Expert Report of Jamie C. DeWitt, Ph.D.

For the plaintiff

In the matter of State of Minnesota v. 3M Company No. 27-cv-28862

Prepared for
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September 22, 2017

Filed in Fourth Judicial District Court
11/17/2017 7:13 PM
Hennepin County, MN

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List of Acronyms

ADME – absorption, distribution, metabolism, excretion

AFFF – aqueous film forming foams

APFO/C8 – ammonium perfluorooctanoate (the ammonium salt of PFOA)

ATSDR – Agency for Toxic Substances and Disease Registry

BMD – benchmark dose

CAS – Chemical Abstracts Service

CDC – Centers for Disease Control and Prevention

ECU – East Carolina University

EDCs – endocrine disrupting compounds

DWEL – drinking water equivalent level

GD – gestational day

GI – gastrointestinal

HAL – health advisory level or health advisory limit

HBV – health based value

HCDWG – Historical Control Data Working Group

HDL – high density lipoprotein

HED – human equivalent dose

HRI – health risk index

HRL – health risk level

IARC – International Agency for Research on Cancer

LD50 – lethal dose 50

LH – luteinizing hormone

LOAEL – Lowest Observed Adverse Effect Level

LOEL – Lowest Observed Effect Level

MDH – Minnesota Department of Health

MOA – mechanism of action

MoA – mode of action

MRL – Minimal Risk Level

N-EtFOSE – N-ethyl-N-(2-hydroxyethyl)perfluorooctylsulphonamide

NHANES – National Health and Nutrition Examination Survey

NHEERL – National Health and Environmental Effects Research Laboratory

NIEHS – National Institute of Environmental Health Sciences

NIH – National Institutes of Health

NJ DWOI – New Jersey Drinking Water Quality Institute

NOAEL – No Observed Adverse Effect Level

NOEL – No Observed Effect Level

NRC – National Research Council

NTP – National Toxicology Program

PFAA – perfluoroalkyl acids

PFASs – per- and polyfluoroalkyl substances

PFBA – perfluorobutanoic acid

PFBS – perfluorobutane sulfonate

PFC – perfluorinated chemicals

PFCA - perfluoroalkyl carboxylic acids

PFDA – perfluorodecanoic acid

PFDoA – perfluorododecanoic acid

PFDS – perfluorodecane sulfonate

PFESA – perfluoroethersulfonic acid

PFHpA – perfluroheptanoic acid

PFHxA – perfluorohexanoic acid

PFHxS – perfluorohexane sulfonic acid

PFNA – perfluorononanoic acid

PFOA – perfluorooctanoic acid/perfluorooctanoate

PFOS – perfluorooctane sulfonate/perflurooctanesulfonate

PFPeA – perfluoro-n-pentanoic acid

PFSA – perfluoroalkyl sulfonic acids

PFTA – perfluorotetradecanoic acid

PFUnA – perfluroundecanoate

PND – postnatal day

POD – point of departure

PPARs – peroxisome proliferator activated receptors (includes PPARα, PPARγ, and PPARβ/δ)

ppt – parts per trillion

PTU – propylthiouracil

RfD – reference dose

RSC – relative source contribution

SETAC – Society of Environmental Toxicology and Chemistry

SD – Sprague-Dawley rat, a strain of rat

SOT – Society of Toxicology

SNUR – Significant New Use Rules

STEM – Science, Technology, Engineering, and Mathematics

SWDA – Safe Water Drinking Act

T3 – triiodothyronine (a thyroid hormone)

T4 – thyroxine (a thyroid hormone)

TDAR – T cell-dependent antibody responses

TGFα - transforming growth factor alpha

TH – thyroid hormone(s)

TIAR – T cell-independent antibody responses

TSCA – Toxic Substances Control Act

TSH – thyroid stimulating hormone

U.S. EPA – United States Environmental Protection Agency

Vd – volume of distribution

WHO – World Health Organization

WY – Wyeth-14,643

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I. Introduction

I have been retained by attorneys for the State of Minnesota to provide expert opinion, from a toxicological perspective, regarding whether perfluorinated chemicals (PFCs), also known as per- and polyfluoroalkyl substances (PFASs) or highly fluorinated chemicals, pose a substantial present and potential hazard to human health.

II. Qualifications

I received Bachelor of Science (B.S.) degrees in Biology and Environmental Science from Michigan State University and Doctor of Philosophy (Ph.D.) degrees in Environmental Science and Neural Science from Indiana University-Bloomington. I completed postdoctoral training in Environmental and Ecotoxicology at Indiana University-Bloomington and in Immunotoxicology at the National Health and Environmental Effects Research Laboratory (NHEERL) at the United States Environmental Protection Agency (U.S. EPA) through a cooperative training agreement with the University of North Carolina at Chapel Hill. During my postdoctoral training at Indiana University, I evaluated the developmental cardiotoxicity of polychlorinated biphenyls and dioxins in wild passerine birds for a project funded by the United States Fish and Wildlife Service. At the U.S. EPA, I evaluated the immunotoxicity of organotin compounds used in polyvinylchloride pipes and of perfluorooctanoic acid (PFOA) as an emerging contaminant in drinking water supplies. The U.S. EPA Office of Water funded both of these projects. Of the eight papers that were published from my postdoctoral training at the U.S. EPA, three focused on PFOA, including a review of the immunotoxicity of PFOA. During this time, I also was a co-author on a paper concerning the developmental toxicity of perfluorooctane sulfonate (PFOS) in an avian model.

In 2008 I joined the faculty of the Department of Pharmacology and Toxicology at the Brody School of Medicine of East Carolina University (ECU) as a tenure-track Assistant Professor. In 2015 I was promoted to Associate Professor with tenure and currently serve in this capacity. I also am an adjunct Associate Professor in our Department of Public Health and am affiliated with the Harriet and John Wooten Laboratory for Alzheimer's and Neurodegenerative Disease Research at ECU. I divide my time among research and scholarly activities (approximately 65%), teaching (approximately 25%), and service (approximately 10%).

My didactic teaching activities are directed toward graduate (masters and doctoral), medical, dental, and physician assistant students. My graduate teaching activities include co-instruction in general and advanced toxicology, and I am the sole instructor for a biomedical statistics course. My lectures to medical, dental, and physician assistant students focus on endocrine pharmacology, and I deliver general toxicology lectures to medical and dental students, as well as additional lectures to dental students on management of poisoned patients. In addition to classroom teaching, I teach and mentor students in my laboratory. I have hosted 23 high school students and 20 undergraduate students through various programs since coming to ECU. I have mentored two masters and three doctoral students through completion of their degrees and am currently mentoring one doctoral student. My department limits faculty to no more than two doctoral students at a time, so I am at the maximum level of graduate student mentoring productivity for my department.

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I am actively engaged in professional, university, and community service activities. Of particular relevance to the topic of PFCs, I helped to write or review several of the documents that I rely on throughout this report, including those from the U.S. EPA, the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), and the U.S. National Toxicology Program (NTP). I was an external peer-reviewer for the U.S. EPA's health effect documents for PFOA and PFOS in 2014. This process required being nominated, selected by the firm hired by the U.S. EPA to oversee the peer-review process, responding to specific charge questions posed by the U.S. EPA, and providing additional feedback on the documents based on my peer-review. In 2014, I was part of the Mechanisms Subgroup for IARC Volume 110. I was invited by the Working Group for Volume 110 in 2013 as this volume included an assessment of the evidence on carcinogenicity of PFOA. As a member of the Mechanisms Subgroup, I helped to write the mechanisms sections for each of the five chemicals included in Volume 110 and as a member of the Working Group for Volume 110, I was a full participant at the Working Group meeting in 2014 when the volume was drafted. Between 2013 and 2016, I reviewed the protocol and the draft report on the immunotoxicity of PFOA and PFOS written by the NTP. Similar to my role as a peer-reviewer for the U.S. EPA health effects documents, I responded to specific charge questions and provided additional feedback based on my peer-review. I currently am reviewing another document concerning PFCs written by a U.S. federal government agency, but due to a confidentiality agreement, cannot disclose the specific information at this time. I also am part of a steering committee to organize a workshop in 2017 entitled "International Workshop Supporting the Dialogue Between Science and Policy on Per- and Polyfluoroalkyl Substances (PFASs)." These roles all highlight that I am regarded as an expert on the toxicity of PFCs by both the national and international scientific communities.

The Society of Toxicology (SOT) and the Society of Environmental Toxicology and Chemistry (SETAC) are professional societies for toxicologists and environmental chemists who are dedicated to the study of agents that may induce adverse health outcomes in humans and wildlife. I support these societies through annual membership fees at both the national and regional (North Carolina SOT and Carolinas SETAC) levels, by presenting data from my laboratory at meetings, and through participation in leadership activities. For example, from 2013-2014 I served as the President of the North Carolina SOT, I currently serve as the Vice-President of the Immunotoxicology Specialty Section of the SOT, and am on the Program Planning Committee for the 2017 annual SETAC meeting. I also serve my university through various committees such as the Institutional Animal Care and Use Committee (2013-present), the Coastal Maritime Council (2010-present), and the Brody Promotion and Tenure Committee (2015-present). I also am dedicated to science education in the community through Science, Technology, Engineering, and Mathematics (STEM) programs and by serving as a docent at a local museum dedicated to estuaries.

My research career has focused on synthetic compounds of industrial significance that are or might become environmental contaminants of concern. Beginning during my postdoctoral training at the U.S. EPA, the bulk of my research focus has been on PFCs, their immunotoxicity, and other associated toxicities. My first PFC publication from my training at the U.S. EPA was the first comprehensive dose-response assessment of the immunotoxicity of PFOA. Since coming to ECU in 2008, I have co-authored 11 primary research articles related to PFC toxicity (first or senior author of seven). These manuscripts include assessments of immunotoxicity, developmental immunotoxicity, developmental neurotoxicity, developmental cardiotoxicity,

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dosimetric anchoring, and epidemiological associations. I have co-authored three review articles and a commentary on PFC toxicity, two book chapters related to PFC immunotoxicity, and edited one of the first comprehensive texts on the toxicity of PFCs. My other publications concern toxicological effects of environmental contaminants, including their impact on human diseases. Overall, I have co-authored approximately 60 scientific publications.

Attached as Appendix A is a copy of my current *curriculum vitae*, which contains a complete list of my publications.

I have not served as an expert witness at trial or in deposition in the past four years.

III. Materials Relied On, Exhibits, Reservations

My expert opinion is based on peer-reviewed scientific literature, including my own scientific publications concerning PFC toxicity. Additionally, as much of the publicly available peer-reviewed scientific literature (including my own scientific publications concerning PFC toxicity) has been reviewed and assessed in what are termed "science assessments" by governmental and quasi-governmental scientific organizations, including, but not limited to, the U.S. EPA, the U.S. NTP, the IARC, and the U.S. Agency for Toxic Substances and Disease Registry (ATSDR), these assessments will be frequently referred to and relied upon. I cite various references in the text of my report and include a list of references in Appendix C. I also cite various studies run or sponsored by 3M, but I do not necessarily rely on all of them.

I may use as exhibits part or all of any of the papers or documents referenced in this report. I may also use as exhibits any graphs or tables drawn from data in any of those papers or documents, or any document considered or cited or relied upon by any other expert in this case.

The opinions expressed in this report are my own and are based on the papers, data, documents, and facts available to me at the time of writing. Should additional relevant information become available, I reserve the right to supplement this report. I also reserve the right to respond to any opinions by other experts in this matter, and to respond to any criticism or comment on my opinions.

IV. Compensation

I am being compensated at the rate of $250 per hour for my time. My compensation does not depend in any way on the content of my opinions or the outcome of this case.

V. Summary of Process

Faced with the general question presented, I undertook to do the following:

- Evaluate toxicity data for PFCs based on evidence from studies of experimental animal models involving exposure to PFCs by various routes and durations, including an assessment of the types of effects that occur, the doses/serum/tissue concentrations at which these effects occur, and the relevance of these effects to exposed humans.

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- Evaluate toxicity data for PFCs based on evidence from studies of primary cells, cell lines, and cells evaluated ex vivo, as well as studies done in silico to understand how PFCs interact with biomolecules, how PFCs may exert action on physiological processes, how PFCs partition within living organisms, how/how rapidly PFCs are excreted from living organisms, how to estimate PFC toxicity, and how these data are relevant to understanding effects of PFCs in exposed humans.

- Evaluate confirmatory findings in health effect data for PFCs based on evidence from epidemiological studies of humans exposed to PFCs occupationally or environmentally, by various routes and durations, at any concentration, including an assessment of the types of adverse health outcomes that have been reported to occur in humans following exposure to PFCs. This is not a detailed evaluation of the epidemiological studies, but rather is an assessment of the health effects that have been reported in association with PFC exposures from epidemiological studies, as a directional check on my opinions.

VI. Summary of Primary Opinions

It is my opinion, based on the weight of the toxicological evidence, with confirmation from certain epidemiological evidence, that PFCs pose a substantial present and potential hazard to human health.

The actual or potential toxicities resulting from exposure to PFCs that are supported by the greatest body of evidence are (in no particular order): cancer, developmental toxicity, and immunotoxicity. While there is evidence that other toxicities also likely follow exposure — including endocrine disruption, liver toxicity, and mammary gland development — the body of evidence for cancer, developmental toxicity, and immunotoxicity is particularly strong based on in vitro studies as well as studies of experimental animal models and epidemiological studies of exposed humans. My general opinion, stated above, is supported by extensive scientific work including assessments by the U.S. EPA, the NTP, the IARC, and the ATSDR. Based on these assessments and other relevant scientific studies, I hold in addition the following more specific primary opinions:

- As reflected in the 2016 IARC assessment, there is substantial evidence that PFOA is correlated with increased incidences of cancer, leading to likely adverse health outcomes in populations of exposed humans. By extension, other PFCs that induce similar toxicities and work through similar mechanisms, such as PFOS, perfluorobutanoic acid (PFBA), perfluorobutane sulfonate (PFBS), and perfluorohexane sulfonic acid (PFHxS), are also likely to induce cancer in exposed humans.

- As reflected in the assessment of PFOA and PFOS by the U.S. EPA, developing organisms are particularly sensitive to adverse health outcomes associated with exposure to these agents. There is substantial evidence that PFOA and PFOS are correlated with developmental toxicity effects, leading to likely adverse health outcomes in populations of exposed humans. By extension, other PFCs that induce similar toxicities and work through similar

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mechanisms, such as PFBA, PFBS, and PFHxS, are also likely to induce developmental toxicity.

- As reflected in the assessment of PFOA and PFOS by the U.S. NTP, the immune system is sensitive to adverse health outcomes associated with exposure to these agents. There is substantial evidence that PFOA and PFOS are correlated with immunotoxicity effects, leading to likely adverse health outcomes in populations of exposed humans. By extension, other PFCs that induce similar toxicities and work through similar mechanisms, such as PFBA, PFBS, and PFHxS, are also likely to induce immunotoxicity.

- As reflected in the assessment of PFCs by the ATSDR, certain highly exposed populations are at increased risk for adverse health outcomes associated with exposure to these agents. There is substantial evidence that in areas of high PFC exposure, either due to occupational exposures or by living near fluorochemical production and/or disposal facilities, there is particular hazard to human health, especially from effects on the liver and the immune system and on developing organisms.

The conclusions and observations in these assessments are supported by additional scientific work including my own extensive research experience with PFCs. This experience started with my postdoctoral research experience and continues to present day. Thus, my opinions also are supported by my knowledge of the published literature relating to PFCs that I have gained from my research endeavors, including writing and submitting scientific manuscripts, review articles, book chapters, commentaries, and grant proposals, from reviewing manuscripts concerning the toxicity of PFCs submitted to scientific journals for publication, from serving as a peer-reviewer or participant for the EPA, NTP, and IARC assessment documents, and from presenting research findings and scientific opinions about the toxicity of PFCs at various scientific meetings.

My opinions are based on a significant and growing body of evidence from experimental animal models, and are supported by epidemiological findings in humans, as described in more detail below.

VII. Background

VII.1 Brief Introduction to PFCs

PFCs are a subset of highly fluorinated, synthetic substances that contain one or more carbon atoms on which the hydrogen substituents have been replaced by fluorine atoms so that they contain a perfluoroalkyl moiety (Buck et al., 2011). PFCs are chemically and thermally stable and have both hydrophobic and lipophilic properties that make them commercially useful in surfactants and polymers (Buck et al., 2011). As a result of these characteristics, PFCs have been used in numerous applications, including processing aids for fluoropolymer manufacture, stain, grease, and water resistant coatings, and aqueous film forming foams (AFFFs) used in fire suppression activities (Buck et al., 2011). A consequence of their extensive use and resistance to degradation is their presence in the environment, including in tissues and blood of wildlife and humans. The US National Health and Nutrition Examination Survey (NHANES) reported

detectable concentrations of PFCs in the serum of 97% of surveyed individuals (Hu et al., 2016), indicating widespread human exposures.

PFCs are enormously diverse (Figure 1) and can be distinguished by chain length and functional group. Järnberg and van Bavel (2007) estimated from published literature that the total number of described synthetic PFCs may exceed 10,000 individual compounds. These compounds vary by the number of carbons ("chain-length"), functional groups present (i.e., carboxylic acid, sulfonic acid, hexanoic acid, etc.), and other physicochemical characteristics (Buck et al., 2011). Not all of these compounds are produced for industrial or consumer uses; some are breakdown products of precursor compounds (Houtz et al., 2013), but nonetheless can contribute to environmental concentrations and to human exposures. It has been estimated that approximately 3,000 PFCs have been intentionally produced (i.e., are not environmental breakdown products) and are being produced for various industrial purposes (Wang et al., 2017).

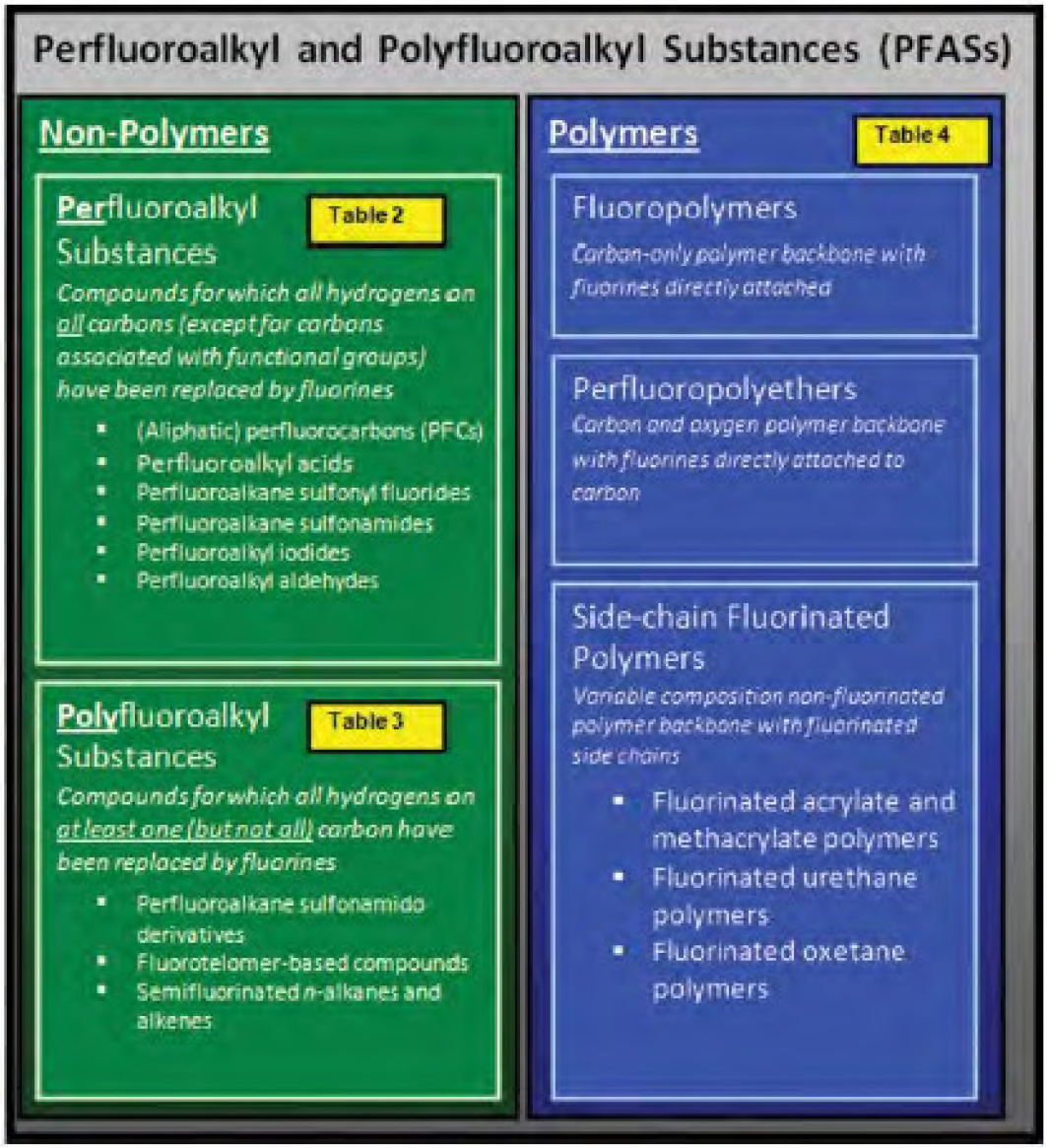

Figure 1. The general classification of PFCs as outlined by Buck et al. (2011).

