APPROACHES TO SCREENING FOR RISK

FROM PHARMACEUTICALS IN DRINKING WATER

AND PRIORITIZATION FOR FURTHER EVALUATION

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Executive Summary

Pharmaceuticals have been discovered in this nation's ambient waters, wastewater, and drinking water at very low levels. EPA has a strategy to respond to this issue, including improving science through research, improving public understanding, identifying partnership opportunities, and taking regulatory action when appropriate. As a part of this strategy, EPA is examining ways to screen and prioritize pharmaceuticals that occur in drinking water for potential human health risk at low concentrations. This white paper summarizes the different approaches taken in six articles considering risk assessment of pharmaceuticals in drinking water, examining the health endpoints used, the data sources, occurrence data, and key distinctions of each approach. The similarities and differences between the approaches are outlined, including the dose metrics used as the health endpoints and the sources of occurrence data.

Introduction

The presence of pharmaceuticals in drinking water is not a new issue. In the 1970's, several researchers reported the presence of clofibric acid, a breakdown product of several blood lipid regulators, and salicylic acid, a breakdown product of aspirin, in waste water. However, as analytical techniques grew more sensitive over the years, many more pharmaceuticals have been detected in ambient water, wastewater, and drinking water.

During 1999-2000, the U.S. Geological Survey carried out the first national survey of the occurrence of pharmaceuticals, hormones, and other chemicals in 139 streams from 30 states. A total of 95 contaminants were targeted, with 80 percent of the streams testing positive for one or more contaminants.

Pharmaceuticals enter water through: flushing unused medications down the toilet or sink; excreting unabsorbed medications into the sewage system; farm animals excreting veterinary drugs into fields where they run off into lakes and streams; and commercial improper disposal methods. Conventional water and wastewater treatment methods allow many pharmaceuticals to pass through unchanged, entering the environment and ultimately the drinking water.

One problem with assessing risk of pharmaceuticals in drinking water is the very large number of pharmaceuticals in use today. Information on the occurrence of pharmaceuticals in drinking water is available only for a limited number of compounds. In addition, many pharmaceuticals are biologically degraded to active metabolites that have not been evaluated.

A number of different approaches have been suggested and published in the peer reviewed literature for screening and prioritizing the hazard posed by low concentrations of pharmaceuticals in drinking water. This white paper summarizes and evaluates a number of risk assessment approaches (including EPA's current approach), that EPA is aware of, that have been described in the literature. This paper is not a comprehensive

compilation of all published approaches. In addition, this paper describes EPA's current activities and research strategy for pharmaceuticals in water.

Approaches Described in the Literature

1. Drinking Water Inspectorate (DWI). 2007. Desk Based Review of Current Knowledge on Pharmaceuticals in Drinking Water and Estimation of Potential Levels.

1.1 Summary of Approach

The DWI (2007) approach consisted of determining a margin of exposure (MOE) for each pharmaceutical by dividing the minimum therapeutic dose by the theoretical maximum intake from drinking water. The drinking water intake was obtained by a modeling approach which used two methods: 1) a deterministic method that resulted in estimates of worst case concentrations in drinking water, and 2) a probabilistic method that resulted in more realistic estimates of the concentrations in drinking water. All pharmaceuticals were first evaluated using the deterministic method, and for those 24 compounds that had the lowest MOEs, further evaluation was done using the probabilistic method.

1.2 Health Endpoint

The health endpoint used was the minimum therapeutic dose (MTD). There was no discussion in the report as to why the MTD was chosen. If an MTD was not available for a pharmaceutical because the drug was topically applied, an MTD of 10 mg was used. For those compounds for which it was not possible to determine an MTD because the required information was not available, as was the case for all the illegal drugs, a very precautionary MTD of 1 mg was used.

1.3 Data Sources

The MTD was obtained from several sources including: RxList (an internet database: http://www.rxlist.com/script/main/hp.asp), the British Medical Association New Guide to Medicines and Drugs (Watts and Crane Associates 2007), and the WHO Model Formulary (Watts and Crane Associates 2007).

