 05/2014 |
| Azithromycin | 83905-01-5 | 3.13 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.001 | 3 | Teva, 09/2014 |
| Benztropine | 86-13-5 | 0.013 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>3<br>10<br>10<br>1 | 3000 | 0.0000043 | 0.01 | Bayshore, 01/2014 |
| Betaxolol | 63659-18-7 | 0.13 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.00013 | 0.4 | Epic, 12/2014 |
| Bisoprolol | 66722-44-9 | 0.6 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.0006 | 2 | Unichem, 09/2011 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Carisoprodol | 78-44-4 | 9.38 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>1<br>1 | 1000 | 0.0094 | 30 | Qualitest, 10/2013 |
| Carvedilol | 72956-09-3 | 0.313 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>1 | 300 | 0.001 | 3 | Apotex, 05/2013 |
| Celecoxib | 169590-42-5 | 2.50 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.0025 | 7 | Actavis Pharma, 08/2014 |
| Cephalexin | 15686-71-2 | 12.5 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>3<br>10<br>3<br>1 | 1000 | 0.013 | 40 | Teva, 07/2012 |
| Cimetidine | 51481-61-9 | 10 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>3 | 1000 | 0.01 | 30 | Teva, 04/2015 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Ciprofloxacin | 85721-33-1 | 6.25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.0021 | 6 | Dr. Reddy's, 08/2011 |
| Clarithromycin | 81103-11-9 | 6.25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.0021 | 6 | AbbVie, 01/2015 |
| Clavulante | 58001-44-8 | 3.13 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>3<br>10<br>3<br>1 | 1000 | 0.0031 | 9 | Apotex, 11/2014 |
| Clindamycin | 18323-44-9 | 7.50 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.0025 | 7 | Ranbaxy, 06/2013 |
| Clonazepam | 1622-61-3 | 0.013 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.0000043 | 0.01 | Teva, 09/2013 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Clonidine | 4205-90-7 | 0.0025 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>1 | 300 | 0.0000083 | 0.0200000 | Boehringer Ingelheim, 06/2012 |
| Clopidogrel | 113665-84-2 | 0.94 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>1 | 300 | 0.0031 | 9 | Bristol-Myers Squibb/Sanofi, 12/2013 |
| Codeine | 76-57-3 | 0.19 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>3<br>10<br>3<br>1 | 1000 | 0.00019 | 0.5 | Qualitest, 10/2013 |
| Cyclobenzaprine | 303-53-7 | 0.19 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>3 | 10000 | 0.000019 | 0.05 | Mylan, 07/2013 |
| Demeclocycline | 127-33-3 | 7[e] | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1[g]<br>10<br>10<br>10<br>3<br>10[g] | 30000 | 0.00023 | 0.6 | Core Pharma, 10/2012 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Diazepam | 439-14-5 | 0.044[a] | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>1<br>1 | 300 | 0.00015 | 0.4 | Actavis, 10/2014 |
| Diclofenac | 15307-86-5 | 1.25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>1<br>1 | 300 | 0.0042 | 10 | Apotex, 03/2015 |
| Digoxin | 20830-75-5 | 0.0016 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 10<br>10<br>3<br>3<br>10<br>1 | 10000 | 0.00000016 | 0.0004 | Lannett, 02/2012 |
| Diltiazem | 42399-41-7 | 1.5 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.0015 | 4 | Valeant Pharma, 10/2014 |
| Doxepin | 1668-19-5 | 0.94 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>3<br>3<br>3<br>10 | 3000 | 0.00032 | 0.9 | Par, 01/2015 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Doxycycline | 564-25-0 | 0.91 [e] | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1[g]<br>10<br>10<br>10<br>3<br>10[g] | 30000 | 0.000030 | 0.08 | Galderma, 12/2014 |
| Drospirenone | 67392-87-4 | 0.038 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 10<br>10<br>10<br>3<br>3<br>10 | 10000 | 0.0000038 | 0.01 | Teva, 04/2012 |
| Duloxetine | 116539-59-4 | 0.50 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>1<br>10 | 1000 | 0.0005 | 1 | Eli Lily, 12/2014 |
| Enalapril | 75847-73-3 | 0.063 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>1 | 300 | 0.00021 | 0.6 | Mylan, 04/2014 |
| Erythromycin | 114-07-8 | 12.5 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>3<br>10<br>3<br>1 | 1000 | 0.013 | 40 | Midloathian, 07/2013 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Escitalopram | 128196-01-0 | 0.13 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>10 | 3000 | 0.000043 | 0.1 | Forest, 10/2014 |
| Ezetimibe | 163222-33-1 | 0.125 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>1 | 300 | 0.00042 | 1 | Merck, 03/2015 |
| Fenofibrate | 49562-28-9 | 0.60 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 10<br>10<br>10<br>1<br>3<br>1 | 3000 | 0.0002 | 0.6 | Apotex, 10/2013 |
| Fenoprofen | 31879-05-7 | 2.5 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.00083 | 2 | Mylan, 08/2012 |
| Fluconazole | 86386-73-4 | 1.25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>3 | 10000 | 0.00013 | 0.4 | Dr. Reddy's, 04/2014 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Fluoxetine | 54910-89-3 | 0.25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>10 | 3000 | 0.000083 | 0.2 | Edgemont, 09/2014 |