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Both PFOA and PFOS are perfluoroalkyl acids (PFAAs), a subset of PFCs, and have eight carbons each. PFOA has a carboxylic acid (-COOH) functional group whereas PFOS has a sulfonic acid (-SO2OH) functional group. PFOA and PFOS thus differ by functional group (carboxylic versus sulfonic acid), but they have the same chain length, which is eight carbons. The U.S. EPA defines long-chain PFCs as perfluoroalkyl carboxylic acids (PFCAs) with eight or more carbons, which includes PFOA, as well as perfluoroalkane sulfonates (PFSAs) with six or more carbons, which includes PFOS and PFHxS (U.S. EPA, 2017b).

The bulk of toxicological research efforts concerning PFCs has focused on PFOA and PFOS, presumably because they were widely produced and prevalently used. These compounds were produced for decades within the US for the fluoropolymer and telomere industry. PFOS manufacture within the US was voluntarily discontinued by the 3M company in 2002 (U.S. EPA, 2017b) and PFOA was phased out between 2006 and 2015 by eight major U.S. manufacturers through the 2010/15 PFOA Stewardship Program (U.S. EPA, 2017b). However, these compounds are still being produced in other countries, are used in the US through existing stocks, and are present in imported items (U.S. EPA, 2017b). Additionally, PFOA and PFOS may result from the breakdown of other PFCs, generally termed as "precursor compounds" (Houtz et al., 2013).

Alternative compounds currently are being produced to replace PFOA, PFOS, and other long-chain compounds phased out by the 2010/15 PFOA Stewardship Program. Many of these fall under the Toxic Substances Control Act (TSCA) and the U.S. EPA has issued Significant New Use Rules (SNURs) for the manufacture and process of alternative compounds (U.S. EPA, 2017b). However, not all PFCs are likely to be subject to TSCA guidelines as some are byproducts of production that may find their way into the environment. For example, in a recent report issued by the U.S. EPA (U.S. EPA, 2017a) concerning PFCs in the Cape Fear Watershed of North Carolina, two perfluoroethersulfonic acids (PFESAs) containing seven carbons each were found in the river and were identified as byproducts of Nafion (another type of PFC fluoropolymer) production, presumably from a Chemours production facility located in Fayetteville, NC. These long-chain PFCs have Chemical Abstracts Service (CAS) numbers, which are unique numerical identifiers for chemical substances (CAS, 2017), but no publicly available peer-reviewed toxicological data are available for these PFCs (although toxicological data may exist as required under TSCA, it has not yet been published in the publicly available peer-reviewed literature). Concentrations reported by the U.S. EPA were up to 73,900 ng/L (U.S. EPA, 2017a); these concentrations are orders of magnitude above the health advisory level (HAL) issued by the U.S. EPA for combined water concentrations of PFOA and PFOS (U.S. EPA, 2016a,b). The presence of these byproducts indicates that long-chain PFCs beyond PFOA and PFOS exist in surface waters in the U.S.

The alternative compounds being produced to replace PFOA, PFOS, and other long-chain compounds are shorter chain PFCs (i.e., short-chain PFCs); such short-chain compounds include PFBA and PFBS, for example. Short-chain PFCs may also be formed from industrial synthesis, by metabolism, and/or by environmental degradation of other PFCs (Butenhoff, 2012b). Although short-chain PFCs are thought to persist in the environment, they are believed by some to be less bioaccumulative and less toxic in wildlife and humans than long-chain PFCs (U.S. EPA, 2017b). However, for many PFCs, especially the short-chain compounds, the number of publicly available peer-reviewed published studies are low compared to studies of PFOA and

PFOS. Beliefs about the low toxicity of short-chain compounds are based on a relatively small database compared to PFOA and PFOS and some of the other long-chain compounds; however, emerging publications indicate that many of these short-chain compounds elicit toxicities similar to the long-chain compounds, but along a different dose continuum. In a commentary on PFCs that I co-authored and that was published in 2017, one recommendation my co-authors and I had for improving the database on short-chain PFCs was to focus human biomonitoring studies on workers at production sites and populations downstream of production sites to account for the relatively short exposure history to these alternative PFCs (Wang et al., 2017). Additionally, we recommended that research is needed to understand PFCs as a group or as several subgroups to develop effect-oriented chemical and biological analyses and predictive models to evaluate the total burden of simultaneous exposure to multiple PFCs, as the current human exposure paradigm is to multiple PFCs, rather than single PFCs (Wang et al., 2017). The toxicological information generated for the long-chain compounds can therefore help to group alternatives and other less well-studied PFCs based on their toxicological profiles or putative toxicological profiles given similarities (i.e., physiochemical properties, persistence, bioaccumulation potential, exposure routes, etc.).

VII.2 Principles of Toxicology

Toxicology is the study of the adverse health effects of exogenous agents on living organisms. Toxicologists tend to classify themselves into sub-disciplines based on the types of potential adverse health outcomes they study. For example, immunotoxicologists evaluate how exogenous agents affect the immune system, neurotoxicologists assess effects of exogenous agents on behavior or neurotransmitter levels, and developmental toxicologists determine how exogenous agents impact developing organisms. These sub-disciplines can be further subdivided, but overall, regardless of sub-discipline, all toxicologists rely on the same key principles of toxicology to establish whether exposure to an exogenous agent is likely to cause harm to living organisms. While a detailed overview of these principles is beyond the scope of this report, some of them are outlined in detail in a basic primer of toxicology for judges and lawyers (Eaton, 2003). Briefly, determining if toxic effects are induced by exposure to exogenous agents requires understanding concepts of dose, toxicokinetic and toxicodynamic factors, the exposure scenario (route, duration, and frequency of exposure), the chemical composition of the agent, factors associated with those exposed (age/lifestage, sex, genetic makeup, health status), and mode (MoA) or mechanism of action (MOA).

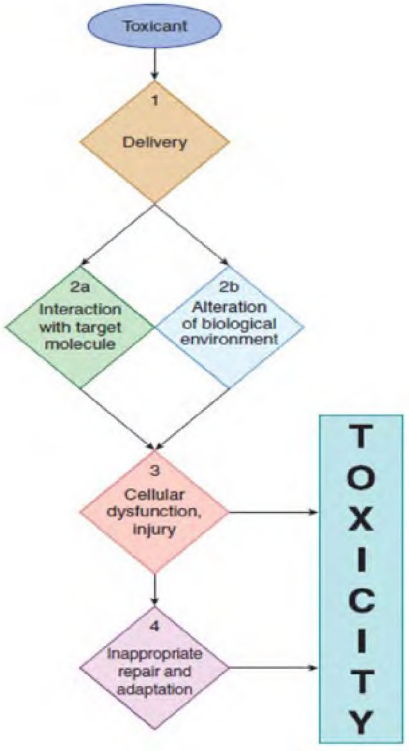

Figure 2. Potential stages in the development of toxicity after exposure to an exogenous agent. From Gregus (2015).

Dose. One key principle is dose measurement and calibration. In other words, how much of the exogenous agent is required to induce a toxic effect? As indicated in Figure 2, the dose of the toxicant at the target

molecule that is sufficient to alter the biological environment is frequently sought and measured. This value may differ from the amount that is given, for example, to test organisms, or that may be present in one particular component of a biological organism (i.e., blood concentration). Although it is an important element, the dose is only one element of the toxicological landscape. For some agents, the occurrence of adverse health outcomes does not always follow a "standard" dose-response curve where an increase in dose leads to an increase in response. Some dose-response curves are U-shaped or inverse-U-shaped, indicating that lower and higher doses produce responses that differ from moderate doses. Therefore, the dose-response relationship is never as simple as the phrase "the dose makes the poison" and adverse health outcomes that do not follow a clear dose-response pattern (i.e., an increase in outcome with an increase in dose) should not be summarily discounted as spurious or lacking in toxicological relevance without further experimentation and analysis.

Toxicodynamic and toxicokinetic factors. Toxicodynamic (processes by which exogenous agents produce effects in the body) and toxicokinetic (distribution of exogenous agents in the body, which includes absorption, distribution, metabolism, and excretion or "ADME") factors also play an important role in understanding how exogenous agents may induce adverse health outcomes. While there are many possible hypotheses about how to specifically apply these factors to complex problems such as risk assessments, Heinrich-Hirsch et al. (2001) have established a simplified model to illustrate how these two factors are related to exposure and an adverse health outcome (Figure 3). It is important to note that "internal dose" generally refers to the amount of an agent that can penetrate across various absorption barriers of an organism (Zartarian et al., 2006). "Toxicity" therefore is also a function of how much of a dose of an exogenous agent is at a target site (i.e., the cellular/subcellular site) integrated over time (Society of Toxicology, 2008).

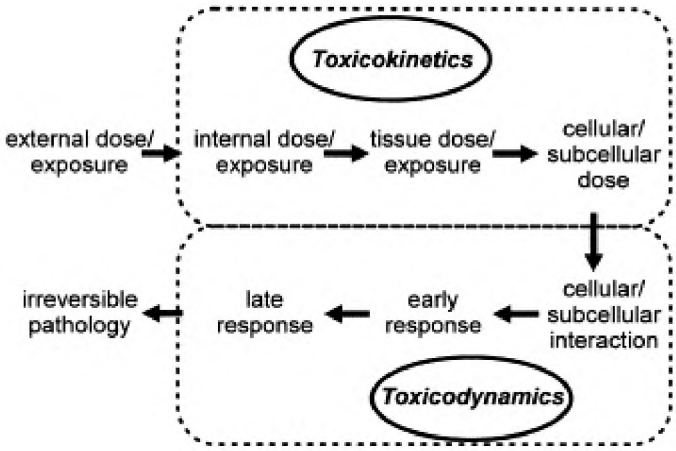

Figure 3. A representation of toxicokinetic and toxicodynamic factors from exposure to adverse health outcome (irreversible pathology). From Heinrich-Hirsch et al. (2001).

Toxicokinetic and toxicodynamic factors are particularly important for understanding the toxicity of PFCs, especially as related to the relevance of measured serum concentrations in experimental animal models and humans to adverse health outcomes. Serum concentrations in humans, whether from the general population or from highly exposed populations (i.e., occupationally exposed or from areas of with high environmental concentrations of PFCs) are used as biomarkers of exposure as exposure monitoring data are generally lacking (ATSDR, 2015). In other words, as data on the amount of PFCs ingested, inhaled, and/or dermally absorbed (see next section) by humans has not been precisely determined, confirmation of exposure is based on concentrations of PFCs in serum. However, serum concentrations do not always reflect the true exposure scenario, i.e., the amount of PFCs taken in by an individual, or the true body burden, i.e., the sum total of PFCs in the body that

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may reach target sites to induce toxicity. Therefore, serum concentrations should be regarded as biomarkers of *exposure* rather than biomarkers of *effect*. Biomarkers of exposure are measurements of compounds that reflect internal doses, biologically effective doses, or target doses whereas biomarkers of effect include changes on a cellular level or markers for early pathological changes in complex disease development (Silins and Högberg, 2011). Biomarkers of susceptibility also have been defined, which is an individual's responses to specific exposures (Silins and Högberg, 2011).

In a 2004 review of the toxicity of PFOA written by a team of authors from DuPont, 3M, Covance (a contract research laboratory), Atofina, and Ineos (chemical/petrochemical companies), some of the known ADME properties of PFOA were highlighted (Kennedy et al., 2004). Greater than 90% of a single oral dose of PFOA was absorbed from the GI tracts of male rats within 24 hours of exposure and levels of PFOA measured in the blood after inhalation or dermal exposure also indicated absorption of PFOA following these routes of exposure. In a study performed by DuPont in 1982 and cited in the Kennedy et al. (2004) review, absorbed PFOA is mostly excreted in the urine, but with some fecal excretion. Kennedy et al. (2004) also noted that the 1982 DuPont study and numerous other published reports indicate a profound difference in blood clearance and urinary excretion between male and female rats, with female animals clearing serum levels more rapidly than male animals. Kennedy et al. (2004) also cited studies indicating sex differences in hamster, rabbits, mice, and cynomolgus monkeys, but sex differences were not always parallel with sex differences observed in rats. Once in the blood, PFOA avidly, but reversibly, binds to plasma proteins (proteins that serve as transporters for endogenous agents in an organism), especially albumin, and distributes mainly to the liver and kidneys, but also is detectable in lungs, heart, skin, testes, muscle, fat, and brain of rats, hamsters, and mice (Kennedy et al., 2004). Lau (2015) noted that the liver, kidney, and blood compartments can account for greater than half of the body burdens of PFAAs. Kennedy et al. (2004) also addressed human biopersistence and stated that humans have the least ability to eliminate PFOA of any species studied. With the exception of sex differences, PFOS exhibits similar ADME properties (Lau et al., 2007). The relatively few studies on ADME properties of short-chain PFCs, such as PFBA and PFBS, indicate that these PFCs also are readily absorbed following oral exposure and are eliminated mainly in the urine, but that they are eliminated from the serum more rapidly than the long-chain PFCs (Chan et al., 2008; Olsen et al., 2009). Whether the short-chain PFCs accumulate in tissues similarly to the long-chain PFCs has yet to be determined, although a small-scale study of tissues from human autopsies suggests that s short-chain PFCs do accumulate in tissues (Pérez et al., 2013).

As a reminder, "internal dose" generally refers to the amount of an agent that can penetrate across various absorption barriers of an organism (Zartarian et al., 2006). With the exception of agents that induce local reactions at the site of contact, i.e., such as burns from acidic or alkaline substances, exogenous agents have to be absorbed across membranes associated with routes of exposure (ingestion, inhalation, dermal; see next section). Some ingested exogenous agents, for example, may be ingested and completely eliminated in feces without ever being absorbed across membranes. They may produce local effects on the gastrointestinal (GI) tract, but if they do not absorb across membranes, they cannot be distributed throughout the body and produce toxic effects at sites distant from the site of absorption. Because PFCs are eliminated in the urine from all routes of exposure (ingestion, inhalation, dermal), this is evidence that they are distributed

throughout the body via the blood, which increases the probability that they may interfere with processes distant from the site of absorption.

Route, duration, and frequency of exposure. The route of exposure is the pathway through which an exogenous agent enters the body. For environmental agents, this is via ingestion (oral), inhalation (lung), or dermal (skin) absorption. Occupational exposures may include injection directly into the bloodstream as well, such as in cases of accidental needle sticks. Common ways by which the general human population is exposed via ingestion is through contaminated food and water. Food can be contaminated while it is growing, or during storage, processing, or cooking. Water is typically contaminated at its source (groundwater or surface water) by direct releases, accidental spills, or atmospheric deposition, and contaminants may still be present in finished drinking water. Inhalation can occur if the exogenous agent is in air as a particle, aerosol, or vapor. Dermal absorption can occur if contaminated media (i.e., soil, sediment, water) get onto the skin and if the exogenous agent has physical-chemical characteristics that allow it to move through the skin. Duration refers to how long the exposure occurs, a single time, over hours, days, weeks, months, or years. Short duration exposures that are associated with a single or a relatively short exposure period (days or weeks when the lifespan of an organism is years) are classified as acute or intermediate whereas exposure periods that constitute a major portion of an organism's lifespan are considered chronic. Adverse health effects that occur following exposure to an exogenous agent also can be termed as acute (occurring immediately after exposure) or chronic (occurring weeks, months, or years after exposure). Frequency is the number of times per hour, day, week, month, or year the exposure occurs.

Chemical composition. This toxicological principle is based on the physical-chemical characteristics of the exogenous agent. Briefly, this relates to whether the agent is fat or water soluble, whether it is positively or negatively charged or neutral in charge, whether it is relatively large or small, acidic or basic, reactive or non-reactive, and how it is shaped. These characteristics affect an exogenous agent's ability to get into living organisms, move around inside organisms, ability to bind to various receptors within organisms, and excretion from organisms. Exogenous agents that appear to be "inert," in other words not chemically reactive in that they do not readily metabolize to a reactive intermediate, nor directly damage cells or membranes, nor create mutations in DNA, for example, can still interact with endogenous biomolecules to induce adverse physiological outcomes through a variety of mechanisms. PFCs fall into this latter category; they are not chemically reactive as far as we know, but can interact with myriad endogenous biomolecules. Therefore, PFCs may be chemically "inert" in some respects, but are still reactive in that they can alter physiological processes through their interactions with endogenous biomolecules.

Factors associated with those exposed. Factors associated with those exposed may have an effect on potential adverse health outcomes that may arise from exposure to exogenous agents. Infants, for example, have immature enzyme systems and may be unable to appropriately detoxify exogenous agents to which they are exposed. A classic example is methemoglobinemia (commonly known as "blue baby syndrome"), a situation that may occur in infants exposed to nitrates in their drinking water. Nitrates are able to oxidize the iron in hemoglobin (the carrier of oxygen in red blood cells) from one valence state to the other, which reduces its efficiency at carrying oxygen. In adults, the enzyme cytochrome b5 methemoglobin reductase can reduce the oxidized iron, but in infants, this enzyme is inefficient and occurs at lower levels than in adults,

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thus making infants at increased risk of methemoglobinemia and the adverse health outcomes that arise from this condition. Many other examples exist to demonstrate that factors associated with age/lifestage, sex, genetic makeup, health status, nutritional status, and others can alter the existence or severity of adverse health outcomes following exposure. Some of these factors can reduce the likelihood of adverse health outcomes; for example, some individuals may rapidly metabolize certain exogenous agents and reduce or eliminate their toxicity. However, many of these factors can render individuals or groups of individuals more susceptible to adverse health outcomes. One goal, therefore, of regulatory guidelines that reduce exposure to exogenous agents that produce adverse health outcomes can be to protect susceptible subpopulations from adverse health outcomes that arise from exposure.

Mode or mechanism of action. "Mechanistic" (MOA) refers to the particular reaction of the exogenous agent with a target molecule or molecules to induce toxicity, i.e., an adverse health outcome or outcomes (Gregus, 2015). "Mode of action" (MoA) is the interaction of an exogenous agent with the cell through functional and anatomical changes that results in adverse health outcomes and is generally regarded as a less detailed understanding of the molecular basis of a toxic effect (OECD, 2012). In general, toxicological studies to identify the MoA and MOA are undertaken once adverse health outcomes following exposure have been observed. These types of studies are particularly valuable in that they can establish pathways between a molecular-level change and a phenotypic (i.e., anatomical or functional change) outcome following exposure and improve extrapolations among species. However, lack of MoA or MOA does not negate findings associated with an adverse health outcome, but rather indicates additional experimental studies are necessary to identify those molecular-level events that lead to the adverse health outcome.

As a general matter, all of the concepts just listed are taken into consideration when studying effects of exogenous agents on living organisms. Toxicologists frequently rely, for ethical reasons, on experimental animal models (e.g. mice and rats) to assess toxicity following exposure to exogenous agents. Therefore, studies in experimental animal models are generally considered valuable for understanding and predicting adverse health effects in humans. Certainly, humans and rodents are not exactly alike, but evaluation of toxicity of exogenous agents in experimental animal models is a cornerstone of human safety evaluation and findings in animal toxicology studies generally are applicable to humans (NRC, 2004). Uncertainty factors and extrapolations based on body weight equivalence, for example, often are applied to values derived from experimental animal models to account for differences between these animal models and humans and to derive factors that are relevant to humans (NRC, 2004). In addition, toxicologists often also consider and rely on the work of epidemiologists, scientists who link exposure to exogenous agents with the number(s) and type(s) of adverse health outcomes observed in human populations, to understand the extent of effects arising from exposures.

