PUBLIC HEALTH RESEARCH ON CECs

Overview of Public Health Research on CECs

The term Contaminants of Emerging Concern (CECs) is broadly defined to include a variety of unregulated chemicals that have been detected in the environment and whose ecological or human health effects are not fully known. One of the most common questions is whether CECs have the potential to cause adverse human health effects at the concentrations that are detected in the environment. Screening level risk assessments have been conducted to address this question based on the current state of knowledge. Meanwhile, public health researchers continue to advance the state of knowledge by studying individual CECs or classes of similar CECs. Toxicity and exposure criteria are currently being developed to facilitate a systematic, consistent, and efficient evaluation of potential human health effects of specific CECs or CEC groups. Several screening level risk assessment studies are briefly summarized below, as well as a discussion of ongoing public health research associated with two examples of CEC classes, disinfection byproducts (DBPs), and endocrine disrupting compounds (EDCs).

Screening Level Risk Assessments

A screening level risk assessment was recently funded by the Water Research Foundation (formerly known as the Awwa Research Foundation) (Snyder et al., 2008). The study addressed the toxicological relevance of EDCs and pharmaceuticals detected in drinking water, and developed human health-based screening levels that could be used to inform treatment goals and analytical detection limits. Acceptable Daily Intakes (ADI) were derived using standard risk assessment methods. ADIs or reference doses (RfDs) are commonly defined as the amount of a chemical a person can be exposed to on a daily basis over an extended period of time (usually a lifetime) without suffering a harmful effect. ADIs were then converted to drinking water equivalent levels (DWELs), which can be directly compared to detected CEC concentrations. The evaluation concluded there was no evidence of human health risk from consuming water with concentrations of EDCs and pharmaceuticals typically detected in treated drinking water (Snyder et al., 2008). The study also showed that dietary exposure to estrogenic chemicals is far greater than the exposure to CECs from drinking water (Snyder et al., 2008). A similar conclusion was reached in a report titled *State of Knowledge of Endocrine Disruptors and Pharmaceuticals in Drinking Water* (Snyder et al., 2009).

Screening level human health risk assessment studies have also been conducted to assess the risks of CECs in potable and non-potable water reuse systems. A recent National Research Council (NRC) report on water reuse conducted a comparative analysis of potential health risks of two indirect potable reuse scenarios in the context of the risks of conventional drinking water supply (i.e., surface water that receives a small percentage of treated wastewater). The committee concluded that the risk from 24 selected chemicals in the two scenarios did not exceed the risk in common existing water supplies (NRC, 2012). A WateReuse Research Foundation study titled “Risk Assessment Study of PPCPs in Nonpotable Recycled Water to Support Public Review” (Kennedy et al., 2012) provided a quantitative human health risk assessment of exposure to CECs via non-potable recycled water. The authors concluded that CECs in recycled water pose much lower risks than other common exposure pathways. A third project examined potential human health risks related to the use of recycled water and associated exposure to trace CECs (Nellor and Soller, 2011). Quantitative risk assessments were conducted for two different groundwater recharge projects in Southern California based on chemicals that are currently regulated or are under regulatory consideration. “Safe” levels of exposure, i.e., screening level tolerable daily intakes (TDIs), were established for CECs in recycled water based on published toxicity information. CECs included prescription drugs, chemotherapy agents, illegal and over-the-counter drugs, veterinary pharmaceuticals, and personal care products. Finally, predictions of future CECs were made based on published literature, relative treatability, and knowledge contributed by multiple experts. Risk metrics to support communication efforts were also proposed (Nellor and Soller, 2011).

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Researchers have also applied screening methods to identify future CECs of potential concern in water reuse systems and establish research priorities (Cotruvo et al., 2010).

A recent Water Research Foundation study developed an alternative method to derive human health screening levels for PPCPs, hormonally-active compounds, and other CECs (Bruce and Pleus, 2011). Screening levels were developed based on minimum anticipated biological effect levels (MABELs) instead of no adverse effect levels (NOAELs) or lowest observed adverse effect levels (LOAEL). The MABEL is the lowest dose at which any measurable effects occur, whether adverse or not, and therefore can result in lower screening values. The MABEL approach provides a promising tool to incorporate increasingly sensitive pharmacological data into the development of screening levels based on scientific evidence rather than extrapolation modeling, thereby decreasing the uncertainty about the protectiveness of resulting screening levels (Bruce and Pleus, 2011). Other researchers have called for better defining the threshold of adverse effects so that preliminary screening values will not be overly conservative (Williams and Word, 2007).

Disinfection Byproducts Research

Disinfection byproducts (DBPs) in drinking water are an emerging and challenging public health issue and have been identified as a public health research priority for drinking water (Li, 2012). Several chlorinated and brominated DBPs including trihalomethanes (THMs) and haloacetic acids (HAAs) are regulated in drinking water on the basis of carcinogenicity. Although most regulatory attention has been focused on chlorinated compounds, brominated DBPs are typically more toxic than chlorinated DBPs and iodinated DBPs are more toxic than brominated DBPs (Plewa et al., 2010). Researchers from the University of North Carolina at Chapel Hill investigated whether exposure to THMs, including bromodichloromethane, HAAs, or other DBPs may be associated with an increased risk of spontaneous abortions (Savitz et al., 2005). Toxic nitrogenous DBPs such as haloacetonitriles (HANs) are another class of toxic emerging DBPs (Mueller et al., 2007). Other CECs such as N-nitrosodimethylamine (NDMA) and other nitrosamines are classified as probable carcinogens and may form during chloramine disinfection in addition to having industrial sources.

