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# Human Health Benchmarks for Pharmaceuticals in Drinking Water

U.S. Environmental Protection Agency
Office of Water (4304T)
Office of Ground Water and Drinking Water
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## ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| AFO | animal feeding operations |
| API | active pharmaceutical ingredient |
| BW | body weight |
| CalEPA | California Environmental Protection Agency |
| CCL4 | Fourth Safe Drinking Water Act Candidate Contaminant List |
| CCL5 | Fifth Safe Drinking Water Act Candidate Contaminant List |
| CSFII | Continuing Survey of Food Intakes by Individuals |
| CSO | combined sewer overflows |
| DWI | drinking water intake |
| DWI-BW | Drinking water intake adjusted for body weight |
| EPA | U.S. Environmental Protection Agency |
| Eq | Equation |
| FDA | U.S. Food and Drug Administration |
| FD&C | Food, Drug, and Cosmetic Act |
| FIFRA | Federal Insecticide Fungicide and Rodenticide Act |
| GAO | Government Accountability Office |
| HHBPs | human health benchmarks for pesticides |
| HHB-Rx | Human Health Benchmarks for Pharmaceuticals |
| HHS | U.S. Department of Health and Human Services |
| IARC | International Agency for Research on Cancer |
| IRIS | Integrated Risk Information System |
| LDD | lowest daily dose |
| LOAEL | lowest-observed-adverse-effect level |
| LOEL | lowest-observed-effect level |
| LTD | lowest therapeutic dose |
| MOU | memorandum of understanding |
| MRTD | maximum recommended therapeutic dose |
| NHANES | National Health and Nutrition Examination Survey |
| NIH | National Institutes of Health |
| NOAEL | no-observed-adverse-effect level |
| NOEL | no-observed-effect level |
| OTC | over the counter |
| POD | point of departure |
| POTWs | publicly owned treatment works |
| RfD | reference dose |
| RSC | relative source contribution |
| s-Dose | screening dose |
| UF | uncertainty factor |
| USDA | U.S. Department of Agriculture |
| USGS | U.S. Geological Survey |

## EXECUTIVE SUMMARY

The U.S. Environmental Protection Agency (EPA), in coordination with the Federal Workgroup on Pharmaceuticals in Water, has developed human health benchmarks for 374 pharmaceuticals (HHB-Rx). EPA selected these pharmaceuticals because they are approved by the U.S. Food and Drug Administration (FDA) and may occur in source waters (surface and groundwater) and/or treated drinking water.

If levels are at or below the human health benchmark, harmful health effects are not likely. The HHB-Rx are nonregulatory and non-enforceable and are intended to provide information to help states, Tribes, and water systems better characterize potential health risks associated with the occurrence of pharmaceuticals in drinking water and prioritize pharmaceuticals for additional monitoring and/or health effects research. For example, if a pharmaceutical occurs in drinking water at levels higher than the benchmark, additional water monitoring or research could be conducted to help ensure protection of Americans' drinking water.

The pharmaceuticals that EPA selected for benchmarks include prescribed medications and some over-the-counter pharmaceuticals. To develop benchmarks for each of the 374 pharmaceuticals, EPA used the lowest oral therapeutic dose from FDA-approved labels. For example, the FDA label for amoxicillin recommends the lowest dose an adult should take to treat infection is 250 mg every 8 hours. EPA used this dose to come up with a daily level of exposure (per kilogram of bodyweight) that a person would have if it was in the drinking water and then considered how much water a person drinks each day to calculate the benchmark (the level at or below which harmful health effects are not likely). EPA developed two benchmarks for each pharmaceutical—one for the general population (all ages) and one for infants, as infants consume more water relative to their body weight and may be more sensitive to the exposure.

This document outlines the approach that EPA used to select these 374 pharmaceuticals and the methodology EPA used to develop the benchmark levels. EPA may update the HHB-Rx as FDA drug labels change and add benchmarks for additional pharmaceuticals in the future as warranted. The benchmarks for these 374 pharmaceuticals, and any future additional benchmarks, will be available on EPA's website at https://www.epa.gov/sdwa/human-health-benchmarks.

# 1. INTRODUCTION

Pharmaceuticals can enter the environment in different ways. One source of pharmaceuticals in the environment is human excretion. Medicines that people take are not entirely absorbed by their bodies; a portion is excreted into wastewater. Some of the other sources of pharmaceuticals in the environment include landfill leachate, flushing leftover medications, and effluent from wastewater treatment plants. Studies have found very low levels of certain pharmaceuticals in drinking water; these levels are much lower than therapeutic dose levels. Research is ongoing to better understand how human pharmaceuticals get into water and how they move through the environment, what levels of pharmaceuticals humans are exposed to through drinking water, and the potential health effects from those exposures.