1.4 Occurrence Data

To calculate the concentration of the pharmaceuticals in drinking water, an approach was used based on a model proposed by the European Medicines Evaluation Agency (EMEA, 2005) for risk assessment of pharmaceuticals in the environment. The DWI model uses an equation based on usage, population, and wastewater production that generates the

predicted concentration in drinking water (PEC_{dw}), which provides a likely estimate of the concentration of the pharmaceuticals in drinking water:

$$PEC_{dw} = \frac{A \times (100-R) \times (100-M) \times (100-W)}{365 \times P \times V \times D \times 100 \times 100 \times 100}$$

Where:
PECdw is the predicted concentration in drinking water (mg/L)
A is the amount of active ingredient used per year in the catchment (mg/yr)
R is the removal rate in sewage treatment (set as a percentage)
M is the percentage metabolized in humans
W is the removal rate in the appropriate drinking water treatment scenario
P is the population under consideration (i.e. for the U.K.; 59,600,000 or the population equivalent for each catchment scenario)
V is the volume of wastewater produced per capita per day (assumed to be 200 L)
D is the dilution factor in the environment (derived as the 5% flow rate)

Five drinking water treatment scenarios were modeled: three scenarios consisted of normal drinking water treatment but different types of source waters (two with high and one with low sewage input), and two scenarios consisted of more advanced treatment from different types of source waters.

Two approaches were used, based on the above equation, to determine the concentrations of the pharmaceuticals in drinking water. The first approach was a deterministic modeling approach where no metabolism, no loss in sewage treatment, no loss or further dilution during transport in rivers between sewage treatment plant discharge points and drinking water treatment intakes, and no loss in drinking water treatment plants was assumed. The total UK usage per year (A in the equation) for each of the medically used pharmaceuticals was set at twice the value estimated from IMS data (http://www.imshealth.com) to allow for uncertainties in the data. (IMS contains information on the total amounts of active ingredients in human pharmaceutical preparations sold in the U.K.). As a consequence of the assumptions made, this is a worst case assessment, and the concentrations estimated will be the highest that could be expected under the most extreme conditions.

The second approach was probabilistic modeling that took into account: metabolism - the range of values used was set as a range from 0% to the value obtained from literature searches; loss in sewage treatment plants - the range of values used was set based on the literature reported range, or the QSAR estimated (EPIWIN) removal percentage loss; dilution factor – used a river flow rate, which was the 5^{th} percentile value from the data supplied covering several years of flow measurements; and loss in drinking water treatment plants - the range of values used was set based on the literature reported range or a default range of 50-100%. The total UK usage per year (A in the equation) for each of the pharmaceuticals was the value estimated from the IMS data.

1.5 Key Distinctions Relevant to Prioritization

This approach consists of two different methods for assessing the concentrations of the pharmaceuticals in drinking water. The first method (deterministic modeling approach) results in a worst case estimate, while the second method (probabilistic modeling approach) may result in a more accurate estimate. The results from deterministic modeling showed that only 10 substances produced MOEs less than 1,000. The deterministic modeling approach is viewed as relatively simple and does not involve literature or database searches for the pharmaceuticals; and thus, can be carried out in a short time period. The probabilistic modeling approach takes into account degradation, metabolism, and loss in drinking water treatment, hence, it may provide a more accurate estimate of the actual concentrations of the pharmaceuticals in drinking water.

The approach used for assessing the health effects uses the minimum therapeutic dose and divides all pharmaceuticals by the same safety factor of 1000. A consideration for this approach is that it does not take into account differing mechanisms of action of the pharmaceuticals, which if known, could lead to the use of a variety of safety factors which may be more representative of the actual toxicity of the compounds.

2. Global Water Research Coalition. 2008. Development of an International Priority List of Pharmaceuticals Relevant for the Water Cycle.