What distinguishes adverse health outcomes from non-adverse effects is not always unambiguous and often relies on professional judgment for identification. Several reports and publications exist to help toxicologists determine which outcomes are adverse versus non-adverse. One such publication from 2012 (Keller et al., 2012) reflects a harmonized opinion of a diverse group of scientists from chemical and pharmaceutical industries, government agencies, and academic institutions. The publication was from a workshop held by a committee formed in 2009 by the International Life Sciences Institute (ILSI) Health and Environmental Sciences

Institute (HESI). Keller et al. (2012) defines adverse and non-adverse/adaptive responses in the following ways:

> "Adverse Effect: A change in morphology, physiology, growth, development, reproduction, or life span of a cell or organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.
>
> Non-adverse/Adaptive Response: In the context of toxicology, the process whereby a cell or organism responds to a xenobiotic so that the cell or organism will survive in the new environment that contains the xenobiotic without impairment of function."

Once adverse effects are identified, they are typically evaluated for dose-response, but again, not all responses follow a simple dose-response relationship where an increase in dose leads to a concomitant increase in response. With this basic toxicological assessment, doses that are unlikely to be associated with adverse health outcomes can be distinguished from those that are. The dose that is unlikely to be associated with adverse health outcomes is termed the No Observed Adverse Effect Level (NOAEL) and is defined as the highest dose that is not statistically distinguishable from unexposed organisms (i.e., a control group or population). Effects may occur at the NOAEL dose, but they are not considered adverse or precursors to adverse effects. The Lowest Observed Adverse Effect Level (LOAEL) is the lowest dose that produces statistically distinguishable increases in the severity or frequency of adverse health outcomes when compared to unexposed organisms. Toxicologists often distinguish the relative toxicity of compounds by comparing the NOAEL and the LOAEL and frequently public health officials for use the NOAEL for establishing protective health guidelines. The NOAEL and LOAEL ideally are based on studies of chronic duration as they indicate adverse health outcomes that occur over a lifetime of exposure. Relative toxicity also can be compared from acute exposures that lead to death as an outcome. These studies typically result in "LD50" values, or the dose of an exogenous agent that leads to death in 50% of a group of experimental animal models. While LD50s can be used to determine or compare the toxic potency of acute doses of exogenous agent, they are not particularly useful for protection of public health as death is an adverse health outcome that is obviously avoided.

However, as previously described, the dose-response is only one concept when determining if adverse health effects are induced by exposure to exogenous agents and not all dose-response patterns follow the typical pattern of an increase in response with an increase in dose. The NOAEL or LOAEL can represent a point of departure (POD), or a particular point on a dose-response curve that is the beginning of extrapolation to lower doses and is an estimated dose, in human-equivalent terms, near the lower end of the observed dose-response range (U.S. EPA, 2012).

By way of example, one group of agents that has been shown to challenge the "dose makes the poison" concept in toxicology is endocrine disrupting compounds (EDCs), agents that disrupt hormones. Many of these agents produce effects at low doses that are not predicted by effects at higher doses and have dose-response curves that are "nonmonotonic." Vandenberg et al. (2012)

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defines these types of dose-response curves as "a nonlinear relationship between dose and effect where the slope of the curve changes sign somewhere within the range of doses examined." In other words, as the dose goes up, the response may go down. This concept is particularly important for PFCs given evidence that indicates they can disrupt hormones.

One way that the U.S. EPA has responded to agents that lack a typical dose-response relationship is through the development of an approach known as the benchmark dose (BMD). Development of the BMD approach also was a response to limitations associated with using the NOAEL to establish protective health guidelines. According to the U.S. EPA (U.S. EPA, 2012), using NOAELs for protective health guidelines is limited to doses used in the particular study containing the NOAEL and does not account for variability or the slope in a dose-response curve. The BMD method, therefore, is an approach that uses mathematical models to fit dose-response data and derive a reference value that is associated with a POD that may not be equivalent to the NOAEL or LOAEL as it takes into account the entire dose-response curve and not a singular point (i.e., the NOAEL or LOAEL). Briefly, the BMD approach used by the U.S. EPA (U.S. EPA, 2012) recommends the use of the 95% lower bound on a BMD (known as the BMDL) as the POD for non-cancer effects. According to the U.S. EPA (2012),

> "Using the lower bound accounts for the experimental variability inherent in a given study and assures (with 95% confidence for the experimental context) that the selected BMR [benchmark response] is not exceeded… Because of the limitations of the NOAEL/LOAEL approach…, the BMD approach is preferred to the NOAEL/LOAEL approach. For instance, a BMD (or BMDL) can be estimated even when all doses in a study are associated with a significant adverse response (i.e., when there is no NOAEL). Note, however, that there are some instances in which reliable BMDs cannot be estimated and the NOAEL/LOAEL approach might be warranted. In particular, the available data may not be amenable to modeling, for example when all exposed groups exhibit a maximum response. In such a case, the observed data provide very little information across the full range of response levels, and BMD models cannot provide reliable estimates within that range (although in such a case, information from the LOAEL is limited, as well)."

While the details of this method are beyond the scope of this report, it is important to mention this approach as it was the predominant approach used by the U.S. EPA to derive reference doses (RfDs) for PFCs.

One last major principle of toxicology is how determinations on cause-and-effect relationships between exposure to a particular exogenous agent and adverse health outcomes are made. In 2006, the International Programme on Chemical Safety (IPCS), an international group of experts, published a framework (Figure 4) for analyzing the relevance of a cancer mode of action for humans (Boobis et al., 2006) and in 2008, extended the framework to a non-cancer mode of action for humans (Boobis et al., 2008). Both of these documents are based on the "Bradford Hill criteria," a set of guidelines written by Sir Austin Bradford Hill in 1965 that allowed for the leap from observation to causation (Hill, 2015). Briefly, the Bradford Hill criteria ask the following questions about associations between two variables: 1) Strength, 2) Consistency, 3) Specificity,

4) Temporality, 5) Biological gradient, 6) Plausibility, 7) Coherence, 8) Experimental intervention, and 9) Analogy. Hill (2015) cautions that

> "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"

Hill's viewpoints were therefore used by the IPCS to draft a framework that would be applicable to both cancer and non-cancer endpoints and that would provide a means for "ensuring a transparent evaluation of the data, identification of key data gaps and of information that would be of value in the further risk assessment of the compound, such as on dose-response relationships, and recognition of potentially susceptible subgroups, for example, based on life-stage considerations" (Boobis et al., 2006). While definitive "yes" and "no" answers are included in the framework, the authors of the framework recognized the need for judgment regarding the sufficiency of weight of evidence (Boobis et al., 2006). Specifically, answers on the left side of the diagram (Figure 4) indicate that weight of evidence for the MoA would be insufficient to support relevancy in humans whereas answers on the right side of the diagram (Figure 4) would indicate that weight of evidence for the MoA would be sufficient to support relevancy in humans or that it would not be possible to reach a conclusion regarding likely relevance in humans given uncertainties in available information (Boobis et al., 2006).

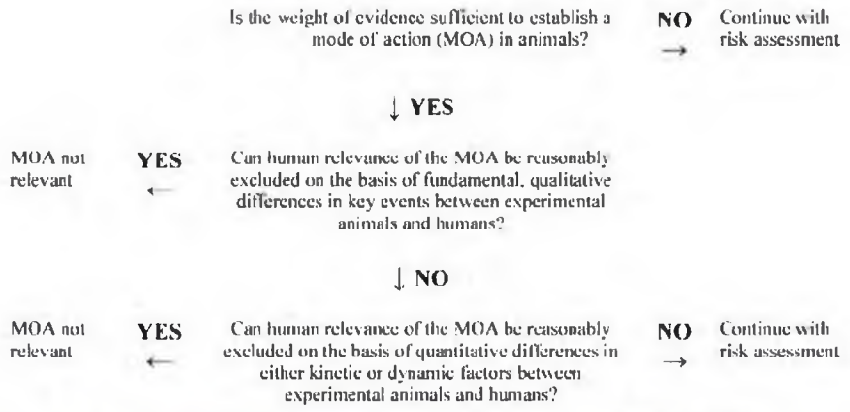

Figure 4. A decision tree for determining human relevance of a MoA for carcinogenicity or toxicity observed in experimental animal models. From Boobis et al. (2006; 2008).

VII.3 Brief Background on PFC Toxicology and Epidemiology

Based on these concepts of toxicity of exogenous agents, toxicologists have determined that exposure to PFCs induces a wide variety of adverse health outcomes in experimental animal models. Epidemiological studies are supportive, showing similar adverse health outcomes in exposed human populations. These toxicological and epidemiological studies indicate that exposure to PFCs pose a substantial present and potential hazard to human health. Although unifying MoAs or MOAs for the various toxicities have not been conclusively identified, a

number of plausible MoAs and MOAs have been uncovered in experimental animal models that have relevancy to exposed humans. These will be discussed in subsequent sections on evidence associated with specific toxicological outcomes.

As stated previously, NHANES has reported detectable concentrations of PFCs in the serum of 97% of surveyed individuals in the U.S. (Hu et al., 2016), indicating widespread human exposures. PFCs are synthetic agents that *do not occur naturally* in the environment, so levels in biological tissues and fluids of humans and other organisms indicate exposure from industrial releases to the environment or from the leaching of PFCs from consumer products. Exposure in the general human population therefore occurs when humans ingest PFCs from contaminated water or food, breathe them in, often from house dusts, or dermally absorb them from water or other materials containing PFCs. As PFCs are used in the textile industry to confer stain and water repellency to textiles such as carpets, children may have high exposures via hand-to-mouth transfer from treated carpets relative to adults (ATSDR, 2015). Areas of high exposure have been recorded in human and wildlife populations (impacts on wildlife populations are addressed in Dr. Ronald Kendall's report and will not be addressed here) living near fluoropolymer manufacturing facilities and people who work in manufacturing facilities generally have higher concentrations of PFCs in their serum (ATSDR, 2015). Again, as stated previously, levels in serum are generally used as biomarkers of exposure (ATSDR, 2015).

For purposes of my opinions, PFOA and PFOS will be the main PFCs of focus due to the volume of toxicological data surrounding these compounds. However, data from studies of perfluorinated carbon chains consisting of four to 16 carbons with sulfonate functional groups (PFOS, PFDS, PFHxS, and PFBS) or carboxylate functional groups (PFOA, PFTA, PFDoA, PFUnA, PFDA, PFNA, PFHpA, PFHxA, PFPeA, and PFBA) that are terminal products, metabolites, or degradation products, may be included as supportive data.

To determine the likelihood of harm to human health following exposure to environmental contaminants, regulatory agencies often use a "weight-of-evidence" approach. Using this approach, the quantity and quality of data related to a particular contaminant, including in vitro (outside of living organisms, usually in cells or tissues), in vivo (in living organisms), in silico (computer-based simulations and models), and epidemiological studies (direct studies of exposed humans), are assessed to determine if they support a likelihood of harm to human health following exposure. This approach often is used by, for example, the U.S. EPA to establish health advisories, guidelines, and regulatory standards, or the IARC to determine the carcinogenicity of agents. However, this is an approach and is not a regulatory requirement. Given that only PFOA and PFOS have been the subjects of broad assessments, other compounds will be evaluated based on relevant (i.e., toxicological) studies published in publicly available peer-reviewed literature.

Three agencies, the U.S. EPA, the U.S. NTP, and the IARC, have completed such weight-of-evidence assessments, or "systematic reviews," for PFOA and/or PFOS. These systematic reviews are thorough evaluations of the body of toxicological evidence concerning PFOA and PFOS and their likelihood of harm to human health following exposure. Each of these reviews are comprehensive of most of the published studies (up to a specified cut-off date determined by the agency sub-committee charged with writing the document) and accumulated knowledge about PFOA and PFOS. In these reviews, although they differ somewhat from agency to agency,

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publicly available peer-reviewed published literature provide the bulk of the reference materials. In some instances, patent filings and industry reports may provide background and support, but generally do not contribute substantially to the reviews. In addition, ATSDR has published a draft toxicological profile for PFCs, which is a succinct characterization of the toxicological and adverse health effects for 13 separate PFCs (ATSDR, 2015). Each of the assessments by the U.S. EPA, the U.S. NTP, and the IARC underwent rigorous peer-review. The ATSDR profile is still only available online as a draft for public comment and has not been fully peer-reviewed or released in its final form. Moreover, for the U.S. EPA, NTP, and ATSDR documents, comments from the public were and are being solicited, giving private citizens, trade organizations, industry scientists, and others the opportunity to offer suggestions and criticisms. This is an extremely important aspect of the development of these documents as it represents *transparency* in the process by which conclusions were reached by these various agencies. The IARC does not include public commentary in its monographs, but scientific participants in the development of a particular monograph formally review one another's work through an established process of internal peer-review and interested parties, such as representatives from community and trade groups, can observe meeting proceedings for a particular monograph. Such weight-of-evidence evaluations are a widely accepted methodology in the toxicological and epidemiological scientific communities.

In formulating my opinions, I use a similar approach that integrates the evidence from various sources to assess the likelihood that exposure to PFCs poses a substantial present or potential hazard to human health. As these agencies (ATSDR, IARC, NTP, U.S. EPA) have completed rigorous, peer-reviewed science assessments of PFCs, a large part of my opinions are supported by these sources.

VII.4 PFCs in the East Metro Population

The eastern Twin Cities metropolitan region ("East Metro") of Minnesota includes sites of high PFC concentration as they include the 3M Cottage Grove manufacturing facility as well as large waste disposal facilities where PFC-bearing wastes were disposed (MDH, 2017d). Some of the municipal drinking water wells in the East Metro area also contain levels of PFCs greater than current health based values (HBVs) established by the Minnesota Department of Public Health (MDH). As a result of the contamination and concerns over health risks induced by exposure to PFCs via drinking water, the MDH conducted three biomonitoring studies of a small sample of residents from the East Metro area (MDH, 2008; 2010; 2015). In the 2008 study, blood from 196 adults from Oakdale, Lame Elmo, and Cottage Grove, MN, was evaluated for levels of PFOA, PFOS, PFHxS, PFBA, PFBS, PFHxA, and PFPeA (MDH, 2008). PFOA, PFOS, and PFHxS were found in the blood of all participants at levels higher than the general U.S. population, but comparable to or lower than levels found in studies of other PFC-contaminated communities (MDH, 2008). PFBA and PFBS were found in a smaller proportion of participants and PFHxA and PFPeA were not found in any participants (MDH, 2008).

A 2010 follow-up study was performed to not only better understand human exposure to PFCs, but to determine if a public health intervention to reduce drinking water exposure to PFCs actually reduced levels of PFCs in the blood of participants (MDH, 2010). In the follow-up study, the same seven PFCs as were measured in the 2008 study were measured in 164 participants. Levels of PFOA, PFOS, and PFHxS, the PFCs that were present in all participants

in 2008 declined by ~25%, 30%, and 22%, respectively, from 2008 to 2010 (Figure 5; MDH, 2010). However, even though levels of these three PFCs had declined in the East Metro region in this two year time period, levels of these PFCs in this subset of East Metro residents were still greater than the general U.S. population, by ~64%, 46%, and 69% respectively, for PFOA, PFOS, and PFHxS (Figure 5; MDH, 2010).

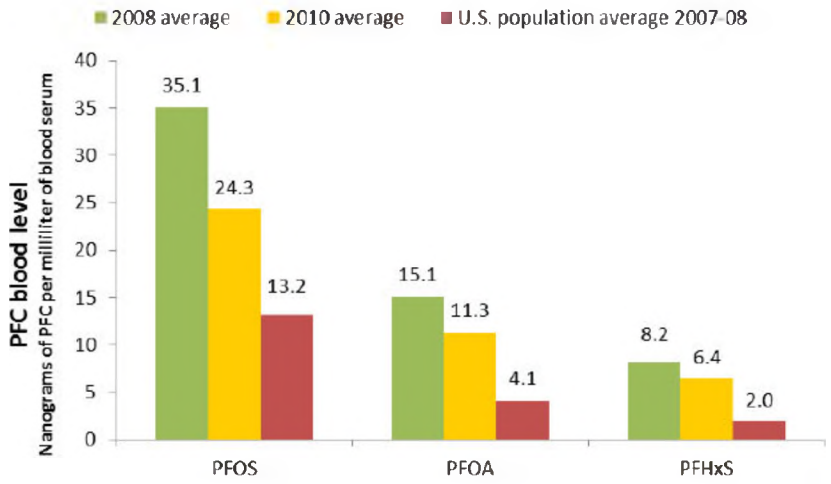

Figure 5. Results of the 2010 East Metro follow up study demonstrating blood levels of PFCs in residents from the East Metro area in 2008 and 2010 and as compared to the blood levels of PFCs in people from the general U.S. population. From MDH (2010).

An additional follow-up investigation in 2014 indicated that while serum concentrations of PFCs in long-term East Metro residents had declined further, they nonetheless remained higher than concentrations in the U.S. general population. (Figure 6; MDH, 2015). Therefore, even with a public health intervention in place to reduce drinking water exposure to PFCs, long-term residents of the East Metro region still carried a disproportionately higher body burden of PFCs relative to the general U.S. population.

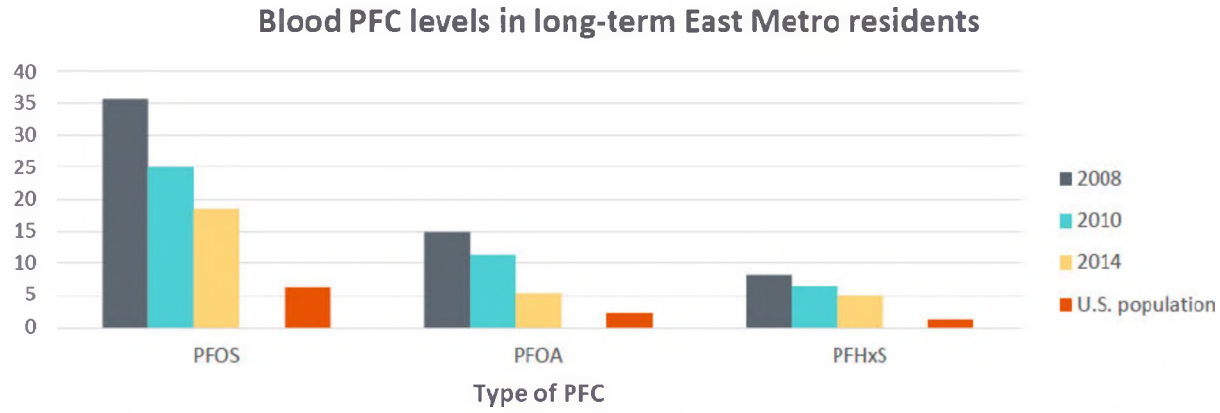

Figure 6. Results of the 2014 East Metro follow up study demonstrating blood levels of PFCs in residents from the East Metro area in 2014 and as compared to the blood levels of PFCs in people from the East Metro in previous years and from the general U.S. population. From MDH (2015).

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Concentrations of PFCs in some of the municipal drinking water wells in the East Metro area contain levels of PFCs greater than current and past MDH HBVs. Therefore, long-term East Metro residents have been exposed to levels of PFCs in their water *above* levels that the MDH currently considers to be safe for human consumption, including sensitive subpopulations. The current HBVs for four PFCs are as follows: PFOA = 0.035 µg/L (MDH, 2017f); PFOS = 0.027 µg/L (MDH, 2017g); PFBA = 7 µg/L (MDH, 2011a); PFBS = 7 µg/L (MDH, 2011b); and PFHxS = 0.027 µg/L (the MDH is using the HBV for PFOS as a protective level for PFHxS; MDH, 2009b). These HBVs are discussed in more detail in section IX. Well monitoring data (Karls, 2017) from Oakdale, for example, indicated that average concentrations PFOA, PFOS, and PFHxS exceeded their respective HBVs in 2012 and that average concentrations PFOA and PFOS exceeded their respective HBVs in 2016. One approach that the MDH takes to address concurrent exposures to multiple chemicals, which is in agreement with, for example, the U.S. EPA, is to derive a health risk index (HRI; MDH, 2017i). The HRI is calculated by first determining the ratio of the measured concentration of an individual chemical to its respective HBV and then summing the ratio for the group of chemicals being evaluated.