In 2012, a memorandum of understanding (MOU) was established to provide a formal mechanism to improve and sustain federal coordination and collaboration on issues related to pharmaceuticals in water between the U.S. Environmental Protection Agency (EPA), U.S. Department of Agriculture (USDA), U.S. Department of Health and Human Services/FDA, and the U.S. Department of Interior/Geological Survey (USGS).[1] As a result of this agreement, the Federal Workgroup on Pharmaceuticals in Water ("Workgroup") was formed to address issues related to pharmaceuticals in water and to provide a forum for the exchange of information on pharmaceuticals in the environment, support coordination of joint studies on pharmaceuticals in the environment, and facilitate interagency consultation on implications of research and analyses derived from shared information.

# 2. METHODS

## 2.1. Background

Nationwide surveys conducted by EPA, USGS, and others have reported pharmaceuticals at very low concentrations (parts per trillion or ng/L range) in finished drinking water, as well as low concentrations in source waters (surface and groundwater) (Batt et al., 2015; Benson et al., 2017; Glassmeyer et al., 2017; Furlong et al., 2017). Pharmaceutical use among Americans of all ages has risen considerably over the past 30 years (NCHS, 2021).[2] At the same time, environmental

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[1] The MOU was developed in response to the Government Accountability Office's (GAO) recommendation made to the Administrator of EPA in an August 2011 report, "Action Needed to Sustain Agencies' Collaboration on Pharmaceuticals in Drinking Water."

[2] According to the 2019 U.S. National Health and Nutrition Examination Survey (NHANES), between the periods of 1988–1994 and 2015–2018, individuals reporting the use of at least one prescription drug in the past 30 days increased 4.4 percentage points (from 31.3% to 35.7%) for adults aged 18–44, 12.3 percentage points (from 54.8% to 67.1%) for adults aged 45–64, and 14.9 percentage points (from 73.6% to 88.5%) for adults aged 65 and over (NCHS, 2021). Individuals are also increasingly taking more than one prescription drug at a time: In the same survey, the percent of adults reporting the use of five or more prescription drugs in the past 30 days increased 3 percentage points for adults aged 18–44, 10.6 percentage points for adults aged 45–64, and 28.1 percentage points for adults aged 65 and over (NCHS, 2021).

measurements of pharmaceuticals and other water contaminants have gotten significantly better—now being able to detect tens or even single digit nanograms per liter (ng/L) (Ternes, 1998; Ternes et al., 1999; Kolpin et al., 2002; Cahill et al., 2004; Furlong et al., 2008; Furlong et al., 2014).

The most widespread potential point source of pharmaceuticals in surface water is wastewater effluent from healthcare facilities and municipal sewage systems (Kostich et al., 2014; Vatovec et al., 2016; Liu and Wong, 2013; Pauwels and Verstraete, 2006). To help reduce point source discharges of pharmaceuticals to surface water, EPA regulations prohibit healthcare facilities from sewering hazardous waste pharmaceuticals (84 FR 5816; February 22, 2019). Other point and nonpoint sources of pharmaceuticals in waters include septic systems, leaking sewer lines and combined sewer overflows (CSOs), landfills, animal feeding operations (AFOs), industrial effluents, and croplands where biosolids are applied (Halling-Sorensen et al., 2007; Phillips et al., 2015; Masoner et al., 2015). Pharmaceuticals can be excreted in a biologically active form, and some users flush expired or unwanted medications down the toilet (Daughton, 2003a,b), which leads to pharmaceuticals in wastewater. Some advanced effluent treatment technologies can lower pharmaceutical concentrations (Snyder, 2008; Rostvall et al., 2018), but they are often costly and are not currently widely implemented. Treatment solutions are not one-size-fits-all; the removal rates of advanced treatment technologies are highly variable depending on the type and class of pharmaceutical. For example, ultraviolet radiation has been shown to be effective in removing more than 95% of tetracyclines and floroquinolones, while removing only 20%–45% of macrolides (Gogoi et al., 2018; Kim et al., 2009). Pharmaceuticals can travel from wastewater treatment facilities to surface water, groundwater, and drinking water (McArdell et al., 2003; Karthikeyan and Meyer, 2006; Zhang and Li, 2011; Glassmeyer et al., 2017; Thanner et al., 2018; Gogoi et al., 2018).

EPA, in coordination with the Workgroup, has developed human health benchmarks for 374 pharmaceuticals currently used in FDA-approved drug products. These human health benchmarks for pharmaceuticals (HHB-Rx[3]) were derived as a resource to assist risk assessors, risk managers, and others in determining whether the level of a pharmaceutical in drinking water warrants further evaluation. The values are intended to be protective of the general population (all ages) and infants (birth to <1 year), a potentially sensitive lifestage with high drinking water exposure (relative to body weight), against adverse, noncancer health effects from unintentional exposure to pharmaceuticals that may be ingested through drinking water. The HHB-Rx do not account for potential carcinogenicity, nor do they consider potential additive (mixture) effects. The HHB-Rx are nonregulatory and non-enforceable and are intended to provide information to help states, Tribes, and water systems better characterize potential health risks associated with the occurrence of pharmaceuticals in drinking water and prioritize pharmaceuticals for additional monitoring and/or health effects research.

[3] HHB-Rx is shorthand for human health benchmarks for pharmaceuticals. Although "Rx" is typically associated with prescribed medications, the HHB-Rx also include some over-the-counter (OTC) pharmaceuticals.