2.1 Summary of Approach

The GWRC (2008) approach is a method that was used to develop a list of pharmaceuticals that are most likely found in water supplies and that may have significant impacts on human and environmental health. These pharmaceuticals are identified for further study because the model results indicate potential exposure. The approach used was to identify major existing prioritization efforts across the world, and evaluate criteria used in these prioritization exercises. A total of 17 criteria were mentioned in the 25 base documents used in this study. From these, seven criteria were used to develop three lists of priority pharmaceuticals. These criteria were: regulation, consumption/sales, physicochemical properties, degradability/persistence, resistance to treatment, toxicity (human) and ecotoxicity, and occurrence in surface waters, groundwater, drinking water, and wastewater. The pharmaceuticals were scored based upon the number of criteria that had been used in each document. Class 1 (high priority) were those pharmaceuticals that were mentioned in five or more of the base documents cited, and that fulfilled more than 4 of the 7 criteria; Class 2 (medium priority) contained pharmaceuticals that were mentioned in more than two of the base documents cited, and that fulfilled more than two criteria, and Class 3 (low priority) were those pharmaceuticals mentioned in two documents of the base documents cited, and fulfilled two or more of the criteria selected.

2.2 Health Endpoint

This was not a risk assessment approach; however, health was considered in the criteria that were used to evaluate the prioritization of the pharmaceuticals in the reports. The criterion of toxicity (human) and ecotoxicity was one of the seven criteria evaluated to select pharmaceuticals from the reports.

2.3 Data Sources

A total of 25 reports and references were used which had the prioritization of pharmaceuticals as the key subject. The number of appearances of pharmaceuticals in the 25 base documents was scored.

2.4 Occurrence Data

No occurrence data were used in this approach. However, occurrence in surface waters, ground water, and drinking water was one of the seven criteria evaluated to select pharmaceuticals from the report.

2.5 Key Distinctions Relevant to Prioritization

As a result of this approach, three lists of pharmaceuticals were developed based on priority. Therefore, this approach may be useful for obtaining lists of pharmaceuticals that could be considered priority compounds for future research and evaluation.

3. Australian Guidelines for Water Recycling, Augmentation of Drinking Water Supplies, May 2008.

3.1 Summary of Approach

The Australian Guidelines for water recycling were developed to establish Drinking Water Guidelines (DWGs) for recycled wastewater in Australia. These guidelines were established for microbial and chemical risk, including pharmaceuticals detected in water.

Pharmaceuticals were divided into two categories: 1) those used solely for humans, and 2) those used for veterinary purposes (some of which may also be used for humans). For those pharmaceuticals used for veterinary purposes, Acceptable Daily Intakes (ADIs) established by the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives, the Australian Therapeutic Goods Administration, and the European Medicines Agency were used to determine guideline values. For pharmaceuticals used solely for humans, the lowest daily therapeutic dose was divided by safety factors ranging from 1,000 to 10,000 to determine a surrogate-ADI. For most pharmaceuticals, a safety factor of 1,000 was applied to the lowest daily therapeutic dose, with an additional factor of 10 added for cytotoxic drugs and another factor of 10 for hormonally active steroids.

The drinking water guidelines for pharmaceuticals were determined based on the following calculation:

Drinking water guideline (µg/L) = (ADI or s-ADI x BW x P)/V, where

ADI = Acceptable Daily Intake (µg/kg-day) as determined by international organizations
s-ADI = surrogate ADI (µg/kg-day) = lowest daily oral therapeutic dose for an adult (mg/day)/safety factor of 1,000 or 10,000
BW = bodyweight (70 kg)
V = volume of water consumed (2 L/day)
P = proportion of s-ADI from water = 100%

The Australian Guidelines then compared calculated drinking water guidelines with the highest concentrations of the pharmaceuticals measured in secondary treated effluent. The margins of exposure for most pharmaceuticals were greater than 1, with many being 1,000 or more. The guidelines concluded that, given that this does not take into account reductions achieved by advanced treatment processes, it is unlikely that pharmaceuticals will be present at levels approaching the recommended drinking water guideline, or cause untoward effects in people drinking water produced from recycled water.