For example, in Oakdale, a region in the East Metro area that contains a Superfund site that includes PFC wastes (MDH, 2016), the HRI was 17.6 in 2012 and 16.9 in 2016. The weighted PFOS concentration for Oakdale in 2012 was 0.275 µg/L (Karls, 2017); its ratio is 0.275 µg/L divided by 0.027 µg/L = 10.2. The weighted PFOA concentration for Oakdale in 2012 was 0.214 µg/L (Karls, 2017); its ratio is 0.214 µg/L divided by 0.035 µg/L = 6.1. The weighted PFHxS concentration for Oakdale in 2012 was 0.032 µg/L (Karls, 2017); its ratio is 0.032 µg/L divided by 0.027 µg/L = 1.2. The HRI for these three PFCs = 10.2 + 6.1 + 1.2 = 17.5. When the ratios of PFBA and PFBS are added in (0.095 and 0.002, respectively), the HRI for these municipal drinking water wells in Oakdale is 17.6. In 2016, the HRI for these five PFCs in Oakdale was 16.9, again, greater than one and an indication that PFC levels in these municipal drinking water wells were greater than the HBV. By early 2007, two municipal wells in Oakdale had granular activated carbon filtration systems; accordingly, concentrations discussed above likely do not represent levels of current exposure (MDH, 2007). However, prior to the installation of filtration systems, long-term residents would have been exposed to higher concentrations of PFCs.

For comparison, although present at lower levels in municipal drinking water wells, the HRI for Cottage Grove in 2012 was 1.7 and in 2016 was 1.5 (based on well monitoring data provided by Karls, 2017).

A HRI greater than one indicates that concentrations in the exposure source (i.e., municipal drinking water wells) are greater than the HBV. In other words, people exposed to the combined concentrations of these five PFCs in their drinking water with these municipal drinking water wells as a source exceeded a level that the MDH considers to be safe for human consumption, including sensitive subpopulations.

VII.5 Chronology of 3M Toxicology Studies on PFCs

As evidenced by documents produced by 3M that I have reviewed, it was clear that the company had been studying PFC toxicology since at least the 1940s. Below is a brief chronology of a few of the numerous toxicological studies on PFCs performed by 3M or their subcontractors:

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- 1949: 3M conducted acute toxicity tests of heptafluorobutyric acid in mice. The results noted "[i]mmediate deaths characterized by respiratory distress. Animals dying later, died after a period of lethargy" (3M_MN05305661).

- 1963: By this point, 3M had determined the acute toxicity of several PFCs, as indicated by a list of LD50 for several of their PFCs, including FC-95 (the potassium salt of PFOS). In a technical brochure, 3M described FC-95 as "moderately toxic" (3M Company, 1963). By way of example, phenobarbital and morphine, have similar LD50s as compared to FC-95 (~100-1000 mg/kg).

- 1978: After being informed about the presence of organic fluorine in the blood of the general population and subsequently discovering organic fluorine in the blood of its own workers, 3M launched a series of 90-day subchronic toxicity studies in rats and monkeys using three PFCs. 3M concluded, based on these studies, that FC-95 was "considerably more toxic to monkeys than anticipated." One of 3M's studies was aborted because all of the dosed monkeys died. PFOA and N-EtFOSE exposure also was associated with various adverse health effects (3MA00593073, 3MA01797217, 3M_MN01663513, 3MA10065004, 3M_MN01663537).

- 1980-83: 3M conducted several teratology studies of PFCs in rats. Initial studies suggested that PFCs induced lens abnormalities and other birth defects in rat fetuses. While further 3M studies suggested that the lens abnormalities may have been caused by a sectioning artifact, as described in section VII.3.b, below, a compound-related effect cannot definitively be ruled out.

- 1987-88: 3M completed two 2-year carcinogenicity studies of PFOA and N-EtFOSE in rats. Although 3M concluded in these studies that neither of the compounds were linked to elevated tumor incidence in rats, subsequent re-examination of the study's findings have established that the conclusions in the reports about tumor incidence were incorrect—i.e., both PFOA and N-EtFOSE did induce tumors in rats (3MA00027126, 3MA00593233, 3MA10025147).

- 2001-2002: 3M completed 6-month toxicity studies of PFOA and PFOS in cynomolgus monkeys. Mortality was observed in both studies. In both studies, monkeys exhibited effects on thyroid hormones and the liver. In addition, monkeys dosed with PFOS exhibited lowered cholesterol and high density lipoprotein (HDL; 3M_MN02343342, 3M_MN03278834).

- 2001-2002: 3M completed 2-year carcinogenicity studies of N-EtFOSE and PFOS in rats. Both studies observed statistically significant hepatocellular combined adenomas and carcinomas in female rats and statistically significant combined thyroid follicular cell adenomas and carcinomas in male rats. (3MB00040027, 3MA00812492).

VII.6 Toxicological Evidence Regarding Human Health

"Of questionable relevance to human health" or "mean serum concentrations in experimental animal models is several hundred times higher than those reported for humans in the U.S. general population" are phrases that often are included in publications authored by scientists from 3M. These phrases occur in publications that focus on liver toxicity, carcinogenicity, developmental toxicity, and endocrine disruption. In many instances, when experimental animal models are exposed to precise concentrations of PFCs on a daily basis for a proscribed amount of time, the resulting serum concentrations are higher than what has been measured in humans from the U.S. general population. While experimental animal models are not tiny humans, they are accepted models for human health in the toxicological sciences as well as other biomedical sciences. As stated previously, serum levels of PFCs in humans are biomarkers of exposure; technically, serum levels in experimental animal models also are biomarkers of exposure and are not biomarkers of effect. PFCs have toxicokinetic complexity – they bind to serum proteins and partition into blood, liver, and kidney, and demonstrate half-life differences among species. This toxicokinetic complexity makes it inappropriate to directly compare serum levels in experimental animal models with serum levels in humans. Additionally, as the human exposure pathways for PFCs have not been fully mapped, serum levels may underestimate exposures and do not capture differences in serum protein binding and storage in the liver and kidney that may exist between humans and experimental animal models. When adverse health outcomes are observed in experimental animal models *in multiple systems/organs/tissues/cells/pathways, in multiple species and stains, across myriad exposure pathways, occur for a range of PFCs,* and *show concordance with epidemiological findings*, the results are ***highly relevant to human health.***

VII.6a 3M Worker Studies

3M has repeatedly suggested that the myriad findings that exposure to PFCs is associated with adverse effects in experimental animal models should be ignored or discounted. They claim that epidemiology studies conducted by 3M regarding its workers demonstrated that, although the workers were more heavily exposed than the average population, they did not suffer adverse health effects. I disagree, for several reasons.

First, as I discuss in more detail in section VIII, numerous epidemiology studies performed by independent experts have identified statistically significant associations between increased exposure to PFCs and adverse health effects that are supported by results of toxicology studies in experimental animal models exposed to PFCs alone. These epidemiology studies include both worker and non-worker populations in the U.S. and around the world, including at levels of exposure within and below blood serum levels measured in East Metro residents.

Second, contrary to 3M's claims, its studies did demonstrate PFC-related adverse health effects in its workers. 3M's worker studies have found statistically significant associations between PFC exposure and health endpoints indicative of adverse effects, including prostate cancer mortality (Gilliland and Mandel, 1993, 3MA00631764; Lundin and Alexander, 2007, 3MA02557439), cerebrovascular disease (Alexander, 2001a, 3MA00417473; Lundin and Alexander, 2007, 3MA02557439), bladder cancer mortality (Alexander, 2001b, 3MA01472304), cholesterol and triglyceride increases (Olsen et al., 2001, 3M_MN02483163; Olsen unpublished draft, 2008, 3MA02543911), self-reported history of gallbladder disease (Olsen unpublished draft, 2008,

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3MA02543911), and endocrine modulation (Gilliland, 1992, 3M_MN03112178; Olsen et al., 1998, 3MA10069722).

Finally, as discussed in more detail by Dr. Philippe Grandjean, I understand that a number of 3M's epidemiology studies of its workers were flawed, undermining the reliability of their findings.

VII.6b PPARα Activation and Peroxisome Proliferation

3M also argues that toxicology studies demonstrating that exposure to PFCs associated with specific adverse effects in rodents—most notably in the liver—do not translate to risks for humans on the basis that these adverse effects are mediated by a process called peroxisome proliferation that rodents are uniquely susceptible to. This is incorrect, in part, as several liver effects observed in PFC studies using experimental rodent models result from impacts on processes other than peroxisome proliferation. Additionally, humans respond to pharmacological agents that act through the receptors that are thought to modulate PFC-associated peroxisome proliferation in rodents.

Peroxisome proliferation is associated with a group of ligand-activated transcription factors know as peroxisome proliferator-activated receptors (PPARs). Three sub-types are known to exist, PPARα, PPARγ, and PPARβ/δ, and each have slight differences in terms of their affinity for ligands and the effects that they produce when activated (Tyagi et al., 2011). Overall, these receptors play a regulatory role in energy homeostasis and metabolic function and when activated, may have both protective and detrimental effects in dyslipidemia, diabetes, adipocyte differentiation, inflammation, cancer, lung diseases, neurodegenerative disorders, fertility or reproduction, pain, and obesity (Tyagi et al., 2011). One consequence of PPARα activation is peroxisome proliferation, an increase in the amount and activity of the peroxisomal enzymes associated with various physiological functions related to energy homeostasis and metabolic function.

Peroxisome proliferation was considered to be a possible mechanism associated with hepatocellular vacuolation, hypertrophy, and tumor production induced by exposure to PFOA and PFOS. However, as discussed in more detail in section VIII, these adverse effects have been demonstrated to occur via mechanisms other than peroxisome proliferation. Studies have demonstrated that hepatocellular hypertrophy and nonneoplastic liver lesions occur in rodent models in which peroxisome proliferation cannot occur because the rodent has been genetically altered to lack the receptors by which peroxisome proliferation is mediated. (Filgo et al. 2015)

Although human PPARα levels are thought to be about 10% of the levels in rodents (DeWitt et al., 2009b), humans are responsive to agents that act via PPARα; the MOA for the fibrate class of drugs designed to lower serum lipids is via PPARα activation. Accordingly, the risk of adverse effects to humans associated with PPARα/peroxisome proliferation cannot be discounted. Further supporting this point, studies in pigs—an animal model that, like humans, is less susceptible to peroxisome proliferation than humans—have shown that peroxisome proliferators may nonetheless pose a risk of carcinogenesis (Luci, et al.2007).

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VIII. Detailed Supported Opinions

VIII.1 Basis and Methodology for Rendering Opinions

As mentioned above, several agencies within the U.S. and on the international level have performed comprehensive science assessments to determine if exposure to PFCs is associated with an increased risk of adverse health outcomes in humans. Three of these assessments are particularly relevant for the questions presented here, and I was involved in each of them either in formulating a decision or as part of the external body of peer-reviewers asked to evaluate the assessments. Specifically, these are: (1) Monograph 110, Some Chemicals Used as Solvents and in Polymer Manufacture, by the IARC of the WHO, (2) the Health Effects Support Document for Perfluorooctanoic Acid (PFOA) and the Health Effects Document for Perflurooctane Sulfonate (PFOS) written by the U.S. EPA, and (3) the Systematic Review of Immunotoxicity Associated with Exposure to Perfluorooctanoic Acid (PFOA) or Perfluorooctane Sulfonate (PFOS) by the U.S. NTP. Additional science assessments have been performed in other countries, but given the comprehensive nature of those three assessment, I do not undertake here any detailed review of assessments in other countries. I also rely here on the Toxicological Profile for Perfluoroalkyls by the ATSDR, which also is particularly relevant. The ATSDR is the part of the Centers for Disease Control and Prevention (CDC) that serves the public by preventing harmful exposures and diseases related to toxic substances, and their assessments are issued after an opportunity for public commentary and peer-review.

In addition to the three assessments and the ASTDR profile just mentioned, my opinion that PFCs pose a substantial present or potential hazard to human health is informed by the following:

1. My extensive research experience with PFCs starting with my postdoctoral research experience and continuing to present day.

2. My knowledge of the published literature relating to PFCs that I have gained from my research endeavors, including writing and submitting scientific manuscripts, review articles, book chapters, commentaries, and grant proposals.

3. From reviewing papers concerning the toxicity of PFCs submitted to and published in publicly available peer-reviewed scientific journals.

4. From serving as a peer-reviewer or participant for the U.S. EPA, NTP, and IARC assessment documents.

5. From presenting research findings and scientific opinions about the toxicity of PFCs at various scientific meetings.

The methodology for rendering my opinion is based on the principles of toxicology detailed in the introduction and an evidence-based integrative approach used by toxicologists to determine the likelihood of harm to human health following exposure to environmental contaminants.

VIII.2 Detailed Supported Opinion – Cancer

It is my opinion, based on the weight of the toxicological evidence, as supported by epidemiological evidence, that PFCs pose a substantial present and potential carcinogenic hazard to human health.

I address first IARC's Monograph 110. By way of background, IARC invites interdisciplinary working groups of expert scientists to review publicly available published studies and to evaluate the weight-of-evidence to determine whether exposure to an exogenous agent can increase the risk of cancer (IARC, 2016). The principles, procedures, and scientific criteria that guide evaluations are described in the preamble to the *IARC Monographs*. These interdisciplinary groups are divided into sub-groups and members of the sub-groups review one another's sections (internal peer-review), which are then submitted to the entire group for review, discussion, and ultimately consensus (although dissenting opinions can be noted) about the classification of the agent under discussion. Agents are classified as carcinogenic to humans (Group 1), probably carcinogenic to humans (Group 2A), possibly carcinogenic to humans (Group 2B), not classifiable as to its carcinogenicity to humans (Group 3), or probably not carcinogenic to humans (Group 4). Classification is based on human data, experimental animal data, and mechanistic data.

I served as a member of the mechanism sub-group of the working group for *Monograph 110* in 2013-2014 (As a reminder, "mechanistic" refers to the particular reaction of the exogenous agent with a target molecule or molecules to induce toxicity, i.e., an adverse health outcome or outcomes (Gregus, 2015)).

PFOA was evaluated in *Monograph 110*, which was published electronically in 2016 (http://monographs.iarc.fr/ENG/Monographs/vol110/index.php) and is freely downloadable. PFOA was classified as Group 2B, possibly carcinogenic to humans, based on limited evidence in humans of a positive association for cancers of the testis and kidney and based on limited evidence in experimental animal models. Limited evidence of carcinogenicity in humans means that a positive association has been observed between the exogenous agent and cancer for which a causal interpretation is considered credible but that chance, bias, or confounding could not be ruled out (IARC, 2006). Limited evidence of carcinogenicity in experimental animal models means that the data suggest a carcinogenic effect but are limited by a small number of experiments, unresolved questions in study design, conduct, or interpretation, exposure increases in incidence of only benign neoplasms or lesions of uncertain neoplastic potential, or evidence of carcinogenicity is restricted to studies that demonstrate promotion in only a narrow range of tissues or organs (IARC, 2006). Put more plainly, the evidence so far tends to show a carcinogenic effect, but more evidence is necessary before that tendency can be proven to be causal.

The IARC working group for *Monograph 110* (IARC, 2016) evaluated data from occupational cohorts, communities of high exposure, and the general human population where PFOA serum concentrations were examined in relation to various types of cancer. The working group determined that there was some evidence of an association between PFOA exposure and cancer of the kidney (Steenland and Woskie, 2012) and bladder (Raleigh et al., 2014) in occupationally-exposed humans. In humans from communities of high PFOA exposure, elevated risks of kidney

and testicular cancer (Viera et al., 2013; Barry et al., 2013) and increased risks for prostate and breast cancer were observed in relation to estimated PFOA serum concentrations (Viera et al., 2013). Two published studies of the general human population available to the working group demonstrated risk ratios (the ratio of the cumulative incidence in the exposed group to the unexposed group) of greater than one (indicating that cumulative incidence in the exposed group is greater than cumulative incidence in the unexposed group) for pancreatic cancer (Eriksen et al., 2009) and prostate cancer (Eriksen et al., 2009; Hardell et al., 2014). Overall, the working group concluded that findings published in peer-reviewed literature established an association between PFOA exposure and cancer, particularly with respect to cancers of the kidney and testis in exposed humans.

The IARC working group for *Monograph 110* used two studies in experimental rodent models as strong evidence that exposure to PFOA (specifically ammonium perfluorooctanoate, the ammonium salt of PFOA) is carcinogenic in experimental animal models. In both studies, male and female (Butenhoff et al., 2012a) or male (Biegel et al., 2001) Sprague-Dawley (SD) rats were given diets containing PFOA. Diets contained 0, 30 (Butenhoff et al, 2012a), or 300 (Butenhoff et al., 2012a; Biegel et al., 2001) parts per million (ppm) of PFOA for two years, which is considered a chronic or lifetime exposure. In these rodent cancer bioassays, male rats exposed to 300 ppm of PFOA had an increased incidence of testicular Leydig cell adenoma relative to unexposed animals. In the Biegel et al. (2001) study, an increased incidence of hepatocellular adenoma and pancreatic acinar cell adenoma was observed. A re-evaluation of the Butenhoff et al. (2012a) data using evaluative criteria from the Biegel et al. (2001) study, revealed an increased incidence of pancreatic acinar cell hyperplasia in male animals given 300 ppm (Caverly-Rae et al., 2014). The working group (IARC, 2016) also reported that two feeding studies in rainbow trout (Benningthoff et al., 2012), an experimental animal model used for hepatic carcinogenesis, demonstrated that dietary exposure to PFOA promotes hepatocarcinogenesis, which was used as additional supportive evidence of carcinogenicity in experimental animal models.

The Biegel et al. (2001) study was co-authored by scientists from Covance Laboratories, Inc., Pfizer, Inc., and the DuPont Haskell Laboratory for Toxicology and Industrial Medicine. It is not clear from the manuscript where the studies were performed or which company performed which analysis. Covance Laboratories, Inc., is a contract research organization that performs scientific studies for various organizations by contract. Pfizer, Inc., is a biopharmaceutical company, so their role in the project is unclear. DuPont Haskell Laboratory for Toxicology and Industrial Medicine was a research laboratory that studied, in part, DuPont products for safety (it appears to now be named the Stine Haskell Research Center). Regardless, this particular study was performed to evaluate potential mechanisms behind tumor production associated with ammonium perfluorooctanoate (APFO or C8) and Wyeth-14,643 (WY), a pharmaceutical compound developed to lower serum cholesterol (not used clinically). Both of these compounds were thought to induce peroxisomal enzymes via the process known as peroxisome proliferation. Therefore, the Biegel et al. (2001) study evaluated the ability of C8, a potential PPARα activator, and WY, a known PPARα activator, to induce tumors in a two-year feeding study in male CD rats. Additional endpoints were evaluated to posit hypotheses about other mechanisms of tumor production.

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The Biegel et al. (2001) study demonstrated that exposure to 300 ppm of C8 over two years was sufficient to induce increased tumor incidence compared to control animals in the liver, testes, and pancreas (Figure 7). While Biegel et al. (2001) concluded that several mechanisms may be

TABLE 2
Summary of Hyperplasia/Neoplasia Incidence in the Liver, Testes, and Pancreas from Rats Fed C8 or WY

	Control		CP-C8		C8 300 ppm		WY 25 ppm	
Lesion	Incidence	%	Incidence	%	Incidence	%	Incidence	%
Liver								
Adenoma	2/80	3	1/79	1	10/76	13#	15/67	22*
Carcinoma	0/80	0	2/79	3	0/76	0	3/67	4
Adenoma/carcinoma combined	2/80	3	3/79	4	10/76	13#	17/67	25*
Testes								
Leydig cell hyperplasia	11/80	14	26/78	33	35/76	46*	46/67	69*
Leydig cell adenoma	0/80	0	2/78	3	8/76	11#	16/67	24*
Pancreas								
Acinar cell hyperplasia	14/80	18	8/79	10	30/76	39#	41/67	61*
Acinar cell adenoma	0/80	0	1/79	1	7/76	9#	25/67	37*
Acinar cell carcinoma	0/80	0	0/79	0	1/76	1	0/67	0
Adenoma/carcinoma combined	0/80	0	1/79	1	8/76	11#	25/67	37*

Note. Values given for incidence of lesions are from all scheduled and unscheduled deaths; %, percent of control.
* Significantly different from the *ad libitum* control group, $p < 0.05$.
# Significantly different from the pair-fed control group, $p < 0.05$.