| Furosemide | 54-31-9 | 0.25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>3<br>3<br>3<br>1 | 300 | 0.00083 | 2 | Excellium Pharma, 08/2012 |
| Gabapentin | 60142-96-3 | 11.3 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>3<br>1<br>3<br>1 | 100 | 0.11 | 300 | Amneal, 08/2014 |
| Gemfibrozil | 25812-30-0 | 15 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 10<br>10<br>10<br>3<br>1<br>1 | 3000 | 0.005 | 10 | Blu Pharma, 09/2014 |
| Glipizide | 29094-61-9 | 0.19 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>10 | 10000 | 0.000019 | 0.05 | Mylan, 08/2013 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Glyburide | 10238-21-8 | 0.016 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>10 | 10000 | 0.0000016 | 0.004 | Teva, 01/2014 |
| Hydrochlorothiazide | 58-93-5 | 0.16 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>10 | 10000 | 0.000016 | 0.04 | Teva, 08/2013 |
| Hydrocodone | 125-29-1 | 0.25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>10 | 10000 | 0.000025 | 0.07 | Purdue, 11/2014 |
| Hydrocortisone | 50-23-7 | 0.25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>10 | 30000 | 0.0000083 | 0.02 | Pharmacia and Upjohn, 08/2014 |
| Ibuprofen | 15687-27-1 | 20 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.0067 | 5[i] | Bryant Ranch, 07/2014 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Imipramine | 50-49-7 | 0.37[a] | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>10 | 10000 | 0.000037 | 0.1 | Mallinckrodt, 05/2014 |
| Indomethacin | 53-86-1 | 0.63 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>1<br>1 | 300 | 0.0021 | 6 | Iroko Pharma, 02/2014 |
| Ketoprofen | 22071-15-4 | 0.94 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.00094 | 3 | Teva, 12/2013 |
| Lamotrigine | 84057-84-1 | 2.81 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>1 | 300 | 0.0094 | 30 | GlaxoSmithKline, 03/2015 |
| Levothyroxine | 51-48-9 | 0.0013 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>3[5]<br>1<br>1<br>10 | 300 | 0.0000043 | 0.01 | AbbVie, 10/2013 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Lisdexamfetamine (prodrug to amphetamine, assessed similarly) | 608137-32-2 | 0.38 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>1<br>10 | 3000 | 0.00013 | 0.4 | Shire, 04/2015 |
| Lisinopril | 76547-98-3 | 0.063 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>3 | 3000 | 0.000021 | 0.06 | Apotex, 02/2015 |
| Lomefloxacin | 98079-51-7 | 20 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.0067 | 20 | G.D. Searle, 05/2006[j] |
| Lorazepam | 846-49-1 | 0.025 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.0000083 | 0.02 | Valeant, 05/2013 |
| Losartan | 114798-26-4 | 0.63 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>1 | 300 | 0.0021 | 6 | Teva, 04/2015 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Lovastatin | 75330-75-5 | 0.13 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>10[f] | 10000 | 0.000013 | 0.04 | Lupin, 06/2014 |
| Mefenamic acid | 61-68-7 | 12.5 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.0042 | 10 | Breckenridge, 03/2014 |
| Meloxicam | 71125-38-7 | 0.094 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.000094 | 0.3 | Lupin, 01/2014 |
| Memantine | 19982-08-2 | 0.25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.00025 | 0.7 | Forest, 10/2013 |
| Meprobamate | 57-53-4 | 3.98[d] | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>3<br>10<br>3<br>1 | 1000 | 0.004 | 10 | Heritage, 08/2013 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Metformin | 657-24-9 | 14.71[a] | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>10 | 10000 | 0.0015 | 4 | Mylan, 04/2012 |
| Methylphenidate | 113-45-1 | 0.25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.00025 | 0.7 | Actavis, 12/2013 |
| Methylprednisolone | 83-43-2 | 0.05 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>10 | 30000 | 0.0000017 | 0.005 | Jubilant Cadista, 03/2011 |
| Metoprolol | 51384-51-1 | 0.31 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>1 | 300 | 0.001 | 3 | Watson, 02/2011 |
| Minocycline | 10118-90-8 | 2.5 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1[g]<br>10<br>10<br>10<br>3<br>10[g] | 30000 | 0.000083 | 0.2 | Par, 02/2014 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Montelukast | 158966-92-8 | 0.081[b] | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>3<br>1<br>3<br>1 | 100 | 0.00081 | 2 | Merck, 03/2015 |
| Naproxen | 22204-53-1 | 6.25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.0063 | 20 | Teva, 01/2014 |
| Nebivolol | 118457-14-0 | 0.031 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.000031 | 0.09 | Forest, 01/2014 |
| Nifedipine | 21829-25-4 | 0.38 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.00038 | 1 | Greenstone, 02/2015 |
| Norfloxacin | 70458-96-7 | 10 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.0033 | 10 | Merck, 01/2013 [k] |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Ofloxacin | 82419-36-1 | 5 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.0017 | 5 | Teva, 04/2014 |