3.2 Health Endpoint

For pharmaceuticals used for veterinary purposes, the health endpoint was the ADI. The health endpoint for pharmaceuticals used solely for humans was the s-ADI, which was the lowest daily oral therapeutic dose for an adult, divided by safety factors ranging from 1,000 to 10,000. A safety factor of 1,000 was applied to the lowest daily oral therapeutic dose, which consisted of a 10-fold factor for sensitive humans, a 10-fold factor for infants and children, and a 10-fold factor for the lowest daily therapeutic dose not being a no effect level. An additional 10-fold factor was applied for cytotoxic drugs, due to the higher level of toxicity associated with these compounds, and another factor of 10 was applied for hormonally active steroids, on the grounds that potential effects on hormonal function and fertility is unwanted in those not being treated.

3.3 Data Sources

ADIs established by the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives, the Australian Therapeutic Goods Administration, and the European Medicines Agency were applied for those pharmaceuticals used for veterinary purposes, and the lowest daily oral therapeutic dose was applied for pharmaceuticals used solely for humans. *(The paper does not state the source of the lowest daily oral therapeutic doses).*

3.4 Occurrence Data

The highest concentrations measured in secondary treated effluent were compared with the drinking water guidelines.

3.5 Key Distinctions Relevant to Prioritization

This approach uses already established ADIs or lowest daily oral therapeutic doses. The approach uses varying safety factors depending on some of the characteristics of the pharmaceutical. It does not take into account different mechanisms of action of the pharmaceuticals (e.g., carcinogenic effects).

4. Report on Pharmaceuticals and Personal Care Products in Illinois Drinking Water, IL EPA, June 2008

4.1 Summary of Approach

The IL EPA developed an approach to screen for potential human health effects from pharmaceuticals and personal care products (PPCPs) at concentrations found in drinking water. This approach was used to develop these screening levels because no guidelines or established standards exist for these chemicals, and often the toxicological information pertaining to these agents is confidential and not readily accessible. This approach was based on the *Australian Guidelines for Water Recycling* (2008) (see above).

The IL EPA utilized the Lowest Daily Therapeutic Doses (LDTDs) and a safety factor of 10,000 to develop their own Acceptable Daily Intakes (ADIs). The maximum concentrations of PPCPs in drinking water that would not result in consumption of PPCPs at concentrations that exceed their ADIs were then developed utilizing the following calculation:

Criterion (ng/L) = [(ADI x BW)/IR] x RSC, where

ADI = Acceptable Daily Intake (ng/kg/d)
BW = body weight (kg)
IR = drinking water ingestion rate (L/d)
RSC = relative source contribution (% of daily intake attributable to drinking water)

The IL EPA approach relied on a BW of 10 kg to be protective of children, an IR of 1 L/d, and an RSC of 100%, because it was assumed that there were no additional sources of exposure, unless an individual had been prescribed the drug. This resulted in screening levels that were at least 3.5 times more conservative than the Australian DWGs, which were based on a BW of 70 kg and an IR of 2 L/d.

The final step in the IL EPA approach was to compare the detected concentrations of PPCPs in drinking water to the DW criterion concentration, and calculate a Hazard Index (HI) for each chemical. Ratios of actual to acceptable exposure concentrations, the HI ratios, are acceptable if the HI does not exceed 1.0.

4.2 Health Endpoint

The ADI is an estimate of the daily amount of a chemical that can be ingested for a life time and is considered safe. In this approach, the ADI was calculated as the LDTD divided by four safety factors, each with a value of 10, and then divided by an assumed body weight of 10 kg.

The safety factor of 10,000 in their screening process took into account extrapolation from a lowest observed effect level (LOEL) to a no observed effect level (NOEL), intrahuman variability (adults vs. children), short-term vs. long-term effects, and therapeutic use vs. non-therapeutic need.

4.3 Data Sources

LDTDs were utilized for the chemicals of concern. *(The paper does not state the source of the LDTDs).*

4.4 Occurrence Data

Water supplies from Chicago and five surrounding communities were sampled. Chicago was selected due to its dense population, and the fact that most of the residents purchase water from the city. The four other communities were selected since they were located downstream, close to a wastewater treatment plant discharge. Samples were collected by agency staff and the water samples were analyzed using methods certified for pharmaceutically active compounds.