Existing epidemiologic studies on regulated DBPs have not revealed a plausible toxicological explanation for the relative risks of cancer and estimated adverse health effects. Unidentified DBPs and water contaminants may play important roles in explaining the observed health effects. DBPs have been an area of research for many years. Some of the more recent studies are being conducted by Canadian Water Network researchers, who are currently developing innovative analytical and toxicity-testing technologies for human health risk assessment to benefit both the water industry and regulatory agencies (Li, 2012). An ongoing Water Research Foundation project is screening regulated DBPs, DBP mixtures, and a few non-regulated emerging DBPs for endocrine activity using bioassays as well as chemical structure, genotoxicity, and/or occurrence (Weinberg, in progress). A project by Swenberg and La (2003) assessed and developed biomarkers that could be used in human studies to quantify internal dose and predict potential health effects from exposure to specific DBPs or families of DBPs. A recent publication from University of Iowa researchers demonstrated a proof of concept of novel formation pathways for iodinated and brominated DBPs as well as factors that influence reaction rates and yields (Valentine et al., 2011). More DBPs are likely to emerge in the future and have lower concentrations of concern compared with THMs and HAAs.

A summary of the state of science on the toxicology of chloramines and continued research needs is currently being funded by the Water Research Foundation (Pleus, in progress). Chloramines research needs were discussed at a workshop attended by an expert panel of scientists, regulators, and water utility professionals. Discussion focused on potential short-term human health impacts of exposure to monochloramines in drinking water, and scientific avenues to address data gaps. The final report for this project will also provide a summary of results from a literature review (Pleus, in progress). DBPs formed from various disinfectants were described by Bull et al. (2001) in a critical review of their occurrence and toxicity. Another study developed a framework for a risk-based DBP model to prioritize future DBP research based on structure-activity relationships (Bull et al., 2006).

EDCs Research

Although many chemicals are suspected or potential EDCs, only a relatively small subset of chemicals has been identified as EDCs. Past research has primarily focused on a relatively select group of man-made compounds including organochlorine pesticides, polychlorinated biphenyls (PCBs), bisphenol A (BPA), alkylphenols, and phthalates, as well as a group of naturally-occurring plant compounds known as the phytoestrogens. Toxicologists

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and endocrinologists have studied low-dose biological effects caused by specific EDCs, including BPA, phthalates, estradiol, and diethylstilbestrol (DES) (von Saal, 2011). These effects included changes in DNA methylation and gene expression, proliferation of prostate cancer cells, regulation of estrogen receptors, and insulin production (von Saal, 2011). Results suggest the possibility of no safe threshold for developmental effects caused by EDCs; additional research is needed.

During gestation and the first few years of life, tissues/organs are forming, the immune system is still developing, and epigenetic markers are being set (Weis, 2011). Epigenetics is the study of "chemical" modifications of DNA and chromatins that are heritable and affect gene transcription but not the DNA backbone. Epigenetics researchers are investigating how an individual can be sensitive to the effect of environmental chemicals (including EDCs) during specific periods of development. Environmental conditions during this time period can determine susceptibility to diseases later in life. Basic research funded by NIEHS is investigating potential fetal origins of adult diseases including coronary heart disease, hypertension, and Type II diabetes (Weis, 2011). Environmental exposure to chemicals, including EDCs, may play an important role in the etiology of diseases, along with nutrition, infection, and stress. Another area of active research is the cumulative impact of exposure to multiple EDCs.

One of the first steps in assessing the effects of EDCs is the development of appropriate methods. Researchers have used a suite of bioassays for laboratory screening for androgenic, thyroid, glucocorticoid, and progestagenic activity (Leusch, in progress) building on previous research. Through EPA's Computational Toxicology Research (CompTox) program, EPA has funded the development of rapid, automated chemical screening technologies (known as high-throughput screening) to evaluate drinking water contaminants for potential toxicity (EPA, 2012). CompTox is researching ways to better address the potential health risks of a large number of chemicals, of which only a small fraction has extensive toxicity testing information. CompTox is currently evaluating over 2,000 chemicals in more than 650 high-throughput assays. Compared with traditional chemical toxicity testing, CompTox is faster, cheaper, and does not rely on animal testing. Results will be used to identify and prioritize potentially toxic chemicals for further screening, potentially informing the Contaminant Candidate List (CCL) and future regulatory determinations. CompTox data on over 3,000 chemicals will be made publically available through databases such as ToxRefDB and ToxCastDB; currently databases contain data on approximately 474 chemicals (EPA, 2012).

Other CECs Research on Public Health

There are a variety of other public health projects on specific CECs. Researchers have conducted biomonitoring (Holzer et al., 2008) and epidemiologic (ATSDR, 2013) studies of human health effects of exposure to perfluorinated compounds in drinking water in Little Hocking, Ohio and in the Ohio River Valley, documenting higher blood serum concentrations of perfluorinated compounds as a result of discharges from a manufacturing facility. Several other examples of public health projects on specific CECs were presented at a recent Water Research Foundation workshop (Deeb and Sedlak, 2013). One project examined the cohort of women and their offspring who were exposed to polybrominated biphenyls (PBBs) as a contaminant of cattle feed in 1973. The Michigan Department of Community Health has followed this cohort for more than 20 years. The project ascertains the occurrence of a number of outcomes in women and their offspring in order to determine if there was evidence of endocrine disruption associated with PBB exposure (Marcus et al., 2004). Another study funded by NIEHS is currently researching prenatal methylmercury exposure in subsistence fishing communities around Lake Chapala, the largest watershed in Mexico, where preliminary studies have documented moderate and ongoing fish contamination (Trasande, in progress).

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