

EXECUTIVE SUMMARY

INTRODUCTION

Analytical technology has made it possible to detect and quantify nearly any compound known to humankind at diminishingly minute concentrations in water. Although the earliest reports of pharmaceuticals and steroid hormones in water date back nearly four decades, it is only within the past decade that the subject has come to the forefront of scientific and public attention. Today we know definitively that trace levels of pharmaceuticals, potential endocrine disrupting compounds (EDCs), and other emerging contaminants do occur in source water, and to a lesser extent, in finished drinking water. Based on research thus far, it appears that many conventional and advanced treatment processes will greatly reduce the concentrations of these compounds. Nevertheless, considering the continued advancements in analytical technologies, today's non-detectable contaminants will be tomorrow's emerging contaminants. If presence/absence becomes our litmus test for risk and subsequent actions, treatment technology will be increasingly, and perhaps unnecessarily, costly and energy intensive. This is an especially important consideration due to the energy cost and greenhouse gas emissions of advanced treatment. For these reasons, it is of utmost importance to determine human health-based screening levels from which meaningful treatment goals and analytical detection limits can be established. This study provides critical information regarding the occurrence and risk assessment for pharmaceuticals and potential EDCs in drinking water. The information in this report will allow utilities and regulators to begin to make informed decisions regarding the relevance of trace pharmaceuticals and EDCs.

STUDY OBJECTIVES

1. Determine a representative group of indicator compounds based on toxicity, treatability, occurrence, structure, and analytical capabilities.
2. Develop robust analytical protocols for selected indicator compounds that provide accurate and precise identification and quantification in drinking water and recycle water matrices.
3. Determine the occurrence of selected pharmaceuticals and potential EDCs in a diversity of U.S. drinking waters.
4. Evaluate the strengths and weaknesses of using an *in vitro* bioassay for measuring estrogenicity in water and various food/beverage items.
5. Conduct risk analysis for selected pharmaceuticals and potential EDCs.
6. Develop communication tools related to pharmaceuticals and EDCs in drinking water.

PROJECT APPROACH

The initial phase of this study involved a thorough review of published literature and databases to determine a representative group of indicator compounds. Of the thousands of

potential candidates, 62 chemicals were chosen for further evaluation based upon likelihood of occurrence, production volume, toxicity, and analytical capability. This suite of chemicals included 20 pharmaceuticals (and active metabolites), 26 potential EDCs, five steroid hormones, and 11 phytoestrogens (natural estrogens from plants). Robust analytical methods using both liquid chromatography with tandem mass spectrometry (LC-MS/MS) and gas chromatography with tandem mass spectrometry (GC-MS/MS) were developed specifically for this project. The resulting method reporting limits (MRL) ranged from 0.2 to 120 nanograms per liter (ng/L, or parts per trillion) depending on instrumental sensitivity and frequency of occurrence in blanks. An *in vitro* cellular bioassay was used to determine the cumulative estrogenicity of compounds extracted from water samples, expressed as estradiol equivalents (EEq). The MRL of the bioassay was 0.16 ng/L, based upon the sensitivity of the assay, the volume of water extracted, and from the laboratory and field blank responses. Water samples were collected from 20 geographically diverse sites within the U.S. In total, more than 300 samples were evaluated during this investigation. Due to the high level of rigor needed for the risk assessment, more than 100 blanks and spiked water samples were analyzed in the course of this study.

To provide context for the EEq values determined in water samples, a series of food/beverage items were also evaluated. These items included vegetable juice, tea, coffee, beer, bottled water, soy sauce, milk, and baby formula. Food/beverage products were also analyzed for the suite of 62 target analytes. The food/beverage items were included in this study only to provide a reference point for relative source contributions. This was not a formal statistically-based market basket study and only a few of each type of product were evaluated.

Risk evaluations assuming exposure through drinking water were conducted for 16 pharmaceuticals, 10 potential EDCs, and three steroid hormones. Acceptable daily intakes (ADIs; also called “screening values”) or reference doses (RfDs) were calculated using methods consistent with EPA approaches for determining levels of exposure to environmental contaminants that are not likely to be associated with adverse health effects. A cautious, conservative approach was taken in the process of developing the ADI values. These levels are commonly defined as the amount of a chemical a person (including sensitive subgroups or subpopulations) can be exposed to on a daily basis over an extended period of time (usually a lifetime) without suffering a harmful effect. Sensitive subgroups include those with chronic diseases, the elderly, children, pregnant women, and others.