EPA has previously developed human health benchmarks for pesticides in drinking water (EPA, 2021a). Using a similar approach for pharmaceuticals, EPA, in coordination with the Workgroup, considered several approaches for benchmark development (see Section 2.5 below) (e.g., Glassmeyer et al., 2017; Benson et al., 2017; MDH 2018; WHO 2012; Daughton, 2010; Snyder, 2010).

## 2.2. Selection of Pharmaceuticals for Benchmark Development

Pharmaceuticals were prioritized as candidates for benchmark development depending on whether they are known (measured) or likely (predicted) to occur in drinking water sources and/or tap water as described in authoritative sources and literature identified by the Workgroup and external peer reviewers.

**Source Information for Candidate List of Pharmaceuticals for HHB-Rx Development**

| Source | Notes | References |
|---|---|---|
| The 50 Most Commonly Prescribed Drugs in America and Their Average Price | Most commonly prescribed medications and therefore more likely to occur in wastewater. | DrugReport, 2020 |
| FDA Flush List | List of 15 APIs sought after for their misuse and/or abuse potential and that can result in death from one dose if inappropriately taken. FDA recommends flushing these medicines down the toilet to help make sure they are not accidentally or intentionally ingested, touched, misused, or abused. | FDA, 2020 |
| EPA's 2006 Targeted National Sewage Sludge Survey | EPA conducted this survey to obtain concentration data for pollutants identified in biosolids to assess their potential risk to human and ecological health. EPA focused its efforts on publicly owned treatment works (POTWs) that treat more than 1 million gallons of wastewater per day, which collectively generate approximately 94% of the wastewater flow in the United States. Samples were collected between August 2006 and March 2007, and analyzed for 145 analytes, including 72 pharmaceuticals, steroids, and hormones. | EPA, 2009 |
| Pharmaceutical monitoring surveys from U.S. federal agencies | EPA, USDA, USGS, and National Park Service reports national surface and drinking water monitoring reports. | Glassmeyer et al., 2017; Benson et al., 2017; Batt et al., 2015; Khan et al., 2017; Kostich et al., 2010; Kostich et al., 2014; Olsen et al., 2013; Bradley et al., 2016; Bradley et al., 2017; Kolpin et al., 2002; Elliot and VanderMeulen, 2017; Lee et al., 2004 and 2011; Fram and Belitz, 2011; |

| Source | Notes | References |
|---|---|---|
| | | Barnes et al., 2008; Focazio et al., 2008; Erickson et al., 2014; Furlong et al., 2017; VanderMeulen, 2015 |
| Other pharmaceutical benchmark efforts (Minnesota Department of Health's Report on Pharmaceutical Water Screening Values) and relevant reports | Other reports largely suggested by external peer reviewers. | MDH 2018; WHO 2012; Benotti et al., 2009; Blair et al., 2013; Bruce et al., 2010; Snyder 2010; Jia et al., 2016; Kugathas and Sumpter, 2011; Stavreva et al., 2012; Wilkinson et al., 2022 |
| Analytical lists used for evaluating pharmaceuticals in water and other media | EPA Methods 1694 and 1698; USGS Methods 2434, 2440, and 2080; and SGS Axys pharmaceutical methods. | EPA 2007a,b; Foreman et al., 2012; Furlong et al., 2014; Furlong et al., 2008; SGS Axys 2022 |
| EPA's Fourth and Fifth Contaminant Candidate Lists (CCL4 and 5) | Seventeen chemicals from CCL4:17a-estradiol, chlorate, equilenin, equilin, erythromycin, estradiol, estriol, estrone, ethinyl estradiol, formaldehyde, manganese, mestranol, metolachlor, nitroglycerin, norethindrone, permethrin, and vanadium. The list also contained three chemicals from the Fifth Safe Drinking Water Act Candidate Contaminant List (CCL5): 17-alpha ethynyl estradiol, desvenlafaxine, and fluconazole. | EPA, 2016; EPA, 2021b |

A total of 696 compounds, including prescription pharmaceuticals, over-the-counter (OTC) pharmaceuticals (e.g., anti-inflammatory drugs, glucocorticoid steroids), nutritional supplements, drug precursors (i.e., chemicals used in the production of a pharmaceutical), drug metabolites, and other compounds (e.g., elements), were identified from the above-noted sources to make a preliminary list of candidates for benchmark development (see the Technical Support Appendix, tab "Full List of Candidates"). The preliminary list of 696 compounds was subsequently refined, as described below, based on several exclusion criteria, such as the removal of duplicate entries and pharmaceuticals lacking current labeling information.

Therapeutic classification was not considered when prioritizing pharmaceuticals as candidates for benchmark development as this approach would not have been practical for the large number of pharmaceuticals evaluated. The therapeutic classifications in the benchmark list of pharmaceuticals include antibiotics, hormones, antidepressants, antineoplastics, antihistamines, analgesics, antacids, anticonvulsants, antihypertensives, antipsychotics, antivirals, beta blockers, blood thinners, and other therapeutic classifications.