Figure 7. Summary table of liver, testis, and pancreatic lesions observed in rats fed C8 or WY for two years. Note the statistically significant increases in hyperplasia (enlargement of organ/tissue) and neoplasia in the liver, testis, and pancreas from rats feed 300 ppm of C8. Red box added for emphasis. From Biegel et al. (2001).

working differently in each organ, their overall conclusion was that C8 and WY exposure produced increases in endogenous growth factors that stimulated growth of tumor cells in these organs. The endogenous factors included an increase in peroxisomes in the liver, an increase of cholecystokinin in the pancreas, and an increase in serum estradiol that targeted Leydig cells of the testes. These latter two factors are hormones, supporting the idea of C8 as an endocrine disrupting compound. Hormones often stimulate growth of cells and as such, may be labeled as "promoters," or chemical carcinogens that promote growth of cancerous cells (Klaunig, 2015).

Evidence that PFOA acts as an endocrine disruptor, and potentially as a promoter, in humans was provided in a 1992 study of 3M workers conducted by Dr. Frank Gilliland, which found "hormonal changes associated with PFOA in humans," including consistent findings of increased estradiol as well as low free testosterone, and unchanged LH [luteinizing hormone]" (Dr. Gilliland's 1992 thesis, 3M_MN03112178 at 3M_MN03112393).

The Butenhoff et al. (2012a) article was co-authored by scientists from the 3M Company and the DuPont Company. The underlying study of the manuscript was conducted by Riker Labs between 1981 and 1983 at 3M's request (3MA00027126). The study report, which was drafted by Conrad King, a consultant hired by 3M, was not completed until five years later, in 1987 (3MA00027126). The study authors noted that the manuscript was actually a summary from this 1987 report that had only been available on the U.S. EPA public docket (Administrative Record AR-226) and that "the increased attention given to the potential health hazards of APFO in the scientific literature in recent years has prompted this detailed summary of the study to make the key findings and conclusions of the study more accessible" (Butenhoff et al., 2012a).

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This particular study was an evaluation of both chronic toxicity and carcinogenicity (i.e., a rodent cancer bioassay) in a two-year feeding study of male and female SD rats. The 1987 final report noted that the incidence of Leydig cell adenomas in rats dosed at 300 ppm was statistically significantly greater than the control group (3MA00027126 at -151) and the 2012 published study reported that an increased incidence in testicular Leydig cell adenomas in male rats fed 300 ppm of C8 was the only neoplastic outcome observed; liver and pancreatic neoplasms were not observed (Figure 8).

Table 8
Incidence of neoplastic microscopic findings for male and female rats in either control groups or groups fed 30 ppm or 300 ppm APFO in their diet for 2 years.

Organ/lesion	Dietary dose group (ppm APFO)					
	Males			Female		
	0	30	300	0	30	300
Adrenal						
Pheochromocytoma, benign	2/49 (4)[a]	4/50 (8)	4/50 (8)	2/50 (4)	0/50 (0)	0/49 (0)
Pheochromocytoma, malignant	0/49 (0)	1/50 (2)	0/50 (2)	0/50 (0)	0/50 (0)	1/49 (2)
Liver						
Hepatocellular adenoma	0/49 (0)	0/50 (0)	0/50 (0)	0/50 (0)	0/50 (0)	0/50 (0)
Hepatocellular carcinoma	3/49 (6)	1/50 (2)	5/50 (10)	0/50 (0)	0/50 (0)	1/50 (2)
Mammary gland						
Adenocarcinoma	–	–	–	7/46 (15)	14/45 (31)	5/44 (11)
Adenoma	–	–	–	3/46 (7)	0/45 (0)	0/44 (0)
Carcinoma	–	–	–	1/46 (2)	0/45 (0)	0/44 (0)
Fibroadenoma	–	–	–	10/46 (22)	19/45 (42)	**21/44 (48)**[†]
Lymphangiosarcoma	–	–	–	0/46 (0)	0/45 (0)	1/44 (2)
Reevaluation by PWG[b]						
Adenocarcinoma				9/50 (18)	16/50 (32)[c]	5/50 (10)[c]
Adenoma				1/50 (2)	0/50 (0)	0/50 (0)
Fibroadenoma				16/50 (32)	16/50 (32)	20/50 (40)
Fibroadenoma (multiple)				2/50 (4)	6/50 (12)	3/50 (6)
Pituitary						
Adenoma	17/48 (35)	17/47 (36)	13/46 (28)	33/46 (72)	39/47 (83)	36/50 (72)
Testes/epididymis						
Leydig cell adenoma	0/49 (0)	2/50 (4)	**7/50 (14)**[†]	–	–	–
Thyroid						
C-cell adenoma	0/43 (0)	2/47 (4)	4/47 (9)	1/50 (2)	0/45 (0)	0/41 (0)
C-cell carcinoma	2/43 (5)	0/47 (0)	0/47 (0)	0/50 (0)	0/45 (0)	0/41 (0)

Bolded values are statistically significant.
[†] Statistically significantly different from controls ($p \leq 0.05$).
[a] Number observed/number examined (%).
[b] Hardisty et al. (2010).
[c] The incidence in the groups sharing this footnote were statistically significantly different from each other ($p < 0.01$, Hardisty et al., 2010).

Figure 8. Summary table of lesions from various tissues observed in rats fed APFO for two years. Note the statistically significant increases in Leydig cell adenomas in male rats fed 300 ppm of APFO. The findings of increased fibroadenoma in mammary glands of female rats fed 300 ppm of APFO was considered by the study authors to be within the norm for background variation of this lesion in SD rats. Red boxes added for emphasis. From Butenhoff et al. (2012a).

However, the 1987 report discounted this finding as within the range of historical control animal data. (*Id.*) Several aspects of this study report are questionable based on consensus principles to guide the use of historic control data of proliferative lesions from chronic rodent bioassays by the Historical Control Data Working Group (HCDWG) under the Scientific and Regulatory Policy Committee of the Society for Toxicologic Pathology (Keenan et al., 2009).

First, the HCDWG asserts that the concurrent control group is the most relevant comparator for determining treatment-related effects in a study. Historic control data "may be useful in the interpretation of rare tumors, marginally greater incidences and/or severity of proliferative

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changes in treated animals compared to controls, and unexpected increases or decreases of tumor incidences in study control animals" and historic control data "from the laboratory that conducted the study under review will likely be more comparable than [historical control data] compiled from several laboratories" (Keenan et al., 2009). Therefore, while it is sometimes appropriate to use historical control data for comparison where a dosed group *does not* exhibit a statistically significant different effect from the experimental control group, it is rarely, if ever, appropriate to use historical control data where a dosed group *does* exhibit a different effect from the experimental control group.

Second, even if it were appropriate to use historical control data, it appears that the historical animal data used were inaccurate, as suggested in a memo sent to 3M by a DuPont scientist shortly after the study report was issued (3M_MN02330325). Moreover, it is apparent that 3M may have been aware that the Leydig cell adenoma finding was a valid treatment-related finding. A phone conversation report between a 3M employee and the veterinary pathologist responsible for the study reveals that the pathologist viewed the effect in the testes to be associated with APFO treatment and "not within normal biological variation" (3MA10014327). A draft version of the report states that, with respect to the Leydig cell tumors, an APFO effect "cannot be ruled out" (3MA01405733). This language is omitted from the final report.

Additionally, given the difference in findings between the Biegel et al. (2001) and the Butenhoff et al. (2012a) studies, a subset of authors from both studies (Butenhoff, Chang, Frame, and Kennedy) and an additional author (Caverly-Rae) performed a re-review of data from the Butenhoff et al. (2012a) and Biegel et al. (2001) studies (Caverly-Rae et al., 2014). The re-review reported that the pancreatic changes observed in the Butenhoff et al. (2012a) study were found to be consistent with the changes observed in the Biegel et al. (2001) study. Therefore, two types of neoplastic changes actually were observed in the Butenhoff et al. (2012a) study.

The authors of the Biegel et al. (2001), Butenhoff et al. (2012a), and Cavalry-Rae et al. (2014) studies discount the applicability of their findings to human health. In this respect, I disagree with their conclusions, which I find to be unsupported by the evidence. It is notable that the authors of the Caverly-Rae et al. (2014) study were scientists from the DuPont Haskell Global Centers, the 3M Company, and a consultant to the DuPont Company, and, as noted above, the Butenhoff et al. (2012a) study was co-authored by scientists from the 3M Company and the DuPont Company. The Biegel et al. (2001) study did not itself associate the observed changes in tumor incidence in animals with a hazard to human health except to note that human Leydig cell adenomas and surrounding hyperplastic Leydig cells secrete large amounts of estradiol. For their part, the Butenhoff et al. (2012a) and Caverly-Rae et al. (2014) studies discounted their findings as evidence that C8 posed a hazard to human health. The Butenhoff et al. (2012a) study affirmatively cited epidemiological studies that reported no association between serum PFOA and liver, pancreatic, testicular, and prostate cancer as evidence that exposure to PFOA was not associated with cancer-related outcomes. The Caverly-Rae et al. (2014) study argued that the type of pancreatic tumor observed in rats is distinctly different from tumors commonly observed in humans and that because there is no known association between other types of peroxisome proliferators and pancreatic tumors in humans, the relevance of the rodent data to human health risk assessment was questionable.

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However, as noted above and discussed in section VII.6b, evidence that carcinogenicity in a rodent model may be mediated by peroxisome proliferation is an insufficient basis upon which to discount the applicability of findings to humans. In addition, as Dr. Grandjean discusses in more detail in his report, epidemiology studies have found statistically significant associations between PFC exposure and various cancers, and, as he concluded, demonstrate that PFC exposure has a substantial potential to cause cancer in humans, particularly with respect to kidney and testicular cancer, and that the same is highly likely with respect to prostate and bladder cancer and possibly with respect to breast cancer. I make additional points, below, which further support that peroxisome proliferation is not the only mechanism by which various types of cancers can be induced by exposure to PFCs.

My opinion that these studies are indicative of carcinogenicity in humans is consistent with that of the IARC. The IARC working group for *Monograph 110* reviewed the data from the Biegel et al. (2001), Butenhoff et al. (2012a), and Cavalry-Rae et al. (2014) studies and deemed the data from these studies to be evidence of the carcinogenicity of PFOA in experimental animal models. Considering these and other studies, the IARC concluded that the weight of all of the evidence, considered together, tended to show a carcinogenic effect.

Mechanistic data linking PFOA exposure to cancer in humans and experimental animal models was considered moderate and not quite strong enough to move PFOA to Group 2A or Group 1. Stronger mechanistic data would have included greater evidence that PFOA is mutagenic or genotoxic, acts as a growth promoter in multiple cell types, or induces carcinogenicity through accepted and recognized pathways. The mechanisms considered in the monograph included PPARα activation and peroxisome proliferation, activation of other nuclear receptors, oxidative stress (including production of reactive oxygen species, decreased antioxidant capacity, and mitochondrial dysfunction), modulation of inflammatory pathways, and modulation of hormone levels (IARC, 2016). Although the working group for *Monograph 110* discussed some studies demonstrating the ability of PFOA to act as a cancer promoter (Abdellatif et al. 1990, 1991, 2003; Benninghoff et al., 2012; Nilsson et al., 1991), an additional study in using the cell transformation assay on Syrian hamster embryo (SHE) cells further supports that PFOA acts as a cancer promoter in the absence of genotoxicity (Jacquet et al., 2011).

The IARC working group for *Monograph 110* also noted that modulation of reproductive hormones by PFOA has been reported in human cells, rodents, and fish, including activation of estrogen receptors, interference with testosterone/estradiol balance, and induction of aromatase, the enzyme that, in part, converts testosterone to estrogen. Interference with these pathways can be associated with cancers of reproductive tissues. Biegel et al. (1995) designed a series of studies to test components of the proposed mechanism by which C8 induces Leydig cell tumors in rats (originally reported in a study by Cook et al., 1992). Biegel et al. (1995) reported that serum estradiol was increased in rats treated with C8 and that this increase was likely due to induction of aromatase in the liver and reduced metabolism/excretion of estradiol. In addition, increases in levels of estradiol and transforming growth factor alpha (TGFα) were measured in the interstitial fluid of the testes, which the authors interpreted as consistent with their hypothesis that estradiol may modulate growth factor expression within the testis (Biegel et al., 1995). TGFα is a ligand for the epidermal growth factor receptor, which activates a signaling pathway for cell proliferation, differentiation, and development, and has been associated with many types of cancers in experimental animal models and humans (NCBI, 2017). Estradiol is a well-known

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growth promoter that has been implicated in several types of cancers of the female reproductive system, notably the endometrium and the ovary, and has been classified as carcinogenic to humans by the IARC (IARC, 2012). Estradiol also may play additional roles in the male reproductive system as evidence is emerging that supports estrogens as prostate cancer-causing agents (Nelles et al., 2011).

Another putative mechanism is inhibition by PFCs of gap junctional intercellular communication (GJIC). GJIC is a process that plays a crucial role in the maintenance of normal cell growth and when inhibited, may be a non-genotoxic mechanism of carcinogenicity (Upham et al., 1998) and a response of cells to agents that promote cell growth (Upham et al., 2009). In two articles published by a single laboratory from Michigan State University, PFOA, PFOS, PFOSA, PFHxS, and PFDA were reported to inhibit GJIC in a dose-dependent manner, with PFOS and PFDA having the most potent effects (Upham et al., 1998; Hu et al., 2002). In a follow-up study published in 2008 (Upham et al., 2009), the authors reported on additional molecular mechanisms associated with PFOA-induced inhibition of GJIC. Dr. John Giesy, a co-author of studies on GJIC, and former consultant to 3M, has testified that chemicals that block cell-to-cell interaction, which occurs through inhibition of GJIC, are "potent cancer promoters" (Giesy Dep. Tr. 68:13-18, 201:3-203:7). These studies with GJIC provide additional evidence that PFCs may induce carcinogenic outcomes via several mechanisms.

Based on the assessment of PFOA by the IARC, the weight of evidence so far tends to show that PFOA can induce cancer as an adverse health outcome in exposed humans. It is also notable that the U.S. EPA has concluded that there is suggestive evidence that PFOA is carcinogenic, and that there are sufficient data to derive a cancer slope factor for this compound (U.S. EPA, 2016c).

Evidence from studies performed by 3M and reviews from governmental agencies also support the conclusion that PFOS and N-EtFOSE are carcinogenic. Between 1981 and 1983, 3M completed a 2-year carcinogenicity study of N-EtFOSEin rats (3MA00593233). Conrad King, a 3M consultant, drafted the final report, which was not complete until 1988 (*Id.*). In this report, 3M concluded that although liver carcinomas were observed in female rats at the highest administered dose, they were "slightly outside" of "reasonable historical control limits" (*Id.*). Again, as I observed above, it is rarely, if ever, appropriate to use historical data to discount a statistically significant finding of an adverse health effect in a treatment group. Further, upon a subsequent independent re-examination of the tissues used in this study, a separate pathologist concluded that "the distinct increases in hepatocellular neoplasms in high dose females combined with increased hyperplastic nodules in both sexes are clear indicators that the test material should be regarded as a liver carcinogen in rats" (3MA10025147). Moreover, in a subsequent study completed by Covance Laboratories at 3M's request, statistically significant increases in combined liver adenomas and carcinomas were found in female rats at the highest administered dose, as well as a statistically significant increases in combined thyroid follicular cell adenomas and carcinomas in male rats at the highest administered dose (3MA00812492).

With respect to PFOS, 3M completed a 2-year carcinogenicity study of PFOS in rats in 2002 (3MB00040027). This study found a statistically significant increase in combined thyroid follicular cell adenomas and carcinomas in male rats from the highest administered dose group, and a statistically significant increase in combined hepatocellular adenomas and carcinomas in

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female rats from the highest tested dose group. In addition to this study, the U.S. EPA's recent review of PFOS concluded that there is suggestive evidence that PFOS is carcinogenic (U.S. EPA, 2016d). In addition, Dr. John Butenhoff, the former manager of 3M's corporate toxicology department and head of 3M's fluorochemical research program agreed that he has characterized PFOS and N-EtFOSE as carcinogenic in rats (Butenhoff Depo. Tr. 193:23-25; 194:1-9).

In short, the weight of the evidence supports the conclusion that PFOS and N-EtFOSE are also carcinogenic to humans.

By extension, other PFCs that induce toxicities similar to PFOA, PFOS, and N-EtFOSE and that work through similar modes or mechanisms of action, are likely to induce cancer as an adverse health outcome in exposed humans as well. I agree with the assessment by the IARC that PFOA is possibly carcinogenic to humans based on evidence in experimental animal models that is supported by epidemiological findings in humans. In addition, the U.S. EPA classifies evidence of carcinogenicity for both PFOA and PFOS as suggestive of carcinogenic potential in humans (U.S. EPA, 2016c,d).

Since the IARC assessment, an additional study of an occupationally-exposed cohort by the C8 Science Panel (Steenland et al., 2015) demonstrated a positive trend of prostate cancer with serum PFOA levels. A study of Danish women reported an increased breast cancer risk associated with PFOSA exposure (Bonefeld-Jørgensen et al., 2014). Published studies of other PFCs exist, but do not report positive associations between serum PFC levels and cancer outcomes. Evidence of cancers of the male and female reproductive system build support for a pathway to carcinogenicity that results from hormone modulation.

VIII.3 Detailed Supported Opinion – Developmental Toxicity

It is my opinion, based on the weight of the toxicological evidence, as supported by epidemiological evidence, that PFCs pose a substantial present and potential developmental toxicity hazard to human health.

VIII.3a Current Evidence of PFC-Induced Developmental Toxicity

The U.S. EPA has identified developmental toxicity as a critical endpoint for PFOA and PFOS toxicity. By way of background, the U.S. EPA established risk assessment guidelines to assess potential health risks to humans following exposure to exogenous agents. See https://www.epa.gov/risk/risk-assessment-guidelines#tab-1. The Health Effects Support Document for Perfluorooctanoic Acid (PFOA) and the Health Effects Document for Perflurooctane Sulfonate (PFOS) were written by the U.S. EPA (U.S. EPA, 2016c,d) to address the presence of PFOA and PFOS in drinking water as part of their regulatory requirements under the Safe Water Drinking Act (SWDA). Both documents are available electronically and are freely downloadable (https://www.epa.gov/ground-water-and-drinking-water/supporting-documents-drinking-water-health-advisories-pfoa-and-pfos). These documents were both reviewed by scientists from within the U.S. EPA and by scientists external to the U.S. EPA. Additionally, when these documents were released in draft form, any party (i.e., private citizen, industry representative, representative from another agency, trade group representative, etc.) was given the opportunity to provide evaluative comments for consideration in revised versions.

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During external peer-review proceedings, these parties also could attend as observers. The process therefore ensured a document that is transparent, responsive, and rigorously reviewed by scientific experts. However, the documents are still in draft form and cannot yet be quoted or cited as official U.S. EPA documents. In this report, they are used as support documents as they reflect a thorough assessment of the toxicological data associated with PFOA and PFOS.

I served as an external peer reviewer to the draft forms released by the U.S. EPA in 2014.

One goal of a science assessment that supports an assessment of risk to human health is to assist in deriving a RfD. As defined by the U.S. EPA (1993), a RfD is an estimate of a daily exposure to the human population that is likely to be without an appreciable risk of deleterious effects during a lifetime and is expressed in mg/kg of body weight/day (mg/kg/day). The RfD includes values for uncertainties in the estimate as well as factors for protecting sensitive subpopulations and is often derived from a NOAEL or LOAEL identified for a critical endpoint (U.S. EPA, 1993). In general, a critical endpoint is an adverse health outcome exhibiting the lowest NOAEL as this seeks to ensure that if that critical toxic effect is prevented, then other toxic effects also are prevented (U.S. EPA, 1993). However, as I addressed above, the U.S. EPA now often uses BMDs, rather than NOAELs or LOAELs to establish RfDs.