| Olanzapine | 132539-06-1 | 0.037[a] | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 10<br>10<br>10<br>3<br>3<br>10 | 10000 | 0.0000037 | 0.01 | Eli Lilly, 12/2014 |
| Olmesartan medoxomil | 144689-63-4 | 0.25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>1 | 300 | 0.00083 | 2 | Daiichi Sankyo, 04/2015 |
| Oxycodone | 76-42-6 | 0.25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>10 | 30000 | 0.0000083 | 0.02 | Purdue, 04/2014 |
| Oxytetracycline | 79-57-2 | 6.25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1[g]<br>10<br>10<br>10<br>3<br>10[g] | 30000 | 0.00021 | 0.6 | No appropriate label. See note.[l] |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Penicillin V | 87-08-1 | 9.38 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.0031 | 9 | Teva, 12/2014 |
| Pentoxyifylline | 6493-05-6 | 5 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>1 | 300 | 0.017 | 50 | Apotex, 09/2014 |
| Pioglitazone | 111025-46-8 | 0.19 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 10<br>10<br>10<br>3<br>3<br>1 | 10000 | 0.000019 | 0.05 | Takeda, 11/2013 |
| Pravastatin | 81093-37-0 | 0.35[c] | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>10[f] | 10000 | 0.000035 | 0.1 | Teva, 01/2015 |
| Prednisolone | 50-24-8 | 0.06 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>10 | 30000 | 0.000002 | 0.006 | Watson, 03/2007 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Prednisone | 53-03-2 | 0.063 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>10 | 30000 | 0.0000021 | 0.006 | Watson, 05/2010 |
| Pregabalin | 148553-50-8 | 1.88 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>1<br>1 | 300 | 0.0063 | 20 | Parke-Davis/Pfizer, 08/2014 |
| Primidone | 125-33-7 | 9.38 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 10<br>10<br>10<br>3<br>1<br>1 | 3000 | 0.0031 | 9 | Amneal, 08/2012 |
| Progesterone | 57-83-0 | 2.5 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>10 | 30000 | 0.000083 | 0.2 | Akorn, 01/2013 |
| Promethazine | 60-87-7 | 0.23 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.000077 | 0.2 | Cardinal, 08/2013 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Propranolol | 525-66-6 | 0.38 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>1<br>10 | 3000 | 0.00013 | 0.4 | Heritage, 01/2014 |
| Propoxyphene | 469-62-5 | 4.88 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.0016 | 4 | Heritage, 10/2010 [m] |
| Quetiapine | 111974-69-7 | 0.63 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 10<br>10<br>10<br>3<br>3<br>10 | 10000 | 0.000063 | 0.2 | AstraZenica, 10/2013 |
| Ranitidine | 66357-35-5 | 2[e] | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>3<br>1<br>3<br>1 | 100 | 0.02 | 60 | Sandoz, 02/2014 |
| Risperidone | 106266-06-2 | 0.0074[a] | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 10<br>10<br>10<br>3<br>1<br>10 | 3000 | 0.0000025 | 0.007 | Apotex, 10/2014 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Rosuvastatin | 287714-41-4 | 0.063 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>10[f] | 10000 | 0.0000063 | 0.02 | AstraZeneca, 07/2014 |
| Sertraline | 79617-96-2 | 0.31 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>10 | 3000 | 0.0001 | 0.3 | Roerig, 06/2014 |
| Sildenafil | 139755-83-2 | 0.13 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.00013 | 0.4 | Pfizer, 03/2015 |
| Simvastatin | 79902-63-9 | 0.063 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>10[f] | 10000 | 0.0000063 | 0.02 | Lupin, 04/2014 |
| Sitagliptin | 486460-32-6 | 1.25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>10 | 10000 | 0.00013 | 0.4 | Merck, 03/2015 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Sulfadiazine | 68-35-9 | 25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>3<br>10<br>3<br>10[h] | 10000 | 0.0025 | 7 | Eon Labs, 06/2013 |
| Sulfamethizole | 144-82-1 | 12.5 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>10[h] | 30000 | 0.00042 | 1 | Roerig, 12/2005 |
| Tadalafil | 171596-29-5 | 0.031 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>1<br>1 | 300 | 0.0001 | 0.3 | Eli Lilly, 01/2015 |
| Tamsulosin | 106133-20-4 | 0.005 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>10 | 3000 | 0.0000017 | 0.005 | Zydus, 10/2014 |
| Temazepam | 846-50-4 | 0.09 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.00003 | 0.08 | Major Pharma, 03/2015 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Tetracycline | 60-54-8 | 18.8 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1[g]<br>10<br>10<br>10<br>3<br>10[g] | 30000 | 0.00063 | 2 | Aptalis, 04/2014 |
| Tramadol | 27203-92-5 | 2.50 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.0025 | 7 | Accord Healthcare, 09/2014 |
| Trazodone | 19794-93-5 | 1.88 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>10 | 10000 | 0.00019 | 0.5 | Apotex, 05/2013 |
| Triamterene | 396-01-0 | 0.47 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>1 | 300 | 0.0016 | 4 | Mylan, 01/2015 |
| Trimethoprim | 738-70-5 | 4.57 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.0015 | 4 | Teva, 03/2014 |