For effects other than carcinogenicity, ADIs were derived by dividing the highest dose at which an effect was not observed (the “no observed adverse effect level” or NOAEL) or the lowest dose at which an effect was observed (the “lowest observed adverse effect level” or LOAEL) in animal or human toxicity studies by uncertainty factors (UFs) to account for extrapolation to potentially sensitive populations. Toxicity data were gathered through bibliographic searches, from information submitted to the U.S. Food and Drug Administration (FDA) as part of the drug approval process, or from drug labels or monographs. For analytes showing positive evidence of carcinogenicity in high dose animal studies and data on tumor incidence per dose level, a linear extrapolation model was used to predict the tumorigenic response at low doses. For analytes with reported evidence of carcinogenicity in animals but no available tumor incidence data, a “virtually safe dose” corresponding to a cancer risk of one in a million was estimated.

For some target EDCs, RfDs or ADIs have been previously established by regulatory agencies such as EPA and some have existing water quality criteria such as maximum contaminant levels (MCLs). However, most of these criteria were established before testing for

endocrine mediated effects became standardized, and are based on non-endocrine toxicity endpoints. For the target EDCs, endocrine-mediated ADIs were established by identifying NOAELs and LOAELs for effects mediated through estrogenic, androgenic, or thyroid-related modes of action (MOAs). Emphasis was placed on data published since the establishment of the existing RfDs or ADIs. ADIs that account for endocrine mediated effects were estimated using methods similar to those described for non-carcinogens.

ADIs were converted to drinking water equivalent levels (DWELs) in units of micrograms per liter ($\mu\text{g/L}$, or parts per billion), by multiplying the ADI by an assumed body weight (70 kilograms, the EPA default adult body weight) and dividing by an average daily drinking water ingestion rate (two liters per day). For carcinogens, DWELs assume that a *de minimis* lifetime excess cancer risk of one additional cancer per one million lifetime exposures (10^{-6}) is acceptable.

RESULTS

Of the 62 target compounds investigated, only three were consistently (>50% frequency) detected in U.S. drinking water despite ng/L (parts per trillion) reporting limits. The herbicide atrazine exhibited the highest frequency of occurrence (83%) followed by the anti-anxiety pharmaceutical meprobamate (78%) and the anti-epileptic pharmaceutical phenytoin (56%). Atrazine also had the highest concentration detected at 870 ng/L, followed by the flame retardants TCPP and TCEP at 510 and 470 ng/L, respectively. It is important to note that the maximum detection of atrazine was less than $1/3^{\text{rd}}$ of the federal drinking water regulation of 3,000 ng/L. Only 11 of the 62 target compounds were consistently detected (>20% frequency) in finished drinking water. In order to gain perspective, consider that of these 11 compounds, only nine would have been detected using an MRL of 10 ng/L and only three would have been detected using an MRL of 100 ng/L. If the MRLs would have been one part per billion (1,000 ng/L), none of the target analytes would have been detected in this study. Again, the point is raised that what is detected is a direct function of how low the analytical method can measure. Therefore, as analytical procedures become progressively more sensitive, water utilities should expect that more pharmaceuticals and potential EDCs will be detected. Advanced treatment processes may provide initial results in lowering concentrations to non-detectable levels; however, as analytical methods are developed with lower MRLs, non-detectable compounds will likely again be detected. Even with current methodology and reporting limits, none of the pharmaceuticals tested in this study were detected in finished drinking water above the calculated health risk thresholds.

