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A catalyst for integrating analytical biology, analytical chemistry, and engineering to improve drinking water safety: The groundbreaking work of Dr. Michael Plewa

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It is interesting how a random encounter can profoundly change your life. My random encounter was with a young graduate student from Michael Plewa's laboratory. The location was the 1999 American Chemical Society (ACS) Conference, where, following his talk, this promising researcher was being unfairly criticized by a well-established scientist. I disagreed with this scientist's criticism, and I encouraged the student how I thought his work was important. That random encounter (and rescue of the graduate student) prompted a 22+ year collaboration with Prof. Michael Plewa, one of the most innovative and thoughtful scientists I have ever known. In 2020, we celebrated the 20th anniversary of our two laboratories working together (and even had t-shirts made with mass spectra and mammalian cell toxicity dose-response curves!). This collaboration has been one of the most scientifically and personally fulfilling experiences in my life. Michael has a deep love for science and inspires all who meet him, especially those of us who are lucky enough to get to work with him.

Dr. Michael Plewa's impact on drinking water safety and disinfection byproducts (DBPs) cannot be overstated. Prior to his work in the DBP area, *there was almost no systematic quantitative toxicology work* beyond the regulated trihalomethanes (THMs), haloacetic acids (HAAs), and bromate (DBPs regulated by the U.S. EPA). Dr. Plewa put this area back on the map and helped scientists (like me) hone in on the more likely sources of the human health effects with his careful measurements and molecular mechanisms of the mammalian cell cytotoxicity and genotoxicity. This was important because hundreds of DBPs were being discovered in drinking water (Richardson, 1998; Richardson, 2011), but almost nothing was known about their toxicity. At the same time, a body of epidemiologic evidence was building for a number of human health effects for DBPs, particularly bladder cancer (Villanueva et al., 2004, 2007; Wang et al., 2007; Bove et al., 2007; Cantor et al., 2010; Costet et al., 2011).

Dr. Plewa's first paper on the cytotoxicity and genotoxicity of drinking water was published in 1981 (Heartlein et al., 1981), and he began his research on the toxicity of municipal wastewaters in 1982 (Hopke et al., 1982). Since that time, he has published >100 highly cited papers in this research area. Importantly, Michael developed and calibrated a mammalian cell chronic cytotoxicity assay and a genotoxicity assay based on immortalized, non-neoplastic Chinese hamster ovary (CHO) cells that represents the largest and most cited toxicity database on DBPs, drinking water, recycled water, and wastewater reuse (Wagner and Plewa, 2017). This CHO assay is now the gold standard for DBP toxicology. Working with analytical chemists, engineers, epidemiologists, toxicologists, and modelers, the data generated from Michael's laboratory contributed to studies that have an impact throughout the

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world. Not only has he generated this database, which includes nearly all major DBP chemical classes identified to-date, but his laboratory was also involved in important discoveries, which include the following:

- Demonstration that DBP toxicity, genotoxicity, and toxicogenomic analyses using assays from bacterial to mammalian to human cells is associated with the halogen leaving group (I > Br >> Cl). Iodinated DBPs (I-DBPs) are the most toxic across all DBP chemical classes (Yang et al., 2014; Plewa et al., 2004a; Plewa et al., 2009).
- A comprehensive review on DBP formation, toxicity, and carcinogenicity, which received a U.S. EPA Scientific and Technological Achievement Award and has been cited >2900 times (Richardson et al., 2007)
- Discovery that nitrogen-containing DBPs (N-DBPs) are more cytotoxic and genotoxic than carbonaceous DBPs (C-DBPs) (Plewa et al., 2004b, 2008a, 2008b; Plewa and Wagner 2009; Muellner et al., 2007)
- Identification of the molecular mechanisms of the cytotoxicity, genotoxicity, and toxicogenomics of haloacetic acids, haloacetonitriles, and haloacetamides (Plewa et al., 2004c; Cemeli et al., 2006; Plewa et al., 2008b; Komaki et al., 2009; Plewa et al., 2010; Attene-Ramos et al., 2010; Pals et al, 2011; Dad et al., 2013, Escobar-Hoyos et al., 2013; Pals et al., 2013; Komaki et al., 2014; Prochazka et al., 2015; Jeong et al., 2016; Pals et al., 2016; Komaki and Plewa 2017; Pals et al., 2017; Dad et al., 2018)
- First comparative toxicogenomic analyses of haloacetic acids, in which he employed a non-transformed human cell line (Muellner et al., 2010; Attene-Ramos et al., 2010; Plewa and Wagner 2012; Pals et al., 2013)
- The resolution of the major sources of toxicity in wastewaters from carbon sequestering processing plants and evaluation of different processes for carbon capture (Dai et al., 2012; Wagner et al., 2014)
- First study to integrate analytical chemistry, analytical biology, and epidemiology in the evaluation of drinking water from 11 European cities (the HiWATE study) (Jeong et al., 2012)
- Demonstration that haloacetonitrile DBPs not only induce direct cytotoxicity and genotoxicity, but also express delayed responses that affect cell cycle, leading to 8N cells and aneuploidy. This was the first such finding for a class of DBPs that may target nuclear topoisomerases (Komaki et al., 2014, 2017; Muellner et al., 2007).
- Identification of X-ray contrast agent-mediated I-DBP cytotoxicity and genotoxicity of disinfected water (Duirk et al., 2011; Wendel et al., 2014; Wendel et al., 2016; Jeong et al., 2017). This work was distinguished by a U.S. EPA Level 1 Scientific and Technological Achievement Award.
- Use of mammalian cell-based methods to evaluate the efficacy of advanced wastewater reuse processes (Zeng et al., 2016; Dong et al., 2016, 2017, 2019, 2021; Page et al., 2020; Lau et al., 2020)
- Identification of the forcing agents for drinking water toxicity (Allen et al., 2022)
- Demonstration that DBPs exert their toxicity in an additive manner (Lau et al., 2020)
- Development of a new *N*-acetyl-L-cysteine (NAC) thiol reactivity assay that can predict cytotoxicity of water samples. This assay is tremendously important because it is not cell-based and can be used by chemists (like myself) to assess potential cytotoxicity. This assay has been demonstrated effective for predicting cytotoxicity across a wide range of samples, including drinking water, surface waters, wastewater, and swimming pool water (Pals et al., 2016; Dong et al., 2017, 2018a, 2018b; Allen et al., 2021).
- Development of quantitative structure activity relationship (QSAR) models for cytotoxicity and genotoxicity of DBPs (Wei et al., 2020). Because of the robust DBP toxicity database developed by Dr. Plewa, these models can predict cytotoxicity and genotoxicity for novel DBPs.
- Development of a new procedure called "TIC-Tox" which allows determination of calculated cytotoxicity and genotoxicity. This procedure is already being widely used; this paper was published in 2017 and already has >100 citations (Plewa et al., 2017).
- Demonstration that DBPs can modulate horizontal gene transfer in bacteria that is linked to the acquisition of antibiotic resistance and virulence factors in wastewaters (Mantilla-Calderon et al., 2019)

Through these important advances, Dr. Plewa has provided invaluable tools for the research community, and he is helping to improve the safety of drinking water. Michael's research is highly creative, innovative, and interdisciplinary. In fact, as a biologist, Michael had a direct impact on the type of treatment introduced for a city's drinking water. Back in 2012, the city of Cincinnati was considering adding UV treatment to their drinking water treatment plant, to provide an additional barrier of protection against harmful pathogens. However, research demonstrated that UV could activate natural organic matter precursors, potentially producing harmful halonitromethane DBPs. Thus, the Greater Cincinnati Water Works reached out to Michael and asked him to evaluate the toxicity of various treatment options using UV, *in order to find the safest treatment process for consumers*. The company built a pilot plant, generated samples under Michael's direction, and he generated the analytical biological data that they used as part of their deliberations. This is the only time I have ever heard of a drinking water plant contacting a toxicologist for help in designing a new treatment system. It was unprecedented. Through Michael's careful quantitative toxicology experiments, he determined that installing the UV treatment after chloramine addition resulted in the lowest toxicity and safest drinking water. These results were published in *Environmental Science & Technology* (Plewa et al., 2012).

Michael also recently had a direct influence on regulatory policy. Due to his comprehensive analysis of >100 DBPs and the discovery of iodo-DBPs and N-DBPs having the highest toxicity, iodoacetic acids and haloacetonitriles were recently recommended to the U.S. EPA for inclusion in the next DBP regulations (as part of their current 6-year review of the DBP Rule).

Dr. Michael Plewa has been with the University of Illinois Urbana-Champaign for 48 years. Throughout his career, he has continued to work at the laboratory bench, advising and

learning from his undergraduate students, graduate students, and postdocs, in concert with his wife and colleague Dr. Elizabeth Wagner (a Phi Kappa Phi Distinguished Member). Michael was also a devoted teacher to his students and postdocs, and many other students and researchers outside his university, including my own students at the University of South Carolina. He also received university-wide and national teaching awards.

Michael is a model for excellence in research. His research is creative and innovative, and it tackles an important human health issue that has remained unsolved for more than 40 years. It is hard to beat Michael's contributions in the field of drinking water DBPs for the protection of human health. He leaves a tremendous legacy.

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