| Active Pharmaceutical Ingredient (API) | CASRN | LTD[1] (mg/kg-bw) | UFs/AFs Applied[2] | | Total UF | Screening Reference Dose (mg/kg) | Screening Water Value[3] (ug/L) | Manufacturer / FDA Label Date[4] (month/year) |
|---|---|---|---|---|---|---|---|---|
| *The screening values are not designed or intended to be used to provide definitive estimates of risk. They are only intended to assist in determining whether the level of contamination in sources of drinking water may warrant further evaluation. Programs or individuals who choose to use these values beyond their intended use take on responsibility for that use. | | | | | | | | |
| Valsartan | 137862-53-4 | 1 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>1<br>3<br>1 | 300 | 0.0033 | 9 | Novartis, 09/2014 |
| Verapamil | 52-53-9 | 2.25 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.0023 | 6 | Apotex, 01/2014 |
| Warfarin | 81-81-2 | 0.025 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>3<br>3<br>1 | 1000 | 0.000025 | 0.07 | Taro, 08/2014 |
| Zolpidem | 82626-48-0 | 0.063 | Carcinogen AF –<br>Intraspecies UF –<br>LOAEL UF –<br>Duration AF –<br>Database UF –<br>Endocrine Activity AF– | 1<br>10<br>10<br>10<br>3<br>1 | 3000 | 0.000021 | 0.06 | Teva, 11/2014 |