The maximum-detected concentrations in finished and distribution drinking water for each of the target pharmaceuticals were used to calculate drinking water equivalent levels (DWELs). The maximum-detected concentrations used are the single highest discrete sample concentrations observed in this study providing a conservative “worst-case” scenario approach. Using this approach, none of the pharmaceuticals detected in drinking water exceeded their corresponding ADI. Nine of the pharmaceutical target compounds were detected in finished drinking water. Two pharmaceutical compounds (norfluoxetine and risperidone) were also detected in distribution drinking water. The remaining nine pharmaceutical target compounds were not detected in either finished or distribution drinking water at the method reporting limits. Four compounds that were detected in either finished or distribution water (carbamazepine, gemfibrozil, phenytoin and risperidone) show some evidence of carcinogenicity in animal

studies, and calculated ADIs and DWELs are based on cancer endpoints. Of the pharmaceuticals that were detected, three compounds (the two antibiotics/antibacterials, sulfamethoxazole and triclosan, and the anti-anxiety agent meprobamate) have calculated DWELs greater than 200 µg/L and therefore appear to be of relatively low toxicity, although available toxicity data of sufficient quality to develop the acceptable daily intake (ADIs) were limited to three or fewer studies for sulfamethoxazole and meprobamate (see Appendix E). Minimum margins of safety, defined as the DWEL divided by the maximum-detected finished or distribution water concentration, were 6,000 for meprobamate, 6,000,000 for sulfamethoxazole and 2,200,000 for triclosan. The estimated potential hazard associated with exposure to the beta-blocker atenolol is also relatively low, with a DWEL of 70 µg/L and a minimum margin of safety 2,700. The margins of safety of three other detected compounds, diazepam (110,000), fluoxetine (41,000) and norfluoxetine (44,000), are also very large.

Using the same approach, the maximum detected drinking water concentrations of potential EDCs were compared to calculated DWELs. Only four of the 13 target EDCs were detected in finished drinking water at or above the method reporting limits. Using the worst-case approach described previously for determining the ADI and based upon the maximum drinking water concentration, none of the potential EDCs examined exceeded the calculated health risk threshold (i.e., DWEL). Atrazine has the lowest calculated DWEL, at 3 µg/L. The maximum detected concentration in finished drinking water was 1 µg/L, yielding a minimum margin of safety of three. Two compounds (bisphenol A and p-nonylphenol) have calculated endocrine-based DWELs greater than 200 µg/L and therefore appear to be of relatively low concern for endocrine-type toxicity based solely upon drinking water exposure. Minimum margins of safety for these compounds were 72,000 for bisphenol A and 16,000 for p-nonylphenol. The toxicity evaluation also indicates that the herbicide linuron is of relatively low concern for endocrine-mediated endpoints, with a calculated DWEL of 70 µg/L and minimum margin of safety of 8,400.

Estrogenicity as determined by the *in vitro* bioassay (E-screen) revealed that the vast majority of finished drinking waters were below the MRL. Only three finished drinking water samples from the entire study had estrogenicity greater than the reporting limit of 0.16 ng/L, with EEq values at 0.19, 0.20, and 0.77 ng/L. In comparison, several food and beverage items had far greater estrogenicity. For instance, vegetable juice had observed EEq values from 1.9 to 3.3 ng/L, while coffee ranged from 11 to 17 ng/L. Various brands of beer exhibited a broad range of results with EEq values ranging from 0.8 to 140 ng/L. The highest estrogenicity was observed in soy-based food and beverage items such as soy sauce (28 – 510 ng/L), soy baby formula (1,500 – 1,900 ng/L) and soy milk (1,900 – 4,200 ng/L). Results from estrogenicity testing of food products are provided simply as a comparative of the bioassay response and not as an indication of health risk. If a bioassay is to be used as a barometer for endocrine disrupting potential of drinking water, it is vital to understand how the assay responds to food and beverages we assume to be healthful.

RECOMMENDATIONS

Without question, the detection of pharmaceuticals and hormones in drinking water, even at extremely low concentrations, is likely to cause concern about the safety of water supplies. A number of factors could fuel this concern, such as the perception that people are being medicated unknowingly, the fact that many of the compounds originate from human waste, and the fact that

some of these chemicals could cause health effects including cancer and developmental effects. Because of this, it is critical that the levels of exposure be placed into proper context. The reality is that nearly any chemical known to man could be detected in water using the most modern and sensitive of analytical instrumentation. All water on earth is reused over the course of time. Pharmaceuticals, hormones, and other chemicals in trace quantities are, and will continue to be, detectable in water. To make wise use of our economic and natural resources, these emerging contaminants of concern must be considered through the same mechanisms that are used to regulate other water contaminants.