### 2.3. Data Collection

Following development of the preliminary list of 696 candidate compounds for benchmark development, publicly available federal databases were utilized to retrieve dosing information

from pharmaceutical labels with FDA-approved uses under the Food, Drug, and Cosmetic Act (FD&C) (Title 21 Chapter 9 of the United States Code). FDA-approved labels for each of the candidate pharmaceuticals with an approved oral adult dose were retrieved primarily from the National Institutes of Health (NIH) DailyMed database (NIH 2022). When information for a pharmaceutical was not available through NIH DailyMed, dosage information was retrieved from a secondary source, the Drugs@FDA database (FDA, 2022). Quality checks were performed to ensure the accuracy of the extracted data from these databases.

### 2.4. Exclusion Criteria

Benchmarks were developed only for those pharmaceuticals with FDA-approved oral dosage information from labels on publicly available federal databases (FDA, 2022; NIH, 2022). A significant portion of the candidate compounds (322 out of 696) were excluded from HHB-Rx development based on the exclusion criteria listed below (Figure 1; to view the complete list of the pharmaceuticals excluded from benchmark development at this time, please see the Technical Support Appendix, tab "Exclusion List").

1. The compound is not an active pharmaceutical ingredient (e.g., chemicals used in the production of a pharmaceutical, metabolites of pharmaceuticals that do not have FDA-approved oral doses).
2. The pharmaceutical was duplicative (synonymous) with another on the list.
3. The pharmaceutical does not have a current, FDA-approved label (e.g., unapproved drugs, homeopathic medicines, nutritional supplements, some OTC medications, discontinued products).
4. The pharmaceutical has a final, peer-reviewed toxicity assessment (e.g., from EPA).
5. The pharmaceutical is a currently registered pesticide chemical regulated under the Federal Insecticide Fungicide and Rodenticide Act (FIFRA). EPA has already developed human health benchmarks for 430 pesticides as a separate effort, using a similar approach (EPA, 2021a).
6. The pharmaceutical is used exclusively for veterinary purposes and has no current human uses (i.e., no human oral dosage information was available).[4]
7. There was insufficient oral dose label information available for a pharmaceutical (e.g., no oral dosage information available from an FDA-approved label on publicly available federal databases (FDA, 2022; NIH, 2022)). Benchmarks were developed only for pharmaceuticals with oral dosage information. No route-to-route extrapolation (i.e., from a nonoral dose, such as injection, inhalation, or a dermal-to-oral route) was performed.

Information on cancer/carcinogenicity was not considered an exclusion criterion. For the user's information, any pharmaceutical that has been listed as a possible carcinogen, probable carcinogen, or as carcinogenic by the International Agency for Research on Cancer (IARC), the California Environmental Protection Agency (CalEPA), and/or the EPA was noted as such in the

[4] Exclusion of veterinary drugs from benchmark development at this time is not associated with an assessment of potential risk; this effort focuses on pharmaceuticals with currently labeled human oral doses.

Technical Support Appendix. Future updates of the benchmarks may consider cancer/carcinogenicity effects information.

Type of therapeutic action (e.g., drug class) was not considered as an exclusion criterion.

The preliminary list of 696 compounds contained 17 chemicals from the Fourth Safe Drinking Water Act Candidate Contaminant List (CCL4):17a-estradiol, chlorate, equilenin, equilin, erythromycin, estradiol, estriol, estrone, ethinyl estradiol, formaldehyde, manganese, mestranol, metolachlor, nitroglycerin, norethindrone, permethrin, and vanadium. The list also contained three compounds from the Fifth Safe Drinking Water Act Candidate Contaminant List (CCL5): 17-alpha ethynyl estradiol, desvenlafaxine, and fluconazole. Benchmarks were developed for seven pharmaceuticals contained in CCL4 and CCL5 (erythromycin, estradiol, ethinyl estradiol, desvenlafaxine, fluconazole, mestranol, and norethindrone) (see the Technical Support Appendix). The remaining CCL4 and CCL5 contaminants were excluded from benchmark development because they were pesticides (metolachlor, permethrin, chlorate, nitroglycerin), elements (manganese and vanadium), metabolites (equilin), or preservatives (formaldehyde), or were discontinued (estrone) or had no label (17a-estradiol, 17-alpha ethynyl estradiol, 17-beta estradiol, equilenin, estriol).