4.5 Key Distinctions Relevant to Prioritization

This approach is based on the utilization of ADIs, calculated from LDTDs, and incorporating a total safety factor of 10,000. However, no scientific rationale is provided for the use of the additional safety factor for "therapeutic use vs. not therapeutic need" that results in a total safety factor of 10,000. A margin of safety is determined, and in this case was estimated to be at least 333, and usually much higher.

5. Risks to Aquatic Organisms Posed by Human Pharmaceutical Use, Kostich and Lazorchak, 2008.

5.1 Summary of Approach

In this publication, the authors present a potency-normalized concentration addition model based on interaction between Active Pharmaceutical Ingredients (APIs) with common modes of action (MOA) (i.e. a potential mixtures risk). The APIs were distributed between narrowly and broadly categorized MOA classes based on descriptions available in the prescribing information. The classes were determined using the World Health Organization's Anatomical Therapeutic Chemical classification system

(http://www.whocc.no/atcddd/indexdatabase/). API exposures that belong to a particular MOA category were expressed as the number of days of water consumption required to ingest what would be equivalent to a single minimum daily therapeutic dose. The only routes of exposure that were considered in the study were either consumption of water or contact with water. The authors also assumed that the critical rate of exposure that induces significant human effects was similar to the minimum therapeutic dose rate. The marketing data was divided by the therapeutic dose to normalize the potency of agents studied.

5.2 Health Endpoint

No health endpoint is presented in the document, although the minimum therapeutic dose was used in the calculation of the exposure rates (the number of days of water consumption required to ingest the equivalent of one minimum daily therapeutic dose of a pharmaceutical). The minimum therapeutic dose values used in the calculations are presented in the paper as supplementary data.

5.3 Data Sources

Data were indirectly obtained from marketing and pharmacological data. A total of 371 active pharmaceutical ingredients dispensed in the United States (U.S.) in 2004 were estimated from marketing data.

5.4 Occurrence Data

No actual occurrence data were used in this study, although pharmaceutical marketing data were used to calculate predicted wastewater concentrations.

5.5 Key Distinctions Relevant to Prioritization

This approach may be a way of screening large groups of agents that may be applicable to metabolites, as well as mixtures of agents. Occurrence data was not used and a dosimetric approach (i.e. the days of water consumption) was used to reach a minimum therapeutic dose.

6. Human Pharmaceuticals in U.S. Surface Waters: A Human Health Risk Assessment, Schwab et al., 2005.

6.1 Summary of Approach

In this publication the author presents a predicted no effect concentration (PNEC) approach to assess human health risks from exposures to active pharmaceutical ingredients (API) in drinking water and via fish ingestion. The PNEC was derived using acceptable daily intake (ADI) values. The ADIs were combined with standard assumptions with regards to potential exposure from drinking water and fish consumption

to derive a PNEC for each API. The PNEC is defined as a "concentration in water at or below which no adverse human health effects are expected." The author derived three categories of PNECs; one for drinking water, the second for water from which potential exposures are limited to fish consumption, and a third for water used both as a drinking water source and as a source of fish consumption. PNECs were derived both for adults and children using equations that are consistent with those used by the U.S. Environmental Protection Agency (U.S. EPA) for developing concentration limits to protect against threshold-type effects, such as the Ambient Water Quality Criteria (AWQC) for the protection of human health or maximum contaminant levels. The equations used are as follows:

1) $$PNEC_{DW} = \frac{1000 \times ADI \times BW \times AT}{IngR_{DW} \times EF \times ED}$$

2) $$PNEC_{F} = \frac{1000 \times ADI \times BW \times AT}{BCF \times IngR_{F} \times EF \times ED}$$

3) $$PNEC_{DW+F} = \frac{1000 \times ADI \times BW \times AT}{(IngR_{DW} + BCF + IngR_{F}) \times EF \times ED}$$

Where:

$PNEC_{DW}$ = PNEC in drinking water, ng/L
$PNEC_{F}$ = PNEC via fish consumption, ng/L
$PNEC_{DW+F}$ = PNEC in drinking water and via fish consumption, ng/L
ADI = Acceptable Daily Intake, µg/kg/day
BW = Body weight of child or adult, kg
AT = Averaging time, day
BCF = Bioconcentration factor for fish, L/kg
$IngR_{DW}$ = Child or adult water consumption, L/person/day
$IngR_{F}$ = Child or adult fish consumption, kg/person/day
EF = Exposure frequency, days/year
ED = Exposure duration, years

The PNECs were then compared to measured environmental concentrations (MECs) from published literature, and to maximum predicted environmental concentrations (PECs), which were estimated using the P*h*ATE model.

6.2 Health Endpoint

The ADI, which was estimated using an API's lowest therapeutic dose, no observed effect levels from animal studies, or human sensitivity to intestinal microflora, was used as the health endpoint in this publication.

6.3 Data Sources

This study used 26 APIs, both prescription drugs and non-prescription drugs. These 26 APIs were extracted by the authors from a publication by Kolpin et al. (2002). The lowest therapeutic doses were obtained from FDA-approved labeling, FDA summary basis of approved documents, material safety data sheets, published information on the substance, standard drug information resources (e.g., Goodman and Gilman), subscription databases, or the manufacturers of the substances.

6.4 Occurrence Data

Concentrations of pharmaceuticals in U.S. surface waters, as reported by Kolpin et al. (2002), were used as a conservative estimate of the concentration of pharmaceuticals in drinking water. This was supplemented by searching the peer-reviewed literature and running the P*h*ATE model (Anderson et al. 2004).

6.5 Key Distinctions Relevant to Prioritization

Aspects of this approach include the use of an ADI determined by the lowest therapeutic dose for an API, which in turn allows the derivation of the PNEC; the use of EPA default exposure factors for adults and children; and perhaps the availability of data on the APIs from various sources.

EPA's Current Activities and Research

EPA is responding to the issue of pharmaceuticals in water using the following four-pronged strategy aimed at:

- improving science;
- improving public understanding;
- identifying partnership and stewardship opportunities; and
- taking regulatory action when appropriate.

EPA is working in three main areas to improve the science concerning pharmaceuticals in water: methods development, occurrence studies, and research. Methods development consists of the development of analytical methods to reliably detect pharmaceuticals in water, wastewater, and biosolids. EPA recently developed methods to analyze approximately 100 pharmaceuticals, personal care products, steroids, and hormones in wastewater and biosolids.

Occurrence studies are needed to better understand the sources and occurrence of pharmaceuticals in water and other sources. EPA is currently investigating and funding a number of studies evaluating the occurrence of pharmaceuticals in wastewater, fish tissues, and biosolids. EPA's Office of Research and Development is engaged in a large number of research projects associated with exposure pathways, health, and aquatic life effects of pharmaceuticals in water. These research projects cover a broad range of areas,

such as treatment and removal technologies, molecular indicators, ecological effects, and persistence in the environment.

EPA is working to improve public understanding about pharmaceuticals in water by developing a website focusing specifically on this issue: http://www.epa.gov/waterscience/ppcp/. EPA is collaborating with Federal, State, and local agencies, and industry and others to build partnerships and address issues regarding pharmaceuticals in water. Examples include partnering with the White House Office on National Drug Control Policy to issue drug disposal guidelines in 2007 to help reduce the quantities of pharmaceuticals entering our nation's waterways, and participating in the World Health Organization Task Force on pharmaceuticals and personal care products in drinking water. EPA has also been working on the development of take-back programs that would allow consumers to properly dispose of unwanted or unused pharmaceuticals.

EPA will use existing regulatory tools, when appropriate, to address pharmaceuticals in water. For example, EPA recently published and is seeking comment on the draft Third Drinking Water Contaminant Candidate List (CCL3) (USEPA 2008). The draft CCL3 consists of 104 contaminants that may require regulation under the Safe Drinking Water Act. EPA used a multi-step process to identify contaminants for inclusion in the draft CCL3, which involved:

- identifying a broad range of potential drinking water contaminants
- applying screening criteria to these contaminants to identify those that should be evaluated further (the preliminary CCL) based on a contaminant's potential to occur in public water systems and the potential for public health concern
- identifying contaminants from the preliminary CCL to include on the CCL3 based on more detailed evaluation of occurrence and health effects
- using expert judgment, and incorporating public input and expert review in the process.