The U.S. EPA health documents were generated after review of a large number of relevant studies, and the weight of the evidence showed a correlation between PFOA/PFOS exposure and various adverse health effects. As discussed in the U.S. EPA health effects documents, a critical endpoint identified for both PFOA and PFOS was developmental toxicity. Among the large number of studies that were considered and that are cited in the respective health effects support documents for PFOA and PFOS (U.S. EPA, 2016c,d), are studies that demonstrate developmental toxicity following *in utero* exposure to PFOA or PFOS. In a two-generation study of PFOA *in utero* exposure was associated with a delay in sexual maturation in both male and female rats (Butenhoff et al. 2004). Studies with PFOS have demonstrated that *in utero* exposure leads to birth defects such as cleft palate, ventricular septal defect, and enlargement of the right atrium in rat pups (Thibodeaux et al. 2003), and significantly reduces the survival of rat pups (Lau et al. 2003). In the end, two studies were used to develop RfDs for each compound, but were supported by findings of other studies that reported adverse health outcomes at similar doses and for similar exposure durations. For PFOA, reduced ossification of bones and accelerated puberty (in males) was observed in CD-1 mice exposed to a range of PFOA doses from gestational day (GD) 1 through GD 17 and were used as the endpoints for deriving the RfD (Lau et al., 2006). The LOAEL identified in this study was 1 mg/kg given to pregnant dams (Figures 9a,b); no NOAEL was identified. All authors of the Lau et al. (2006) study were members of the U.S. EPA and levels of PFOA in the serum were reported for both dams and the offspring. Additional endpoints reported in the study included 1) birth outcomes, such as time to birth, condition of the newborns, and number of live offspring; 2) offspring parameters, such as number of offspring and body weights throughout the lactational period, age of eye opening, and age of puberty (vaginal opening in females and preputial separation in males); and 3) teratological assessment of offspring collected at GD18 for external abnormalities, skeletal examination, and visceral evaluation.

TABLE 2
Mouse Reproductive Outcome and Fetal Teratology, Examined at Term

	PFOA dosage (mg/kg)						
	0	1	3	5	10	20	40
Dams examined (#)	45	17	17	27	26	42	9
Dams with FLR (#)	3	2	1	7	12	37	9
Dams with FLR (%)	6.7	11.8	5.9	25.9*	46.1*	88.1*	100*
Implants (# per litter with FLR)	7.0 ± 4.0	10.0 ± 3.0	13.0	11.6 ± 1.2	10.8 ± 1.2	11.5 ± 0.6	11.9 ± 0.5
Implants (# per live litter)	12.9 ± 0.4	13.1 ± 0.4	11.6 ± 0.9	11.5 ± 0.5	12.6 ± 0.6	10.2 ± 2.1	—
Live fetuses (# per live litter)	12.5 ± 0.4	13.0 ± 0.4	10.8 ± 0.9	11.1 ± 0.4	11.7 ± 0.8	7.2 ± 2.0*	—
Prenatal loss (% per live litter)	4.1 ± 1.4	1.0 ± 0.7	7.4 ± 2.5	2.4 ± 0.8	7.7 ± 3.3	25.9 ± 11.7*	—
Fetal body weight (g)	1.05 ± 0.02	0.98 ± 0.03	1.03 ± 0.04	1.03 ± 0.04	0.98 ± 0.05	0.86 ± 0.11*	—
Notable skeletal findings (*n*)	13	6	7	11	5	5	—
Ossification (number of sites):							
Sternebrae	5.9 ± 0.1	6.0 ± 0.1	6.0 ± 0.1	5.5 ± 0.3	5.7 ± 0.2	4.0 ± 1.1*	—
Caudal vertebrae	4.3 ± 0.3	4.1 ± 0.1	4.0 ± 0.2	4.3 ± 0.3	3.7 ± 0.2	2.1 ± 0.7*	—
Metacarpals	7.7 ± 0.2	7.3 ± 0.3	7.6 ± 0.2	6.6 ± 0.5	6.8 ± 0.4	5.2 ± 1.4*	—
Metatarsals	9.3 ± 0.3	8.9 ± 0.4	9.1 ± 0.3	8.2 ± 0.6	8.6 ± 0.4	6.2 ± 1.6*	—
Proximal phalanges (forelimb)	4.8 ± 0.8	1.8 ± 1.0*	2.2 ± 0.9*	2.9 ± 0.9	1.0 ± 0.6*	0.0 ± 0.0*	—
Proximal phalanges (hindlimb)	3.9 ± 0.9	0.4 ± 0.3*	1.5 ± 1.0	2.8 ± 0.9	1.0 ± 0.6*	0.0 ± 0.0*	—
Reduced ossification (%):							
Calvaria	13.5 ± 9.2	62.5 ± 15.5*	66.7 ± 13.0*	22.7 ± 10.4	35.0 ± 12.7	55.0 ± 20.0*	—
Supraoccipital	14.7 ± 4.0	33.3 ± 10.5	28.6 ± 8.5	27.3 ± 9.2	45.0 ± 9.4*	90.0 ± 10.0*	—
Unossified hyoid	0	0	0	0	0	26.7 ± 19.4*	—
Enlarged fontanel	17.3 ± 9.1	66.7 ± 21.1*	53.6 ± 15.8*	18.2 ± 9.6	45.0 ± 20.0	95.0 ± 5.0*	—
Notable visceral findings (*n*)	10	6	6	11	5	5	
Tail defects (curly, bent) (%)	0	0	0	20.5 ± 5.7*	5.0 ± 5.0*	11.7 ± 7.3*	—
Limb defects (club, bent) (%)	0	0	0	5.7 ± 2.8*	0	5.8 ± 3.9*	—
Microcardia (%)	0	0	0	0	5.0 ± 5.0*	30.0 ± 18.3*	—

Note. Data represent means ± SE of litters examined as indicated. One-way ANOVA indicates significant differences ($p < 0.05$) in number of live fetuses and prenatal loss. Asterisks denote significant differences from controls ($p < 0.05$) by Fisher's exact test for full litter resorptions (FLR) and by Dunnett's *t*-test for other parameters.

Figure 9a. Summary table of teratogenic outcomes observed in mice exposed to PFOA from GD1-17 of gestation. Red box added for emphasis. From Lau et al. (2006).

TABLE 5
Developmental Landmarks of Mouse Pups Exposed to PFOA *In Utero*

	Eye opening		Vaginal opening			First estrus		Preputial separation		
PFOA (mg/kg)	*N*	Age (days)	*N*	Age (days)	Body Weight (g)	*N*	Age (days)	*N*	Age (days)	Body Weight (g)
0	22	14.8 ± 0.1^{a}	47 (20)	$28.4 \pm 0.3^{a,b}$	18.0 ± 0.2^{a}	47 (20)	$29.9 \pm 0.4^{a,b}$	56 (22)	30.5 ± 0.2^{a}	25.0 ± 0.3^{a}
1	8	15.2 ± 0.2^{a}	21 (8)	27.4 ± 0.5^{b}	18.2 ± 0.5^{a}	21 (8)	28.2 ± 0.6^{b}	22 (8)	26.7 ± 0.2^{b}	$20.3 \pm 0.3^{b,c}$
3	8	$15.5 \pm 0.1^{a,b}$	21 (7)	$28.8 \pm 0.4^{a,b}$	$17.7 \pm 0.4^{a,b}$	21 (7)	$30.2 \pm 0.4^{a,c}$	20 (7)	27.1 ± 0.2^{b}	$19.4 \pm 0.6^{b,c,d}$
5	17	16.0 ± 0.2^{b}	43 (16)	29.9 ± 0.4^{a}	$17.7 \pm 0.4^{a,b}$	43 (16)	31.8 ± 0.5^{c}	46 (16)	28.2 ± 0.2^{c}	$18.3 \pm 0.5^{c,d}$
10	13	17.2 ± 0.3^{c}	27 (12)	29.3 ± 0.3^{a}	16.7 ± 0.3^{b}	27 (12)	$30.2 \pm 0.3^{a,c}$	28 (11)	28.5 ± 0.3^{c}	17.5 ± 0.7^{d}
20	3	17.9 ± 0.8^{c}	8 (2)	31.3 ± 0.5^{c}	19.3 ± 0.4^{a}	8 (2)	31.3 ± 0.5^{c}	4 (2)	31.7 ± 1.1^{d}	20.8 ± 1.2^{b}

Note. Data represent means ± SE of numbers of litters (for eye opening) or individual pups (for vaginal opening, first estrus, and preputial separation) examined as indicated. For eye opening, N = litter; for other landmarks, N = individual animal; numbers in parenthesis indicate litters represented. ANOVA indicate significant treatment effect in all parameters examined ($p < 0.05$). Significant differences ($p < 0.05$) between each dose group were determined by Duncan's multiple range test and are depicted by different letters (*a*, *b*, *c*, and *d*).

Figure 9b. Summary table of developmental landmarks observed in mice exposed to PFOA from GD1-17 of gestation. Red box added for emphasis. From Lau et al. (2006).

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For PFOS, increased motor activity and decreased habituation were observed in male SD rats exposed to a range of PFOS doses from GD 0 through postnatal day (PND) 20 (Butenhoff et al., 2009b). The LOAEL identified in the study was 1.0 mg/kg and the NOAEL was 0.3 mg/kg (Figure 10).

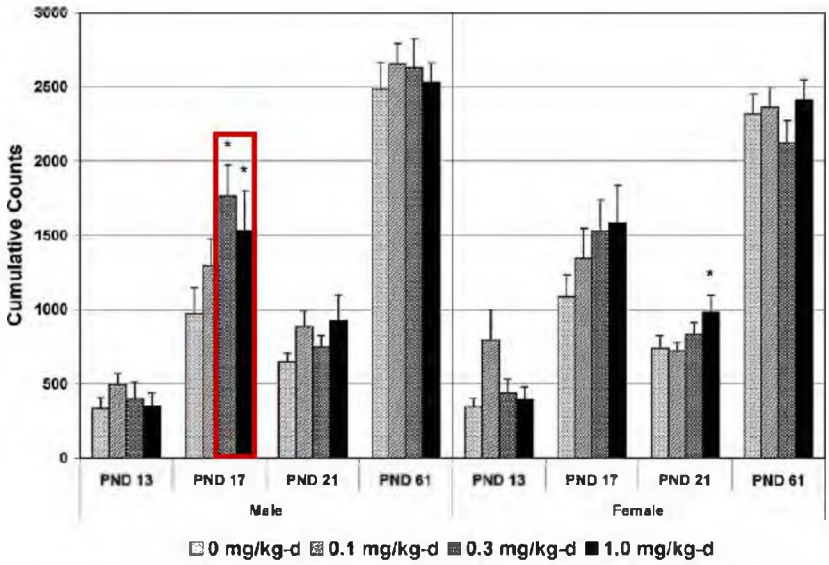

Figure 10. Summary figure of motor activity in male rats orally exposed to PFOS from GD0 through PND20. Red box added for emphasis. From Butenhoff et al. (2009b).

As both of these studies (Lau et al., 2006 and Butenhoff et al., 2009b) measured serum PFOA/PFOS concentrations, the U.S. EPA was able to calculate human equivalent doses (HED) for the LOAEL and NOAEL (when applicable) and use the HED for the RfDs. The HED is the human serum concentration, estimated from serum concentrations in experimental animal models (in units of mg of PFC/L of serum), which would be associated with the NOAEL and/or LOAEL in the experimental animal studies. Another way that the U.S. EPA (U.S. EPA, 2016d) explained the HED is that

> "The HED values are the predicted human oral exposures necessary to achieve serum concentrations equivalent to the NOAEL or LOAEL in the animal toxicity studies."

In both the PFOA and PFOS documents, pharmacokinetic models were used to estimate the HEDs. The HEDs for the NOAELs calculated for PFOA was 0.0053 mg/kg/day and for PFOS was 0.00088 mg/kg/day.

The U.S. EPA determined the RfD for PFOA, based on the HED calculated from the LOAEL identified in the Lau et al. (2006) study, to be 0.00002 mg/kg/day, which reflects uncertainty associated with intrahuman variability (i.e., sensitive subpopulations), toxicodynamic differences between animals and humans, and the use of a LOAEL instead of a NOAEL. The U.S. EPA determined the RfD for PFOS, based on the HED calculated from the NOAEL identified in the Butenhoff et al. (2009) study, to be 0.00003 mg/kg/day, which reflects uncertainty associated with intrahuman variability and toxicodynamic differences between animals and humans. Therefore, these were doses that, based on the evidence at the time, were believed not be associated with adverse health outcomes in exposed humans.

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Several other studies were considered supportive of the RfDs determined for PFOA and PFOS, based on similarities in dose, exposure duration, and the identification of NOAELs and/or LOAELs. One of the studies was my first postdoctoral paper from a project concerning PFOA (DeWitt et al., 2008), and another was from work performed during my postdoctoral training and as a faculty member at ECU (DeWitt et al., 2016b). The U.S. EPA noted that these studies, as supported by epidemiology data, identified suppression of an immune system response as an area of concern for humans and experimental animal models exposed to PFOA. The U.S. EPA noted that although the DeWitt et al. (2008) study identified a NOAEL from which the HED could be derived, the Lau et al. (2006) study was chosen as it, and similar developmental studies, indicated that lifetime consequences to PFOA exposure may occur for a less-than-lifetime exposure. However, the RfD derived from the Lau et al. (2006) study was supported by a RfD determined from the DeWitt et al. (2008) study and both had identical HEDs of 0.0053 mg/kg/day. Therefore, the DeWitt et al. (2008) study played an important role in supporting the RfD ultimately derived for PFOA.

The Lau et al. (2006) study was co-authored by scientists from the U.S. EPA, whereas the Butenhoff et al. (2009) study was co-authored by scientists from the 3M Company as well as scientists from two different contract research facilities, Biotechnics, LLC and WIL Research Laboratories. While these two studies used different species of rodents, different exposure doses and durations, and evaluated different endpoints, they both demonstrated that developing organisms are sensitive to PFC exposure. The Lau et al. (2006) authors did not attempt to extend directly the results of their study to comparisons with exposed humans, but noted that mice may be a good model for human health risk assessment of PFOA and that developmental endpoints may be appropriate for understanding other PFCs. The Butenhoff et al. (2009) study authors noted that mean serum concentrations of PFOS in the dams (pregnant female rats) reported in a companion article (Chang et al., 2009) were several hundred times higher than those reported for females in the U.S. general population. However, the HED calculated by the U.S. EPA was based on a serum concentration of 10.87 mg/L reported in the Butenhoff et al. (2009) study, which was *lower* than measured PFOS serum concentrations in, for example, a human developmental epidemiological study of maternal PFOS levels and motor or mental development in their offspring, which reported a mean maternal serum concentration of 35 mg/L (Fei et al., 2008). Therefore, given uncertainties that exist between experimental animal responses and human responses, *measured* serum concentrations in experimental animal models generally should not be *directly* compared to *measured* serum concentrations in humans.

In June 2017, a systematic review of the epidemiological literature concerning associations between PFC levels and developmental outcomes and using a process similar to the U.S. NTP (see Detailed Supported Opinion – Immunotoxicity, section VIII.4), was published by scientists from the U.S. EPA (Rappazzo et al., 2017). The authors observed consistent evidence for a positive association between PFCs and

1. Altered serum lipids,
2. Altered immunity (vaccine responses and asthma),
3. Altered renal function, and
4. Altered age at menarche.

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Rappazzo et al. (2017) noted that while the above four endpoints had the strongest evidence for a positive association with PFCs, findings of developmental perturbations associated with PFC blood levels were diverse and include cardiometabolic effects, neurological, neurodevelopmental and attention effects, and thyroid changes. They also noted that these early-life impacts on physiological parameters have the potential to increase an individual's disease risk trajectory as they age into adulthood.

Supportive of these findings and in another critical review of the literature surrounding exposure pathways for PFCs, the authors concluded that individuals experience a higher exposure intake to PFCs as infants and toddlers than during adulthood (Winkens et al., 2017). This conclusion was largely based not only on empirical measures of higher PFC concentrations in infants and toddlers as compared to adults, but on higher uptake rates per body weight for infants and toddlers and differences in behavior (being breastfed, mouthing behavior, and more contact with the ground and accompanying dusts) between children and adults (Winkens et al., 2017). Thus emerging evidence supports the U.S. EPA assessment that developing organisms are a susceptible group.

Based on the assessment of PFOA and PFOS by the U.S. EPA and on additional published materials, developing organisms are sensitive to adverse health outcomes associated with exposure to these agents. The weight of the evidence shows that that PFOA and PFOS can induce developmental toxicity as an adverse health outcome in exposed humans. At least one study (Das et al. 2008) has also reported developmental effects, including delayed eye opening and delayed sexual maturation in mice exposed *in utero* to PFBA. By extension, other PFCs that induce toxicities similar to PFOA and PFOS and that work through similar mechanisms, such as PFBA and PFHxS, are likely to induce developmental toxicity as an adverse health outcome in exposed humans as well. I agree with the assessment by the U.S. EPA that PFOA and PFOS are developmental toxicants to humans based on evidence in experimental animal models that is supported by epidemiological findings in humans.

VIII.3b Historic Evidence of PFC-Induced Teratogenicity

Since at least 1980, studies conducted or funded by 3M have shown that PFCs induce teratogenic and developmental defects in laboratory rats. In a 1980 study (3MA00356530), SD rats were exposed to 0, 1, 5, or 10 mg/kg of FC-95 (a mixture of PFCs) from GD6-15. Teratogenic changes were noted in the eyes of all FC-95 dose groups, but only the 10 mg/kg dose group had statistically higher abnormalities relative to the control group (the number of fetuses examined were very small for the control, 1, and 5 mg/kg groups, making statistically detectable differences between those groups unlikely). The abnormality was described as "an arrest in development of the primary lens fibers forming the embryonal lens nucleus, followed by secondary aberrations of the secondary lens fibers of the fetal nucleus." One lens abnormality was observed in the control group and 66.7%, 57.1%, and 40% of fetuses exposed to 1, 5, and 10 mg/kg, respectively, had eye abnormalities. In this particular study, the eye abnormality observed in the control group was considered by the authors to be an artifact.

In a 1981 study of FM-3422, a long-chain PFC also known as N-EtFOSE (3MA00326722), teratogenic changes to the eyes of SD rat fetuses exposed from GD6-15 also were described as "an arrest in development of the primary lens fibers forming the embryonal lens nucleus

followed by secondary aberrations of the secondary lens fibers of the fetal nucleus. The proportions of fetuses with the lens changes were significantly higher in all FM-3422 groups than in the control group." No lens abnormalities were observed in the control group and 64.3%, 56.9%, and 50.7% of fetuses exposed to 25, 37.5, and 75 mg/kg, respectively, had eye abnormalities (all statistically different from the control group). The discussion in this report was nearly identical to the discussion in the 1980 report. Besides lens abnormalities, rat fetuses examined in this study exhibited other malformations, including nonossification of cranial bones, bipartite vertebrae, cleft palate, and blood in the kidney parenchyma.

At least three other studies with two different PFC compounds (T-2999CoC and T-2998CoC) were performed in 1981 (3MA01508403, 3MA10008766, 3MB00012976), either with SD rats or with Fisher-344 rats, to verify the findings of the previous two studies. However, unlike the previous study, these additional studies reported lens abnormalities in the control groups and concluded that the lens findings observed across all groups were not abnormalities but artifacts. Regardless, there were still statistically significant increases in lens abnormalities in the highest dose groups relative to the control groups, which the authors did not attempt to explain. A study also was performed by the DuPont Haskell Laboratory in 1982 (3MA00248385) in response to information relayed to them by the 3M Company that exposure to C8 was possibly teratogenic because of lens changes in the eyes of near-term offspring rats.

By way of background, artifacts in sections of tissue evaluated histopathologically are not considered pathological findings, but findings associated with tissue handling, processing, fixation, storage, etc. (Chatterjee, 2014). Artifacts in tissues may include rips, tears, folds, forceps marks, cloudiness, etc. (Chatterjee, 2014). In these three latter studies, the lens abnormality was reclassified as an artifact of freehand sectioning used as part of the Wilson technique. With this technique, soft tissues are typically fixed in a solution known as Bouin's solution, which hardens soft tissues and decalcifies the bones (Burdan et al., 2005). Once the tissues are preserved, they are cut with a razor blade or other sharp cutting instrument. With an embryo, cuts are made at specific points (Figure 11) so that microscopic evaluation of internal organs can be performed. James G. Wilson designed, developed, and established this protocol in 1959 and with minor modifications, it is still widely used in teratological assessments today (Seegmiller et al., 2012). Any laboratory that evaluates teratological outcomes will have technical staff who are highly skilled with this technique and who use it routinely to assess fetuses.