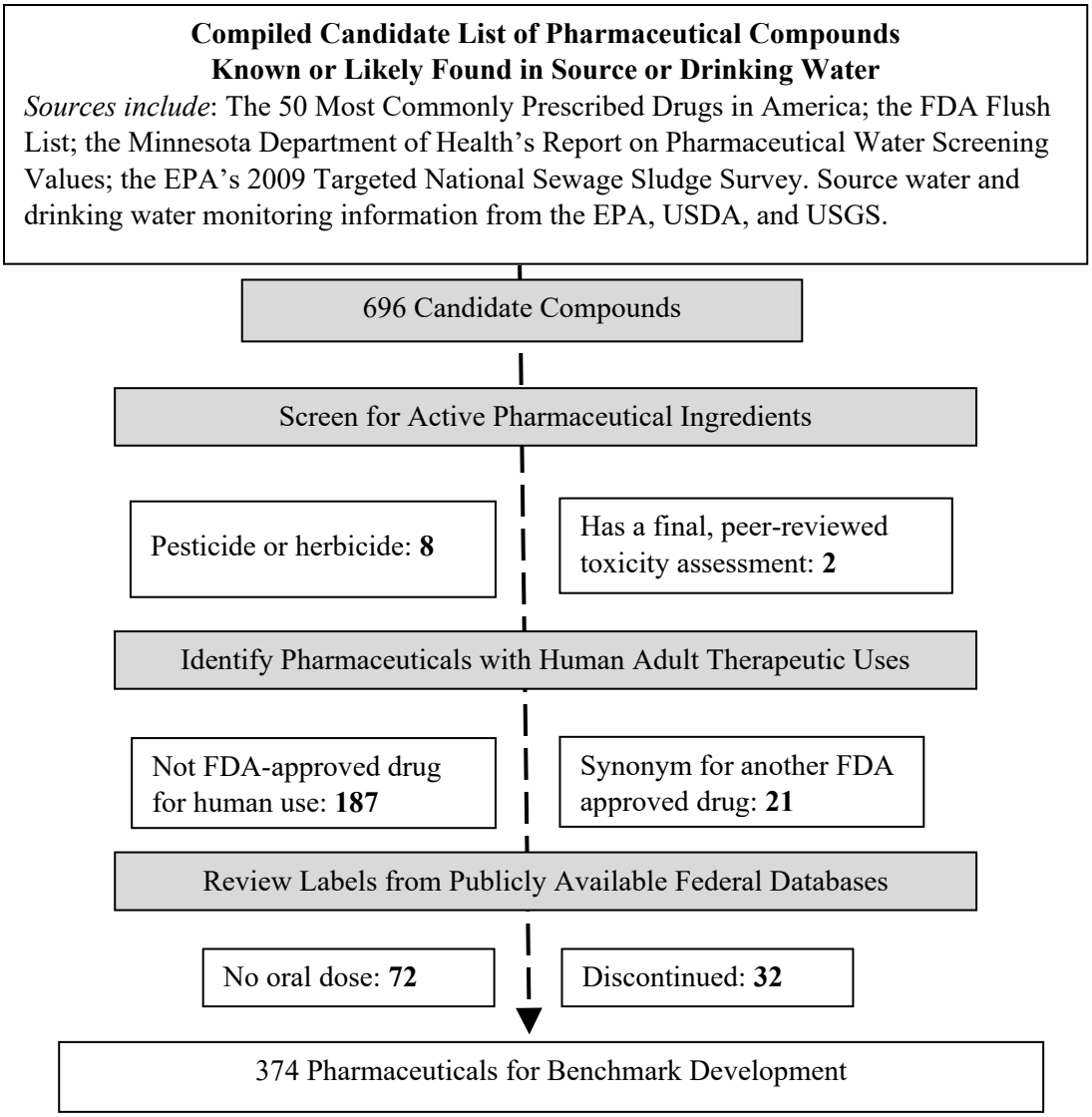


*Figure 1: Process for selecting candidate pharmaceuticals for HHB-Rx development.*

### 2.5. Development of a Proxy Point of Departure

While therapeutic doses provide a health benefit for individuals intentionally ingesting prescription or OTC pharmaceuticals, the potential effects of unintentional, low-level, long-term exposures to nontargeted individuals are not well understood. EPA, in coordination with the Workgroup, considered several alternatives in selecting a proxy for the point of departure (POD; i.e., the toxicological dose-response point that marks the beginning of a low-dose extrapolation and generally corresponds to an estimated low- or no-effect level (EPA, 2012)), for benchmark calculation.

EPA traditionally develops reference doses (RfDs) for noncarcinogenic effects to estimate oral toxicity for substances (e.g., pesticides, industrial chemicals, metals). An RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure of the human population to a substance that is likely to be without an appreciable risk of deleterious effects

during a lifetime. An RfD can be derived from a POD from laboratory animal dosing studies or epidemiology studies from which a no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL), or benchmark dose[5] can be derived, with application of uncertainty factors (UFs), to account for variability and uncertainty in the available data. Total UFs applied for any particular chemical are limited to no more than 3,000, per EPA policy (EPA, 2002).

Evaluation of human and animal toxicological data from the peer-reviewed literature, when available, is the preferred approach for traditional RfD development. For this effort, EPA, in collaboration with the Workgroup, decided that using the pharmaceutical lowest therapeutic dose (LTD; also referred to as the lowest clinically effective dose or the minimum therapeutic dose) as a proxy for the POD would be a practical way to develop benchmarks for the large number of pharmaceuticals that were evaluated in this project. For the 374 selected pharmaceuticals, the Workgroup opted to use the LTD for adults (i.e., the minimum *total* daily dose adjusted for adult body weight at which a therapeutic effect is achieved) as the POD. The LTD was determined for the formulated drug product and was not adjusted to reflect percent active pharmaceutical ingredient. The LTD has been used as a proxy POD in similar efforts to develop pharmaceutical benchmarks for drinking water (Webb et al., 2003; Schwab et al., 2005; NRMMC, EPHC, NHMRC 2008; Cunningham et al., 2009; Bull et al., 2011; WHO, 2012; MDH, 2018).