EPA identified 287 pharmaceuticals in its initial listing of a broad range of potential drinking water contaminants in the draft CCL3 that had data to indicate a potential to occur in drinking water and health effects. The health data used was primarily from the FDA's Database on Maximum Recommended Daily Doses and the occurrence data was from the U.S. Geological Survey's Toxic Substances Hydrology Program's National Reconnaissance of Emerging Contaminants, and TRI and high production volume chemical data. Further screening moved approximately 10 percent of the pharmaceuticals to the preliminary CCL. Only one of the pharmaceuticals, nitroglycerin, was included in the draft CCL3. EPA is currently reviewing public comment on the draft CCL3.

Summary

EPA is working in a number of areas to address pharmaceuticals in drinking water. One of these areas is screening and prioritizing the potential human health risk from low levels of pharmaceuticals in drinking water. This white paper summarizes six articles that address this issue. Five of these articles present approaches for screening and prioritizing the risk or hazard from pharmaceuticals in drinking water. The sixth article (GWRC, 2008) does not present a risk assessment approach; it is a description of a method that was used to develop a priority list of pharmaceuticals in drinking water.

Four of the articles, (DWI, 2007; Australian Guidelines, 2008, IL EPA, 2008, and Schwab et al., 2005) use a hazard index type of approach to assess the hazard from pharmaceuticals in drinking water. This approach consists of comparing the measured or modeled environmental concentrations of pharmaceuticals in drinking water with a health screening level. The farther apart the two values are, the lower the risk. This comparison may be expressed as a margin of exposure (DWI, 2007, Australian Guidelines, 2008), a hazard index (IL EPA, 2008) or a ratio (Schwab et al. 2005).

The fifth article (Kostich and Lazorchak, 2008) presents a different approach in which the number of days of water consumption required to ingest the pharmacological activity equivalent to one minimum therapeutic human daily dose is calculated. In addition, this paper presented an approach to evaluate the potential effects on aquatic organisms from pharmaceuticals in drinking water.

The health dose metric used in the DWI article is the minimum therapeutic dose without a safety factor (DWI, 2007). This is similar to the IL EPA approach and the Australian Guidelines, which both used the lowest daily therapeutic dose (LDTD) in their calculations; however, IL EPA divided the LDTDs by a safety factor of 10,000, while the Australian Guidelines divided the LDTDs by safety factors ranging from 1,000 to 10,000 (IL EPA, 2008, Australian Guidelines, 2008). Schwab et al. (2005) also used the lowest therapeutic dose divided by a safety factor, but they used varying safety factors depending on the adequacy of the data. The minimum therapeutic doses in all four approaches were obtained from pharmaceutical databases or from published literature.

All of the articles used different types of occurrence data. DWI (2007) and Schwab et al. (2005) both used models to calculate the estimated concentrations of pharmaceuticals in drinking water. IL EPA (2008) sampled water supplies in Chicago and the surrounding areas to obtain analytical drinking water data. Kostich and Lazorchak (2008) used pharmaceutical marketing data to calculate predicted wastewater concentrations, which were used to calculate the exposure rates, while the Australian Guidelines (2008) used the highest concentrations measured in secondary treated effluent.

Each of the articles presented approaches in which the results showed little to no risk from pharmaceuticals in drinking water; however, none of the approaches considered exposure of different life stages, other than the use of the 10 kg child in the calculations. In addition, none of the approaches made use of the Food and Drug Administration's

extensive database on adverse drug reactions. This data could be used to modify the uncertainty factor that is applied to each pharmaceutical. An additional issue is that only one of the approaches (Australian Guidelines, 2008) addressed carcinogenic or chemotherapeutic drugs.

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