Figure 11. Points where transversal sections (a-h) would be made on a 21 day-old rat fetus, with Bouin's solution and Wilson's freehand method. Modified from Burdan et al., 2005.

Dr. John Butenhoff has testified that the sectioning artifact was produced because the laboratory technicians responsible for sectioning the fetuses used the same razor to section the control groups and then the dosed groups. Thus, in his view, the razor became blunt by the time it was used for the fetuses of the dosed group, causing the purported sectioning artifact (Butenhoff Depo. Tr. 140:22-25; 141:1-16).

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This rationale is unpersuasive for several reasons. First, the practice described by Dr. Butenhoff would be inconsistent with good laboratory practices as the technicians doing the sectioning would have been blinded to the treatment groups, as would be consistent with good laboratory practices. Therefore, sectioning would have occurred in a random order and not would have occurred by treatment group.

Secondly, artifacts in tissues prepared for histological examination may occur randomly or systematically depending on how samples from different groups are treated. For example, a good laboratory practice would ensure that representative samples from all groups are included in a processing or staining batch so that all samples from one group are not processed or stained in a different batch from another group. This would ensure that certain types of artifacts are spread evenly across all groups. If good laboratory practices are incorporated, it would be highly unusual for artifacts to be disproportionately spread across dose groups, as evidenced by the studies reporting lens findings in treated groups but not in control groups, even in those studies with lens findings in the control groups as (some) treated groups had a statistically higher findings relative to the control groups. All of the reports for the studies indicated that the experiments were conducted according to good laboratory practices. Thus, assuming that good laboratory practices were followed in the studies mentioned above, there was no valid reason to discount eye abnormalities as artifacts where there were statistically significant differences between the control group and the various dose groups.

Finally, if such an artifact was produced by sectioning fetuses from the dosed groups with a dull razor, it seems likely that additional artifacts would have been observed throughout the dosed fetuses in a variety of tissues. It seems highly unlikely that a dull razor would produce a similar artifact in a similar location in multiple fetuses.

In a 1981 memo (3MA00360639), E.G. Lamprecht, DVM, PhD, a Research Veterinary Pathologist who had signed off on the previous two reports of lens findings as well as the studies that reported the lens findings as artifacts, attempted to summarize the "incorrect interpretation" of the studies with toxicological findings. Dr. Lamprecht noted the similarity between the observed abnormality and the Fraser developmental lens abnormality, and claimed that, because the observed abnormality did not develop into a cataract postnatally, as would occur with the Fraser abnormality, it was his view that labeling the finding as a teratogenic response was in error. But Dr. Lamprecht was wrong. He assumed that the findings were *exactly the same pathology as the Fraser developmental lens abnormality*. The Fraser abnormality is thought to arise from genetic mutations (Muggleton-Harris et al., 1987) and progresses to a cataract as the animals age. Because in a follow-up study (Experiment No. 0680TR0020), offspring raised to PND21 failed to demonstrate a lens finding, Dr. Lambrecht concluded that the findings in rat fetuses was an artifact and not a teratogenic change. However, one of the six general principles of teratology developed by Wilson in 1973 (the same Wilson who developed the Wilson technique) is:

> "The four manifestations of deviant development are death, malformation, *growth retardation*, and *functional deficit*" (Emphasis added, from Rogers, 2015).

Dr. Lambrecht had no evidence that the observed eye abnormality was in fact the Fraser abnormality; in fact, the lens finding could just as likely have represented a delay in eye

development in the exposed groups relative to the control group that corrected by the time the postnatal assessment was made. As data were not collected along a postnatal developmental trajectory, it was not possible to determine if this finding represented a developmental delay, i.e., growth retardation. Similarly, as the vision of the offspring at PND21 was not assessed, it also was not possible to determine if the lens finding was associated with a functional deficit. Therefore, given the lack of consistent artifacts in control groups, the lack of studies to determine if the finding was a delay in development, and the lack of functional vision assessments, it is an incorrect interpretation that the lens finding was just an artifact of the sectioning technique.

Supportive of an ocular toxicity are inhalation and dermal toxicity studies which have noted eye irritation in adult animals (Griffith and Long, 1980; Kennedy et al., 1986) following PFOA exposure, and developmental studies that have noted delays in eye opening following PFOA exposure (Lau et al., 2006; Abbott et al., 2007; Wolf et al., 2007), PFOS exposure (Lau et al., 2003), PFBA exposure (Das et al., 2008), or PFNA exposure (Das et al., 2015) exposure.

VIII.4 Detailed Supported Opinion – Immunotoxicity

It is my opinion, based on the weight of the toxicological evidence, as supported by epidemiological evidence, that PFCs pose a substantial present and potential immunotoxicity hazard to human health.

An early suggestion that PFCs may affect the immune system can be found in 1978 studies by 3M. In a 90-day study of PFOS fed to rats, lesions to the hematopoietic tissues (including the thymus, bone marrow, spleen, and mesenteric lymph nodes) were observed (3MA00593073, 3M_MN01663537). A 90-day study of APFO fed to monkeys resulted in findings of hypocellularity of bone marrow and atrophy of lymphoid follicles of the spleen and lymph nodes (3MA00593073, 3MA01797217). These tissues are associated with the body's immune response; changes in their weights and signs of histopathology in their cells are considered warning signs of immunotoxic effects. Additional studies would be warranted to determine the functional implications of such effects, i.e., the ability of the immune system to mount an appropriate response.

The most recent review of the immunotoxicity of PFCs was conducted by the NTP. By way of background, the U.S. NTP systematically reviews data on particular exogenous agents to determine their likelihood to pose a health hazard to humans. Briefly, through the Office of Health Assessment and Translation (OHAT), NTP systematic reviews are a method for answering specific research questions (Figure 12) and "use[] a predefined, multistep process to identify, select, critically assess, and synthesize evidence from scientific studies to reach a conclusion" (NTP, 2015). Therefore, the NTP systematic review process, much like the IARC and U.S. EPA processes, is an assessment of the existing scientific literature designed to analyze the quantity and

Figure 12. A schematic of the NTP systematic review process. From NTP (2015).

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quality of scientific studies related to a particular question that is relevant to environmental health.

The assessment titled Systematic Review of Immunotoxicity Associated with Exposure to Perfluorooctanic Acid (PFOA) or Perfluorooctane Sulfonate (PFOS) was undertaken by the U.S. NTP (NTP, 2016) to determine whether exposure to either chemical is associated with immunotoxicity in humans. The resulting review is available electronically and is freely downloadable (https://ntp.niehs.nih.gov/pubhealth/hat/noms/pfoa/index.html). This document was evaluated by a team composed of scientists from the NIEHS (the NIH section under which the NTP resides) and contract research organizations, and was reviewed by scientists external to the NIEHS/NTP during protocol development and draft report development. It was also reviewed by a team of external peer-reviewers prior to the final release. Additionally, prior to the external peer-review process, outside parties (i.e., private citizens, industry representatives, representatives from other agencies, trade group representatives, etc.) were given an opportunity to provide evaluative comments. During external peer-review proceedings, these parties also were permitted to attend as observers. Like the IARC and U.S. EPA, the NTP follows a process that seeks to generate a final assessment that is transparent, responsive, and rigorously reviewed by scientific experts. In my report here, the NTP monograph is used as a support document as it reflects a thorough assessment of the immunotoxicological data associated with PFOA and PFOS.

I served as an external peer reviewer of the NTP assessment during protocol development and draft report development from 2013-2016.

Based on a systematic synthesis and integration of evidence from published studies, the NTP assessment concluded that:

> "PFOA and PFOS are presumed to be immune hazards to humans and to alter immune function in humans. Exposures to PFOA and PFOS are associated with changes in multiple immune outcomes in both experimental animal and epidemiological studies. The strongest bodies of evidence to inform the evaluation of PFOA- and PFOS-associated immunotoxicity are on the antibody response." (NTP, 2015).

As depicted in Figure 13, "presumed" is a term that the NTP used to demonstrate high levels of evidence from studies in experimental animal models and moderate levels of evidence in studies of exposed humans.

The NTP undertook to evaluate the immunotoxicity of PFOA and PFOS because of widespread human exposure to PFOA and PFOS, and because of the availability of data concerning these PFCs in relation to immunotoxicity in both humans and non-human animals (NTP, 2015). An important component of this particular review was the evidence synthesis, which included a quality assessment of individual studies evaluated in the review as well as a confidence rating of the body of evidence for a particular immunotoxicological health outcome. While this approach is detailed in the NTP monograph, it adds somewhat to the evidence syntheses performed in the IARC and U.S. EPA documents in that it assigns measures of risk of bias to particular studies, as well as measures of confidence for the overall body of data. Briefly, risk of bias in particular

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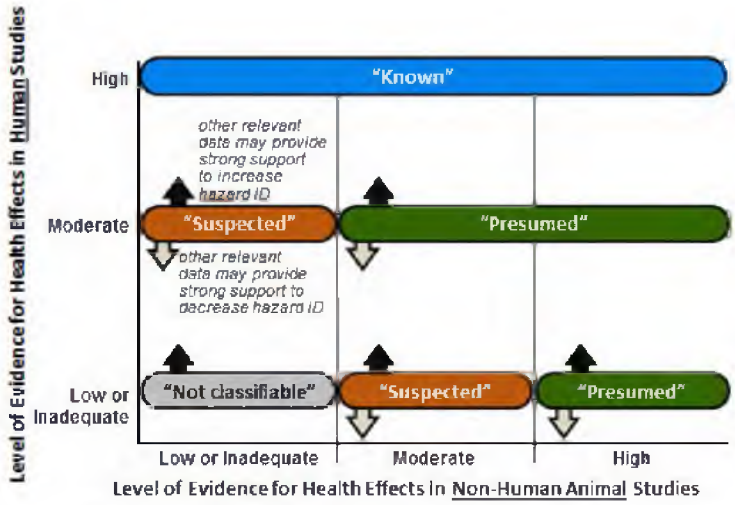

Figure 13. A schematic demonstrating how levels of evidence were classified in the systematic review of PFOA and PFOS. From NTP (2015).

studies was based on, for example, whether study authors were blind to experimental groups or if animals were distributed randomly to treatment and control groups. Overall confidence in the quality of evidence for each immune outcome was evaluated as "high," "moderate," "low," or "very low" and can be found in the OHAT Handbook for Conducting a Literature-Based Health Assessment (http://ntp.niehs.nih.gov/go/38673, see STEP 5).

My research contributions represent a substantial part of the NTP systematic review of the potential hazard to human health following exposure to PFOA or PFOS.

The NTP concluded that exposures to PFOA and PFOS were associated with changes in multiple immune outcomes in both experimental animal models and humans.

For PFOA, this conclusion was based on (a) a high level of evidence from animal studies and moderate evidence from human studies of suppression of antibody responses (a measure of the adaptive immune system), as well as (b) a high level of evidence from animal studies and a low level of evidence from human studies of increased hypersensitivity-related outcomes (NTP, 2015). In their assessment of the data for PFOA, the NTP also considered other immune-related endpoints that had been reported in epidemiological studies or in studies of experimental animal models. These included changes in disease resistance or infectious disease outcomes related to immunosuppression, suppression of natural killer cell activity (a marker of the innate immune system), and autoimmunity-related effects and outcomes.

Changes in disease resistance or infectious disease outcomes. The NTP regarded the database for these outcomes as inadequate due to a lack of experimental animal studies on this endpoint and a limited number of epidemiological studies evaluating this endpoint.

Suppression of natural killer cell activity. The NTP regarded the database for this outcome as inadequate due to a limited number of experimental animal studies on this endpoint and a lack of epidemiological studies evaluating this endpoint.

Autoimmunity-related effects and outcomes. The NTP regarded the database for these outcomes as inadequate due to a lack of experimental animal studies on this endpoint and a limited number of epidemiological studies evaluating this endpoint.

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For PFOS, this conclusion was based on a high level of evidence from animal studies and moderate evidence from human studies of suppression of antibody responses (NTP, 2015). Each of these conclusions were supported by a body of evidence indicating that these PFCs affect multiple aspects of the immune system (NTP, 2015). In their assessment of the data for PFOS, the NTP also considered other immune-related endpoints that had been reported in epidemiological studies or in studies of experimental animal models. These included changes in disease resistance or infectious disease outcomes related to immunosuppression, suppression of natural killer cell activity (a marker of the innate immune system), and autoimmunity-related effects and outcomes.

Changes in disease resistance or infectious disease outcomes. The NTP regarded the database for these outcomes as sufficient to classify PFOS as "suspected to be an immune hazard to humans" (see Figure 11) based on a low level of evidence in humans and a moderate level of evidence in experimental animal studies.

Suppression of natural killer cell activity. The NTP regarded the database for these outcomes as sufficient to classify PFOS as "suspected to be an immune hazard to humans" (see Figure 11) based on an inadequate level of evidence in humans and a moderate level of evidence in experimental animal studies.

Autoimmunity-related effects and outcomes. The NTP regarded the database for these outcomes as inadequate due to a lack of experimental animal studies on this endpoint and only one epidemiological pilot study evaluating this endpoint.

It is important to note here that while the NTP considered the weight-of-evidence strongest for the ability of PFOA to suppress antibody responses and to induce hypersensitivity and of PFOS to suppress antibody responses, the entirety of the database on immune effects was considered in their systematic review. Therefore, lack of evidence for particular immune endpoints (i.e., disease resistance/infectious disease outcomes, suppression of natural killer cell activity, and autoimmunity-related effects and outcomes) should not be interpreted as evidence *against* the occurrence of such outcomes, but that the evidence was insufficient to make a definitive classification as to the hazard.

Seven manuscripts that I co-authored were used in this NTP monograph and four were selected as studies in experimental animal models supportive of suppression of antibody responses in which the NTP had a high level of confidence. The following discussion provides a brief overview of these four studies:

- In DeWitt et al. (2016b), we evaluated suppression of T cell-dependent antibody responses (TDAR) and T cell-independent antibody responses (TIAR) in a wild type mouse model and the TDAR in a PPARα knockout model, which is a mouse that had been genetically altered to lack a functional PPARα. We found that exposure to $\geq$ 1.88 mg PFOA/kg suppressed the TIAR and 30 mg PFOA/kg suppressed the TDAR in both wild type and knockout mice. The findings demonstrate that exposure to PFOA induces adverse effects on the ability of the immune system to function an appropriate response, as by suppression of antibody responses, and that it does so in a manner not mediated exclusively by PPARα.

- In Hu et al. (2010), we sought to evaluate the developmental effects of PFOA on the TDAR. Pregnant wild type mice were exposed to 0, 0.5, or 1 mg PFOA/kg and offspring were examined. Litter weights were statistically decreased by 10% in the 1 mg/kg group. The TDAR did not differ in female offspring by dose. While we concluded that 0.5 and 1 mg PFOA/kg did not induce developmental immunotoxicity, we noted that in a pilot study, 5 mg PFOA/kg induced high (75%) neonatal toxicity. We therefore concluded that C57BL/6 mice are more sensitive to overt developmental toxicity of PFOA and to potential developmental immunotoxicity.

- In DeWitt et al. (2009a), we sought to evaluate the potential role of elevated corticosterone production on effects on the TDAR reported in DeWitt et al. (2008). We dosed adrenalectomized (adx) or sham-operated C57BL/6N female mice at several dose levels ranging from 3.75 mg PFOA/kg to 30 mg PFOA/kg and evaluated the TDAR as it related to corticosterone levels and liver markers. The data demonstrated that the immunosuppressive effects of PFOA were not the result of liver toxicity or a stress-related corticosterone response, as had been argued in a publication by DuPont authors (Loveless et al., 2008).

- In DeWitt et al. (2008), we sought to evaluate the effects of PFOA exposure on both humoral and cellular immunity and report the results of several experiments. Of note were the dose-responsive effects of PFOA on the TDAR. Wild type mice received 0 through 30 mg PFOA/kg for 15 days. From these data, we identified a NOAEL of 1.88 mg PFOA/kg, a LOAEL of 3.75 mg PFOA/kg, and a BMD of 3 mg PFOA/kg in relation to the effects of PFOA exposure on the TDAR. This was the first peer-reviewed publication, to our knowledge, on the dose-responsive effects of PFOA on the TDAR in a mouse model.

Antibody responses are accepted measures of immune function. In particular, suppression of the antigen-specific antibody response is regarded as a sensitive predictor of immunotoxicity as it requires cooperation of multiple cells and signals within the immune system (Luster et al., 1992). For example, the U.S. EPA has suggested that this response be included in immunotoxicological assessments of pesticidal compounds and agents that may fall under the Toxic Substances Control Act (i.e., U.S. EPA Health Effects Test Guidelines OPPTS 870.7800 Immunotoxicity). The NTP likewise regards reduction in this response as an indicator of decreased immune function or immunosuppression that may indicate a greater risk of disease (NTP, 2015).

The antigen-specific antibody response is fairly straightforward to evaluate in experimental animal models and in humans. In animal models, an antigen, which is an agent that stimulates antibody production, in injected into the bloodstream and then antibodies against the antigen are measured in the blood sera a specific amount of time later, usually at the peak of antibody production. Both primary (IgM) and secondary (IgG) antibody responses can be measured, although secondary responses generally require a booster injection before collection of blood for measurement of antibodies. The human analog is vaccinations; antibody responses to vaccines can be measured as well. Several epidemiological studies have measured anti-vaccine antibody responses in which the NTP had moderate confidence. This confidence rating was moderate, and not strong, based largely on possible effects from co-exposures to other agents, including other PFCs, which could have confounded the observed associations (NTP, 2015). Regardless, overall

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evidence associated with immunotoxicity following PFOA or PFOS exposure is strong given that similar responses have been observed in both humans and experimental animal models.

Suppression of immune responses in rodents by exogenous agents is predictive of suppression of immune responses in humans; in other words, observations of suppression of immune responses in rodents is translatable to the human condition following exposure to the same exogenous agents (Selgrade, 2007). This relationship is depicted in Figure 14. The cellular and humoral immune response to vaccination, for example, is regarded as a sensitive indicator of immune suppression and can reflect susceptibility to infectious and neoplastic diseases (DeWitt et al., 2016a).

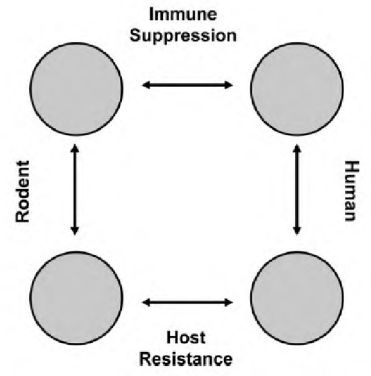

Figure 14. A parallelogram model to illustrate the relationship between immune suppression and increased risk of disease in rodent models and humans. From Selgrade (2007).

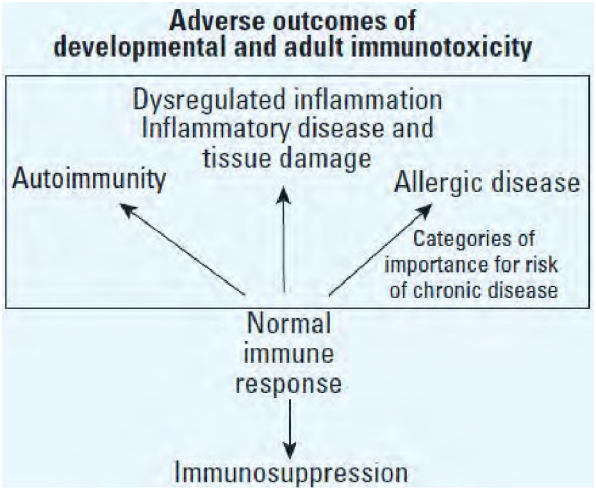

Figure 15. Adverse outcomes of immunotoxicity. Adopted from Dietert et al. (2010).