The LTD (mg/kg-day) is calculated as presented in Eq. 1 by dividing the lowest (total) daily dose (LDD) for adults identified from FDA-approved label information (mg/day) by 80 kg (i.e., mean weight for U.S. adults ages 21 and older based on National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2006 as reported in Chapter 8 of EPA's *Exposure Factors Handbook* (EPA, 2011)).

$$\text{Proxy Point of Departure (POD)} = \text{LTD (mg/kg-day)} = \frac{\text{Lowest Daily Dose (mg/day)}}{\text{Mean Adult Body Weight (kg)}} \qquad \text{(Eq. 1)}$$

EPA, in collaboration with the Workgroup, considered several alternatives to the adult LTD for the POD. One alternative approach was to use the maximum recommended therapeutic dose (MRTD), that is, the upper dose limit beyond which a drug's efficacy is not increased and/or undesirable adverse effects begin to outweigh beneficial effects in the targeted patient population. Although MRTD information is readily available on public databases and has been used in other pharmaceutical benchmark studies (Benson et al. 2017), the LTD was selected because it is more similar to the LOAEL approach used in chemical risk assessment at EPA.

Pediatric/non-adult LTDs were also considered but were not used for several reasons. First, all of the pharmaceuticals are actively labeled for adult use. Some of the pharmaceuticals are labeled for both adult and pediatric/non-adult use, but none of them are labeled for pediatric/non-adult use only. Second, for water-soluble pharmaceuticals, adults have lower total body water on a per

[5] This approach involves dose-response modeling to obtain the levels corresponding to specific responses near the low end of the observable range of the data (EPA, 2012).

weight (or percentage) basis and thus a lower volume of distribution than infants or small children; as a result, adult LTDs tend to be lower on a per body weight basis and thus result in more protective benchmarks (Milsap and Jusko, 1994; Batchelor and Marriott, 2015; Benedetti and Baltes, 2003). Third, although other approaches (MDH 2018; Suchomel 2018) have used non-adult dosing to calculate a small portion (32%) of benchmarks to increase health protection, the non-adult to adult LTD comparisons in those cases were similar (within ~10x). Further, as described below in *Screening Dose Approach*, EPA applied an uncertainty factor of 3,000, of which 10x was applied to account for variation in sensitivity among the members of the human population (intraspecies variation), including sensitive human populations. Thus, the HHB-Rx developed using the adult dose labeling information are expected to be similar to those developed using pediatric/non-adult dose information. For added health protection for children, as described in the *Human Health Benchmark Calculation* section, benchmarks were derived for infants (birth to <1 year) as well as the general population (all ages).

Using FDA-approved label information from publicly available federal databases (FDA, 2022; NIH, 2022), the lowest (total) daily dose (LDD) (mg/day) for adults was identified for each pharmaceutical using the following process and decision logic:

- When several labels, formulations, or indications (i.e., use for a particular disease or condition) were retrieved for a single pharmaceutical, the indication with the lowest LDD (mg/day) for adults was selected. LDDs were not adjusted for percent active pharmaceutical ingredient in a given formulated drug product. Doses on FDA labels are reported in percent active ingredient; thus, no adjustment for formulation was necessary (FDA, 2022; NIH, 2022). This approach of using dosage information from FDA labels without adjustment for formulation is consistent with other similar efforts, including the Minnesota Department of Health (MDH, 2018) and the Water Research Foundation (WRF, 2010).
- For pharmaceuticals with indications that call for ramp-up (i.e., gradually increasing) dosing regimens, the lowest maintenance dose for an adult in the general population was selected to be health protective (e.g., lisdexamfetamine; the starting dose is 30 mg/day, and dosage may be adjusted in increments of 10 mg/day or 20 mg/day at weekly intervals up to a maximum dose of 70 mg/day). Thus, the selected LDD was 30 mg/day because the dose may increase or may be effective at 30 mg/day).
- For pharmaceuticals occurring only in combination with one or more pharmaceutical(s) in a single formulation, the LDD for adults was selected from a combined formulation for each pharmaceutical irrespective of the formulation. For example, the LDD for clavulanate of 375 mg/day for adults (based on 125 mg clavulanate dose every 8 hours) is based on a label for an amoxicillin/clavulanate formulation since clavulanate is only available in combination products, whereas the LDD for adults for amoxicillin is 750 mg/day based on a separate label listing a dose of 250 mg amoxicillin every 8 hours.
- For pharmaceuticals with “as needed” dosing indications, the LDD was calculated by multiplying the lowest dosage by the minimum number of times administered per day to calculate the lowest total daily therapeutic dose (e.g., the codeine label states, “The

recommended dose is 15 to 60 mg every 4 hours as needed for pain," so the calculated LDD is 90 mg/day (15 mg × 6 times per day)).