# Footnotes to Appendix A

[1] The LTD was calculated for each API using dosing recommendations identified from each applicable FDA approved label for the corresponding API. The majority of LTDs were calculated using an adult (>18 yoa) body weight (BW) of 80 kg. However, some LTDs were calculated using a non-adult age range (<18 yoa) based on the dosing and administration label information. LTDs calculated based on non-adult age ranges are identified with one of the following designations

[a] LTD calculated using dosing recommendations for 12-17 years of age (Mean weight for 17 yoa used – 68 kg)

[b] LTD calculated using dosing recommendations for 6-14 years of age (Mean weight for 14 yoa used – 61.5 kg)

[c] LTD calculated using dosing recommendations for 8-13 years of age (Mean weight for 13 yoa used – 56.9 kg)

[d] LTD calculated using dosing recommendations for 6-12 years of age (Mean weight for 12 yoa used – 50.3 kg)

[e] LTD calculated using BW dosing information directly from the corresponding label for any <18 years of age, no separate calculations

[2] AFs for certain APIs were evaluated on a pharmaceutical class basis due to the way information available was presented on both the FDA label and additional information sources.

[f] Statin class APIs were evaluated together when assigning an Endocrine Activity AF. APIs included in this class evaluation were Atorvastatin, Lovastatin, Pravastatin, Rosuvastatin, and Simvastatin. The APIs were all assigned an Endocrine Activity AF of 10.

[g] Tetracycline class APIs were evaluated together when assigning AFs for Cancer and Endocrine Activity. APIs included in this class evaluation for AFs were Demeclocycline, Doxycycline, Minocycline, Oxytetracycline, and Tetracycline. The APIs were all assigned a Cancer AF of 1 and an Endocrine Activity AF of 10.

[h] Sulfonamide class APIs were evaluated together when assigning an Endocrine Activity AF. APIs included in this class evaluation were Sulfadiazine and Sulfamethizole. Sulfamethoxazole, an API evaluated to serve as a comparison to MDH developed health-based guidance values, (Table 2), was also evaluated along with the other sulfa class pharmaceuticals. The APIs were all assigned an Endocrine Activity AF of 10.

[3] The Screening Water Value was calculated for each API using an RSC value of 0.8 based on the assumption that the majority of the exposure to a particular API for an individual that does not have a prescription would be through ingestion of contaminated drinking water. A RSC of 0.2 was used to calculate the Screening Water Value of APIs commonly found in both prescription only and OTC products. Screening water values calculated using a RSC of 0.2 are identified with the following designation:

[i] API commonly found in prescription and OTC products.

[4] This evaluation included the most prescribed APIs as well as APIs most commonly included on monitoring lists and most likely to be looked for in Minnesota. A current and approved FDA label was the primary source for information concerning the LTD calculations and UF/AF application. Rather than providing hyperlinks that may become outdated or broken, the manufacturer name and date of the label are provided as information that can be used to identify the label used by MDH in this evaluation. Some APIs included in this evaluation do not have current FDA labels available, have been discontinued, or other special circumstances. They have been identified in the appendix with the following designations:

[j] Lomefloxacin: There is an identified label in DailyMed from 2006 that was used for this evaluation. However, there are currently no active products on the market at this time. Lomefloxacin was included in the evaluation as it has only recently been discontinued.

[k] Norfloxacin: No identified label in DailyMed could be identified as the API was discontinued in the United States. The FDA Drugs Database has an archived label from 2013 located here, http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/019384s066lbl.pdf , which was used in this evaluation. Norfloxacin was included in the evaluation as it has only been recently discontinued and is still monitored for in MN.

[l] Oxytetracycline: There is an identified label in DailyMed from 1987, however this label was too outdated and not used in the evaluation. Other sources were relied upon to provide relevant data for the evaluation. Oxytetracycline was still included in the evaluation because it was evaluated along with others in the tetracycline class and it is still monitored for in MN.

[m] Propoxyphene: There is an identified label in DailyMed from 2010 that was used for this evaluation. However, it was removed from the market in 2010 due to new information from a study that showed serious adverse cardiac effects at therapeutic doses. Propoxyphene was included in the evaluation as it has only recently been discontinued and is still monitored for in MN.

[n] Sulfamethizole: There is an identified label in DailyMed from 2005 that was used for this evaluation. However, there are currently no active products indicated for human use on the market at this time. Sulfamethizole was included in the evaluation as it has only recently been discontinued and is still monitored for in MN.

[5] When an endocrine active API had endocrine activity as the intended effect, both a LOAEL-NOAEL UF of 10 and an Endocrine Activity AF of 10 were applied to be protective of low level potencies. However, in the case of Levothyroxine, a LOAEL-NOAEL UF of 3 and an Endocrine Activity AF of 10 was applied. This was done because Levothyroxine is designed to mimic endogenous thyroid hormone, acting just as the normal hormone would. Because this is almost identical to an endogenous hormone which is already present in humans, a LOAEL-NOAEL UF of 10 was not warranted.