The analysis of ultra-trace (<0.000001 mg/L) organic contaminants in drinking water is costly and may not lead to significant benefits in protecting public health. Even the most advanced and costly water treatment processes will not be able to removal all contaminants to less than the detection limit of the most sensitive analytical procedures. Therefore, it is imperative that toxicological relevance be established and considered to place concentrations of the various compounds into the context of human health. For utilities that wish to know whether pharmaceuticals and potential EDCs are present in their water sources, it is recommended that they choose a limited set of indicator chemicals as opposed to large suites of compounds. From the data presented in this study, and previous AwwaRF studies (e.g., AwwaRF project 2758), it is suggested that appropriate pharmaceutical indicators include meprobamate, phenytoin, atenolol, and carbamazepine. For steroid hormones, it is recommended that estrone and progesterone are the most useful indicators as they have the highest occurrence levels in a number of studies. In terms of potential EDCs, it is difficult to access the most reliable indicators since no formal studies regarding which of these chemicals are capable of exerting endocrine impacts to humans at levels relevant to drinking water have been conducted. The U.S. EPA's Endocrine Disruptor Screening Program (EDSP) is underway and will determine which chemicals are of greatest risk for endocrine disruption to the environment and to human health. It is recommended that utilities use *in vitro* bioassays carefully. While the bioassays are capable of extreme sensitivity, the link between cellular bioassay response and impacts to human endocrine function has not been established. Therefore, the detection of *in vitro* estrogenicity does not imply human health risk, nor does the absence of estrogenicity promise safety. This study shows the fallibility of using *in vitro* estrogenicity alone in assessing endocrine disrupting potential, as some common dietary items contain far greater estrogenicity than impaired source waters. Certainly these food items are not considered a health risk. Considering that food items are not labeled, or often even tested, for emerging contaminants, it is difficult to argue that the choice of exposure from food is any less involuntary than would be exposure from tap water.

The evaluation of toxicological relevance provided here indicates that, although some pharmaceuticals and potential EDCs were detected in U.S. drinking waters, there is no evidence of human health risk from consumption of these waters. Furthermore, for the pharmaceuticals and potential EDCs detected in water, exposure to people through water is expected to be small compared to exposures to potentially hazardous compounds through prescription and non-prescription medications, food and beverages, occupational exposures, and residential activities (e.g., cleaning products, personal care products, hobby chemicals, pesticides). Moreover, the concentrations of some potential EDCs (e.g., plasticizers) are orders of magnitude greater in food products than in drinking waters, which may negate any appreciable gains achieved by advanced water treatment in attempts to minimization of human exposure.

It is recommended that utilities establish open communications within their organizations and to the public. Given the sensitivity of analytic detection instrumentation, utilities must try to

help the public and key stakeholders understand that the presence of a compound in trace concentrations does not necessarily represent a health risk. Conveying risks related to this class of contaminants is conceptually no different than communicating with the public about the presence of other contaminants detected in water supplies. Information such as ADI or DWEL is critical to helping utilities make the necessary comparisons to put this issue in context. Utilities in the U.S. should stay abreast of developments within the federal and state regulatory agencies.

The study presented here is certainly not all inclusive or entirely comprehensive; however, it is intended to catalyze discussions and collaboration on additional needed studies among the water industry, regulatory agencies, and the public.

From this study, we recommend utilities consider the following points in emerging contaminant programs:

1. If monitoring is desired, consider a limited subset of indicator compounds that occur at higher concentrations and frequencies.
2. For monitoring programs, increase the frequency of blanks, replicates, spikes, and other QA/QC measures due to higher variability in ultra-trace methods.
3. Be sure that a part of any emerging contaminant program focuses on understanding what laboratory data mean from a human health standpoint.
4. Consider a strategic plan to understand which chemicals are of greatest current concern based on occurrence and potential health impact, and which ones may be on the horizon.
5. Be prepared to communicate the information obtained from monitoring studies and to help the public understand what the data mean.
6. Remain abreast of developments within local and federal regulatory agencies and participate as stakeholders whenever possible.

Follow the research in this area of emerging concern, and communicate key findings as they are developed. This should include continued addressing of emerging contaminants in appropriate meetings and conferences.