- For pharmaceuticals with both preventive and therapeutic uses, the LDD was selected among all uses (e.g., penicillin: the lowest dose for prevention of recurrence is 125 mg twice daily (LDD = 250 mg/day), while the lowest dose for treatment of infection is 125 mg every 8 hours (LDD = 500 mg/day). Therefore, the LDD for prevention of recurrence was selected).
- For pharmaceuticals with specific instructions for sensitive populations (e.g., women who are pregnant or likely to become pregnant, people with preexisting conditions or other co-indications), the LDD for the average patient population was selected to ensure consistency in endpoint selection for all 374 benchmarks. Pharmaceutical labels may vary significantly with regard to sensitive populations: specific directions for sensitive populations may or may not be included, and the sensitive population can differ by label, indication, or pharmaceutical. To calculate the screening dose, EPA applied a composite uncertainty factor of 3,000, of which 10x was applied to account for intraspecies variation (i.e., sensitive human populations). For example, the digoxin label states, "Therapy is generally initiated at a dose of 250 micrograms (0.25 mg) once daily in patients under age 70 with good renal function, at a dose of 125 micrograms (0.125 mg) once daily in patients over age 70 or with impaired renal function..." In this case, 0.25 mg/day was selected. To provide information about sensitive populations, information regarding contraindications found in the labels is included in the Technical Support Appendix.

### 2.6. Sources of Lowest Daily Dose Information

LDDs were selected from dosage and administration information that is publicly available on federal databases. The NIH DailyMed database (NIH, 2022) was the primary source for obtaining LDD information from drug labels. When information for a pharmaceutical was not available through NIH DailyMed, the Drugs@FDA database (FDA, 2022) was used as a secondary source. LDDs, LTDs, and benchmark calculations were verified by EPA, and additional quality assurance checks were performed by FDA and a contractor.

### 2.7. Screening Dose Approach to Develop HHB-Rx

RfD development at EPA includes application of UFs to account for variability and uncertainty in the available data (EPA, 2002). A similar approach was used to derive a screening dose (s-Dose) for each pharmaceutical. Since the proxy PODs for pharmaceuticals are based on LDDs from labels, EPA, in coordination with the Workgroup, chose to follow a modified approach to account for uncertainty when calculating benchmarks for pharmaceuticals. In EPA's chemical risk assessment practices, the total UFs applied for any chemical are limited to no more than 3,000 (EPA, 2002). An s-Dose was calculated for each of the pharmaceuticals selected for HHB-Rx development by dividing the adult LTD by a composite uncertainty factor of 3,000 (Eq. 2).

In this approach for HHB-Rx, the composite uncertainty factor of 3,000 accounts for the following:

- Interspecies extrapolation: A UF of 1 is applied because the POD is the LTD for human adults and an extrapolation from nonhumans to humans is not relevant.
- Intraspecies variation: A UF of 10 is applied to account for variation in sensitivity among the members of the human population.
- Subchronic-to-chronic study extrapolation: A UF of 10 is applied to account for exposure duration because there is only one screening dose for each pharmaceutical (based on the LTD).
- Uncertainty in extrapolating from lowest-observed-effect level (LOEL) to no-observed-effect level (NOEL): A UF of 10 is applied because a pharmaceutical LTD is more akin to a LOEL than a NOEL.
- Database deficiencies: A UF of 3 is applied to account for potential additional adverse health effects that could occur below or at the LTD.

$$\text{s-Dose (mg/kg-day)} = \frac{\text{Adult LTD (mg/kg-day)}}{3000} \qquad \text{(Eq. 2)}$$

## 2.8. Human Health Benchmark Calculation

To account for exposure via drinking water, multiple drinking water exposure scenarios were considered to determine the most protective scenario for these screening-level benchmarks. Consistent with EPA's previously published human health benchmarks for pesticides (HHBPs; EPA 2021a), the following exposure scenarios were considered: acute or 1-day exposure for children, acute or 1-day exposure for females 13 to <50 years, chronic (noncancer) for the general population, and chronic (noncancer) for females 13 to <50 years. Unlike the human health benchmarks for pesticides that were based on acute and chronic reference doses developed using studies with short- and long-term exposure durations, there is only one screening dose for each pharmaceutical (based on the LTD). As a result, developing pharmaceutical benchmarks for various exposure durations is not possible.

Instead, two HHB-Rx were derived for each pharmaceutical: one for infants (birth to <1 year), a developing lifestage with high exposure via drinking water/body weight and potentially of greater susceptibility, and another benchmark for the general population (all ages), to provide risk assessors with options to determine whether further evaluation of a site is needed (Eqs. 3 and 4). EPA recognizes that formula-fed infants (1 to <3 months) ingest more drinking water via reconstituted infant formula (0.249 L/kg bw-day; Kahn, 2013) than do infants birth to <1 year of age (0.143 L/kg bw-day). However, EPA selected the drinking water intake rate for infants of birth to <1 year because it is based on more statistically robust data as indicated by the 2019 Chapter 3 of the *Exposure Factors Handbook* (EPA, 2019). Specifically, the study data for infants (birth to <1 year) have a greater sample size (n = 374) than the study data for formula-fed infants (n = 90). Furthermore, the infant (birth to <1 year) data are more recent (2005–2010 NHANES) than the formula-fed infant data (1994−1996 and 1998 Continuing Survey of Food Intakes by Individuals (CSF II)). For these reasons, EPA selected infants, birth to <1 year, for the exposure factor used for the infant benchmark.

The relative source contribution (RSC) included in the benchmark calculation (Eqs. 3 and 4) describes the portion of the total oral exposure attributed to drinking water sources (EPA, 2000); the remainder of the exposure is allocated to other routes or sources. The rationale for this approach is that for pollutants exhibiting threshold effects, the objective of the human health benchmark is to ensure that an individual's total exposure from all sources does not exceed that threshold level. Exposures other than drinking water may include, but are not limited to, exposure to a particular pollutant from the diet and dermal and inhalation exposures. In the case of pharmaceuticals, the major source of exposure is expected to be intentional oral ingestion for therapeutic uses. For individuals in the general population and infants who are not intentionally ingesting pharmaceuticals for therapeutic doses, there is the potential for unintentional human oral exposure via drinking water. Other non-drinking water sources and routes of exposure for the general population and infants are not anticipated. As specified in the EPA's 2000 Methodology, "if it can be demonstrated that other sources and routes of exposure are not anticipated for the pollutant in question (based on information about its known/anticipated uses and chemical/physical properties), then EPA would use the 80 percent ceiling" for the RSC (EPA, 2000, Section 4.2.3). Thus, an RSC of 0.8 was applied for both the general population and infant benchmarks (i.e., 80% of potential exposure to a given pharmaceutical is attributed to drinking water). Infants may also be exposed to pharmaceuticals via infant formula (powder or liquid) itself as opposed to the drinking water for reconstitution of powder-based formula. There is limited available information about pharmaceutical occurrence in infant formula. However, because most drug residues attach to the milk fat and most dairy-based infant formulas contain non-fat protein ingredients, it is expected that there would be low, if any, pharmaceutical exposure from infant formula ingestion (FDA, 2015).

Benchmarks for infants (birth to <1 year) and the general population (all ages) were calculated as presented in Eqs. 3 and 4. Benchmarks were rounded to one significant figure. These benchmarks are intended to help the public, water suppliers, and federal and state agencies better understand when pharmaceuticals found in the water supply may pose a risk to human health and to prioritize monitoring and research efforts. The benchmarks may be used to determine whether the level of a pharmaceutical in drinking water warrants further evaluation, including monitoring or additional research.

**Benchmark for Infants (Birth to <1 Year) (µg/L) =**

$$\frac{\text{s-Dose (mg/kg-day)} \times 1000\ (\mu\text{g/mg}) \times \text{RSC}}{\text{Infant DWI-BW Rate (L/kg bw-day)}} \qquad \text{(Eq. 3)}$$

Where:

| | |
|---|---|
| s-Dose | = screening dose (i.e., Adult LTD/3,000) |
| RSC | = 0.8 |
| Infant DWI-BW Rate | = 0.143 L/kg bw-day. This rate represents the 90th percentile value of the 2-day average, consumer-only estimate of combined direct and indirect community water |

ingestion based on the NHANES 2005–2010 data for infants (birth to <1 year) as reported in EPA's 2019 update for Chapter 3 of the *Exposure Factors Handbook* (Table 3-21).

**Benchmark for General Population (All Ages) (µg/L) =**

$$\frac{\text{s-Dose (mg/kg-day)} \times 1000\ (\mu\text{g/mg}) \times \text{RSC}}{\text{All Ages DWI-BW Rate (L/kg bw-day)}} \qquad \text{(Eq. 4)}$$

Where:

| | |
|---|---|
| s-Dose | = screening dose |
| RSC | = 0.8 |
| All Ages DWI-BW Rate | = 0.0338 L/kg bw-day. This rate represents the 90th percentile value of the 2-day average, consumer-only estimate of combined direct and indirect community water ingestion based on the NHANES 2005–2010 data (all ages) as reported in EPA's 2019 update for Chapter 3 of the *Exposure Factors Handbook* (Table 3-21). |

## 3. RESULTS

HHB-Rx for infants (birth to <1 year) and the general population (all ages) were calculated for 374 pharmaceuticals (see the Technical Support Appendix). These benchmarks are all available on EPA's website at https://www.epa.gov/sdwa/human-health-benchmarks.

The HHB-Rx provide information to assist risk assessors, risk managers, and others in determining whether the level of a pharmaceutical in drinking water warrants further evaluation, including monitoring or additional research to fill data gaps and allow for a complete risk assessment. The HHB-Rx are nonregulatory and non-enforceable. EPA expects to update the HHB-Rx as drug labels change and to derive HHB-Rx for additional pharmaceuticals in the future as warranted.

## 4. HOW TO VIEW THE HHB-Rx

To view the table of HHB-Rx and supporting information online go to https://www.epa.gov/sdwa/human-health-benchmarks.

## 5. FOR MORE INFORMATION

For more information regarding the derivation of HHB-Rx, contact Czarina Cooper (Cooper.Czarina@epa.gov) in EPA's Office of Water.

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