Suppression of immune responses is not the only consequence that arises from modulation of the immune system. Immunomodulation by exogenous agents can result in not only immunosuppression, but also autoimmunity, dysregulation of inflammation leading to inflammatory disease and tissue damage, and allergic disease (Figure 15; Dietert et al., 2010). Immunomodulation that occurs during development is especially problematic. Increases in childhood immune-based diseases following exposure to exogenous agents have been documented throughout the literature and a growing body of evidence supports the hypothesis that chronic diseases such as asthma, have fetal origins (DeWitt and Keil, 2017). Therefore, agents, such as PFCs, that induce immunomodulation in developing organisms, have the potential to increase the risk of later-life diseases and disorders. Several epidemiological studies have reported associations between serum PFC levels and suppression of the TDAR, including Granum et al. (2013), Grandjean et al. (2012), and Stein et al. (2016).

I understand that Dr. Grandjean addresses immunological effects seen in PFC epidemiology studies in greater detail in his report.

Based on the assessment of PFOA and PFOS by the U.S. NTP, the immune system is sensitive to adverse health outcomes associated with exposure to these agents. The weight of the evidence illustrates that PFOA and PFOS can induce immunotoxicity as an adverse health outcome in

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exposed humans. By extension, other PFCs that induce toxicities similar to PFOA and PFOS and that work through similar mechanisms, such as PFBA, are likely to induce immunotoxicity as an adverse health outcome in exposed humans as well. I agree with the assessment by the U.S. NTP that PFOA and PFOS are immune hazards to humans based on evidence in experimental animal models that is supported by epidemiological findings in humans.

VIII.5 Detailed Supported Opinion – Other Notable Toxicological Findings

As discussed above, there is a large body of evidence that exposure to PFCs leads to adverse health outcomes in a variety of experimental animal models, wildlife species, and humans. A few specific toxicological findings are of special note as they have been discounted as toxicologically irrelevant by 3M scientists, but evaluation of the actual findings suggest that they are *not* toxicologically irrelevant. Three particular toxicological outcomes associated with exposure to PFCs that have not yet been discussed are thyroid hormone disruption, liver toxicity, and mammary gland development.

VIII.5.a Thyroid Hormone Disruption

One of the findings of the C8 Science Panel was a probable link between PFOA exposure and thyroid disease. Specifically, the panel found a positive association between measured PFOA exposure and medically validated thyroid disease, which was defined as hyperthyroidism in women and hypothyroidism in men (C8 Science Panel, 2012).

Briefly, the proper regulation of thyroid hormones is crucial to the growth, development, and metabolic function of organ systems in the body. Hyperthyroidism is overproduction of thyroid hormones and hypothyroidism is underproduction of thyroid hormones. Thyroid hormone production is a complex interplay among the hypothalamus of the brain, which secretes thyrotropin releasing hormone, the anterior pituitary gland, which secretes thyroid stimulating hormone (TSH), and the thyroid gland itself, which secretes the thyroid hormones (TH) triiodothyronine (T3) and thyroxine (T4; Dong and Greenspan, 2015). Complex feedback loops balance the production of these hormones as well as dietary iodide, which is necessary for the biosynthesis of thyroid hormones, and efficacy of a variety of enzymes involved in TH biosynthesis and peripheral conversion (Dong and Greenspan, 2015). TH is mostly bound to plasma proteins (thyroxine-binding globulin, transthyretin, and albumin) while in blood circulation; only 0.04% of T4 and 0.4% of T3 are free, but this free component is the biologically active component (Cooper and Ladenson, 2011).

The C8 Science Panel did not elucidate all of the underlying causes of thyroid disease, or the mechanisms of disease, in their probable link report, yet found convincing correlations. Additional studies of human populations and the association between thyroid disease and/or TSH/TH and PFCs have been published and support a positive association between thyroid disease and PFOA and to an extent, PFOS. Although few published studies in experimental animal models have specifically evaluated TH following PFOA exposure, a handful have included markers of thyroid gland function following exposure to PFOS or other PFCs. Exposure to PFOS during adulthood has been associated with suppression of TH in monkeys (Seacat et al., 2002) and in rats and mice (Thibodeaux et al., 2003), and with suppression of T4 in rats developmentally exposed (Lau et al., 2003). Other studies in rodents also have reported

decreases in serum T4 (Curran et al., 2008; Yu et al., 2009a,b) without changes in T3 and/or TSH, which suggests possible interference with biosynthesis or peripheral conversion enzyme

A study published in 2005 by Luebker et al., examined thyroid hormone effects in rat pups exposed *in utero* to PFOS (Luebker et al., 2005, 3M_MN03095624). The results showed a statistically significant decrease in free T4, as measured using an analog assay, and an increase in TSH—which is indicative of hypothyroidism. The study authors discounted the free T4 observation, however, as resulting from a bias in the analog measurement technique. As discussed below, this asserted bias in the analog measurement technique is questionable. The study authors purported to correct this bias by measuring free T4 using the equilibrium dialysis radioimmunoassay (ED-RIA) method. However, they only ran this ED-RIA assay for a limited number of samples from the control and lowest dose group. Thus, the study did not provide any data on whether, under the ED-RIA assay, free T4 was in fact significantly decreased at higher PFOS doses. Although, the manuscript states that "the data . . . did not suggest a hypothyroid state in pups," this conclusion is not supported based on the fact that the analog assay demonstrated a significant decrease in free T4 and the study authors did not obtain sufficient measurements of free T4 using the ED-RIA assay.

In a study published in 2007 (Chang et al.), which included three co-authors from the 3M Company (S-C Chang, D.J. Ehresman, and J.L. Butenhoff) as well as funding for the project, in part, by the 3M Company, the authors suggest that that a certain type of assay used to evaluate serum TH has led to a negative bias in reported results concerning free levels of T4. In other words, according to Chang et al. (2007), an assay known as the analog assay has led to erroneous reports of decreased T4 due to the ability of PFOS to produce binding interference in the assay. According to Chang et al. (2007), PFOS binds to the sites in the assay intended for the binding of unbound T4, thus reducing the apparent amount of T4. The authors (Chang et al., 2007) argue that an assay that combines direct equilibrium dialysis followed by radioimmunoassay (ED-RIA) will not produce negative biases. They performed a series of studies to test their hypothesis that decreases in T4 would not be evident when the ED-RIA assay method was employed and generated data that they claim is supportive of their hypothesis.

The claim by Chang et al. (2007) is questionable for several reasons. First, it is generally understood by the scientific community that changing a paradigm in science, for example discounting a method generally accepted by the scientific community as valid (methods commonly used in assessment of TH status) requires confirmatory studies by several laboratories; one study is considered insufficient to discount a generally accepted method. Additionally, epidemiological data from the C8 Science Panel support an association between medically diagnosed thyroid disease and serum PFOA and additional studies support associations between other PFCs and thyroid disease and TH status, thus providing strong supportive evidence that the thyroid gland and/or the hypothalamic-pituitary-thyroid axis is adversely affected by exposure to PFCs.

In addition, Chang et al. (2007) claim that results reported in previous studies, reduced serum free T4 without a concomitant increase in TSH, do not fit the clinical profile of hypothyroidism and are further evidence of a negative bias in assay techniques. However, *low free T4 can exist without concomitant increases in TSH in a condition known as central hypothyroidism*. In this situation, levels of TH are reduced but levels of TSH may be normal, low, or slightly elevated

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(Gupta and Lee, 2011). The putative etiologies of central hypothyroidism include genetic defects, tumors, vascular dysfunction, inflammation, iatrogenic, and others (Gupta and Lee, 2011). In a study to further understand the TH effects of PFOS exposure, Yu et al. (2011) gave propylthiouracil (PTU), an anti-thyroid drug used to treat hyperthyroid, alone and in combination with PFOS to determine if PFOS was acting at the level of TH biosynthesis (PTU blocks biosynthesis at the level of the thyroid gland and blocks conversion of T4 to T3 in the periphery). The authors reported that PFOS appears to be acting at the level of the periphery, by increasing metabolism of T4 rather than acting at the level of TH biosynthesis (Yu et al., 2011). Therefore, at a very minimum, additional studies are necessary before TH/thyroid disease can be ruled out due to assay discrepancies.

Some of the thyroid hormone effects seen in laboratory animals exposed to PFOA and PFOS have also been noted in laboratory animals exposed to PFBA. In a 28-day and 90-day studies of PFBA in rats, a statistically significant dose-dependent reduction in total T4 and free T4 in male rats resulting from exposure to PFBA was seen at high doses. (Butenhoff 2012b). Thus, it is likely that the thyroid hormone effects seen in long-chain PFCs—including potential evidence of hypothyroidism—could be applicable to PFHxS and short-chain PFCs like PFBA and PFBS.

VIII.5.b Liver Toxicity

Liver enzymes are often measured clinically to determine the functionality of the liver. When liver enzyme levels are skewed, physicians must often carefully interpret the findings in terms of the characteristics of the patient and the appropriate reference ranges for that patient and possibly do additional diagnostic evaluations to determine if liver function is compromised (Giannini et al., 2005). Changes in liver enzymes can be transient and increases can be mild and such changes do not necessarily indicate a serious liver problem, but elevations in liver enzymes can indicate inflammation or damage to cells in the liver (Giannini et al., 2005). However, from a toxicological perspective, when concordance is observed among organisms, such as changes in liver enzymes in exposed humans and in exposed experimental animal models, even if the changes do not follow the same pattern, this is a signal of a shared target pathway/cell/tissue/organ.

Numerous epidemiological studies have measured liver enzyme levels and provide evidence of a positive association between PFOA and several liver enzymes (U.S. EPA, 2016c). Myriad studies in experimental animal models also report changes in liver enzymes (U.S. EPA, 2016c). These findings in experimental animal models support the findings in epidemiological studies. While the U.S. EPA assessment of PFOA noted that no evidence of liver damage has been reported in human epidemiological studies, histological evaluations of livers from experimental animal models reveal pathological changes (U.S. EPA, 2016c).

Several studies have suggested that liver toxicity from PFOA exposure in experimental animal models is not relevant to humans as liver toxicity is mediated by PPARα. Human PPARα levels are thought to be about 10% of the levels in rodents (DeWitt et al., 2009), but humans are responsive to agents that act via PPARα; the MOA for the fibrate class of drugs designed to lower serum lipids is via PPARα activation. Additionally, studies with experimental animal models lacking a functional PPARα also demonstrate liver toxicity (DeWitt et al., 2016b). Therefore, by extension, other PFCs that induce toxicities similar to PFOA and that work

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through similar mechanisms, such as PFBA, are likely to induce liver toxicity as an adverse health outcome in exposed humans as well.

VIII.5.c Mammary Gland Development

Low dose exposure to PFOA during development has been reported to delay mammary gland development in mice. The U.S. EPA (U.S. EPA, 2016c) summarized the findings of these studies and they are presented in Figure 16.

Table 3-21. Studies of Pregnant CD-1 Mice Following Administration of PFOA

Dose (mg PFOA /kg/day)	Timing	Endpoints	Reference
0, 0.01, 0.1, 0.3, 1	GD 1 to PND 21	Liver histopathology: periportal inflammation; clinical chemistry; impact of postweaning HFD	Quist et al. 2015
0, 5	GD 1-17, 8-17, or 12-17	Body weight; mammary gland morphology GD 18 (dams) and PNDs 10 and 20 (dams, female pups)	White et al. 2007
0, 5 20	GD 7-17, 10-17, 13-17, 15-17 GD 15-17	Body weight; developmental landmarks and growth to PND 189; mammary gland morphology of female pups up to 18 months	White et al. 2009; Wolf et al. 2007
0, 3, 5	GD 1-17 Cross-fostered at birth	Body weight; developmental landmarks and growth to PND 245; mammary gland morphology of female pups up to 18 months	White et al. 2009; Wolf et al. 2007;
0, 5	GD 8-17 Cross-fostered at birth	Mammary gland morphology of dams and female pups on PNDs 1, 3, 5, and 10	White et al. 2009
0, 0.3, 1.0, 3	GD 1-17	Liver weight; mammary gland morphology of female pups on PNDs 7, 14, 21, 28, 42, 63, and 84	Macon et al. 2011
0, 0.01, 0.1, 1	GD 10-17		
0, 1, 5	GD 1-17	Body weight; reproductive parameters; mammary gland morphology of F0, F1, and F2 females	White et al. 2011
0, 1 + 5 ppb in drinking water to both groups	GD 1-17 Drinking water started on GD 7 and continued to F2 generation		
0, 3	GD 1-17	Wild-type, PPARα-null, and hPPARα vv/129 mice; pup body weight at PNDs 14 and 20 plus mammary gland structure	Albrecht et al. 2013
0, 0.01, 0.1, 0.3, 1	GD 1-17 Study included both CD-1 and C57BL/6 mice	Body weight; net body weight; absolute and relative liver weight on PNDs 21, 35, and 56; serum estradiol and progesterone; mammary gland morphology	Tucker et al. 2015

Figure 16. Summary of studies that have evaluated mammary gland development in mice developmentally exposed to PFOA. From U.S. EPA, 2016c.

In March of 2017, the New Jersey Drinking Water Quality Institute (NJ DWQI) recommended health-based maximum contaminant levels for PFOA in drinking water (NJ DWQI, 2017). The NJ DWQI (2017) asserted that delayed mammary gland development and increased liver weight were the most sensitive non-carcinogenic endpoints with sufficient data for dose-response modeling. Based on their model, the NJ DWQI derived a target human serum level, which they describe as analogous to an RfD but on a serum level basis, of 0.8 ng/mL (NJ DWQI, 2017). The NJ DWQI (2017) chose mammary gland development as a sensitive endpoint as it represents a structural change in an organ that persists to adulthood, which makes it a valid endpoint for risk assessment. The U.S. EPA (U.S. EPA, 2016c) did not select delayed mammary gland development as the critical endpoint for derivation of the RfD as pups nursing from afflicted dams did not suffer effects on body weight and afflicted dams did not appear to differ from controls during a lactational challenge assay (volume of milk produced during a measured nursing period). However, the U.S. EPA did regard studies of delayed mammary gland development as supportive of the RfD that was derived for PFOA from other developmental endpoints (U.S. EPA, 2016c). Therefore, delayed mammary gland development represents an adverse health outcome that occurs at low doses and that persists into adulthood. By extension, other PFCs that induce toxicities similar to PFOA and that work through similar mechanisms,

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such as PFBA, are likely to induce impacts on mammary gland development as an adverse health outcome in exposed humans as well.

VIII.6 Detailed Supported Opinion – Toxicity Associated with Areas of High Exposure

It is my opinion, based on the weight of the toxicological evidence, as supported by epidemiological evidence, that PFCs pose a substantial present and potential hazard to human health in areas of high PFC exposure, either due to occupational exposures or by living near fluorochemical production facilities, especially from effects on the liver and the immune system and on developing organisms.

As previously mentioned, in addition to the systematic reviews of the IARC, the U.S. EPA, and the U.S. NTP, I also rely on the draft Toxicological Profile for Perfluoroalkyls by the ATSDR. ATSDR is the part of the CDC that serves the public by preventing harmful exposures and diseases related to toxic substances (ATSDR, 2017), and their assessments include an opportunity for public commentary and peer-review. The toxicological profile available through the ATSDR's web site is still the 2015 draft version available for public comment (https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=1117&tid=237), but the public comment period ended on December 1, 2015 (ATSDR, 2017). While the final document could differ from the draft document given the scope of public comments, the draft document has undergone internal ATSDR reviews and was reviewed by a panel of peers. Like the other documents discussed for cancer (IARC), developmental toxicity (U.S. EPA) and immunotoxicity (U.S. NTP), the ATSDR document also is a systematic review of the current literature. Additionally, the document is somewhat broader in scope than the other three documents as it includes "perfluoroalkyls," and does not focus exclusively on PFOA and PFOS.

I did not serve as an external peer reviewer for this 2015 draft document nor did I submit comments during the public comment period. My decision to use this document is based on the public health mission of the ATSDR and my understanding of their review process, which is rigorous and transparent. The ATSDR summarized findings from epidemiological studies and determined the following health effects were consistently associated with PFOA and PFOS serum levels:

1. Increases in serum lipid levels.
2. Decreases in birth weight.
3. Increases in uric acid levels.
4. Alterations in biomarkers of liver damage.
5. Carcinogenicity.

In their summary of findings from studies of experimental animal models, the ATSDR determined the following health effects were primary effects:

1. Liver toxicity.
2. Developmental toxicity.
3. Immunotoxicity.

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The ATSDR toxicological profile also examined, summarized, and interpreted available toxicologic information to determine levels of exposure that present a significant risk to human health (ATSDR, 2015). One of the values that the ATSDR derives is similar to a RfD or HAL that the U.S. EPA calculates. The analogous value derived by the ATSDR is the minimal risk level (MRL), which they define as

> "an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure." (ATSDR, 2015)

Although the overall document addresses the toxicity of PFCs beyond PFOS and PFOA, the ATSDR chose to derive specific MRLs only for compounds for which they deemed a sufficiently broad database. With regard to PFCs, the ATSDR determined that PFOA and PFOS had a database of evidence sufficiently rich enough to derive MRLs for the oral route of exposure. For both compounds, the ATSDR determined that adverse hepatic effects, adverse immunological effects, and adverse developmental effects were sensitive endpoints associated with exposures in rodent (rat and mouse) species. Using an approach very similar to the U.S. EPA approach for derivation of RfDs, the ATSDR derived MRLs based on hepatic effects that were supported by LOAEL values for developmental toxicity and immunotoxicity. For PFOA, the MRL was 0.00002 mg/kg/day and for PFOS, it was 0.00003 mg/kg/day. These MRLs are equivalent to the U.S. EPA RfDs for both PFOA and PFOS.

The MRL and RfD values derived by the ATSDR and U.S. EPA, respectively, were calculated to protect the most sensitive subpopulations, i.e., those with the greatest risk of exposure and/or those who are most vulnerable to health effects following exposures, from a lifetime of exposures. In the state of Minnesota, residents of the East Metro area have putatively higher exposures to PFCs than do members of the U.S. general population, given levels in municipal drinking water wells and levels measured in blood. States may institute health based values for protection of their residents that are more stringent than U.S. EPA health based values, for any exogenous agent to which their residents may be exposed. The U.S. EPA also notes that their HALs may change given new evidence (U.S. EPA, 2016a,b). In 2017, following the release of HALs by the U.S. EPA, the MDH released updated guidance values for PFOA and PFOS that were more protective than the U.S. EPA HAL to reflect the potential for mothers to pass along PFCs to fetuses and nursing infants (MDH, 2017b). The MDH acknowledged that while the U.S. EPA HAL is protective for most people, they wanted to take additional steps to protect the highly sensitive developing organism and so revised their HAL based on a newly developed toxicokinetic model (MDH, 2017b).

Because part of the mission of the ATSDR is to help public health professionals and others address the needs of persons living or working near hazardous waste sites, their toxicological profile documents contain sections on the relevance of toxicity and toxicokinetic data to public health (ATSDR, 2015). A majority of the document dissects these health effects by type of health effect (death, systemic, immunologic, and reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic), and indicates whether they are "less serious" or "serious" effects (ATSDR, 2015).

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The ATSDR (2015) also identified populations that may be particularly susceptible to PFCs, including populations with high exposures, those with existing high serum cholesterol or other existing cardiovascular risk factors, hypertension, or compromised liver function. By way of example, the ATSDR (2015) identified such populations to include those who work at or are located near fluorochemical facilities and those involved in activities with prolonged use of perfluoralkyl-containing products, such as those involved in the application of protective coatings for textiles and papers. Based on the assessment of PFCs by the ATSDR, certain populations are at increased risk for adverse health outcomes associated with exposure to these agents. I agree that in areas of high PFC exposure, either due to occupational exposures or by living near fluorochemical production facilities, increased health risks, especially those associated with effects on the liver and the immune system and on developing organisms, likely exist.

Some of the adverse health outcomes have been associated with PFC serum concentrations in highly exposed human populations, most notably residents in the mid-Ohio Valley who were exposed via drinking water due to PFOA contamination of water supplies by a DuPont production facility. These studies, known as the "C8 Health Project" established probable links between serum PFOA concentrations and the following adverse health outcomes:

1. Cardiovascular disease (high cholesterol),
2. Pregnancy and pregnancy outcomes (pregnancy-induced hypertension and preeclampsia),
3. Autoimmune disease (ulcerative colitis),
4. Thyroid disease, and
5. Cancer (kidney and testicular).

These C8 Health Project studies thus support the conclusion that humans exposed to PFCs have an increased risk of adverse health outcomes. In addition, studies exploring myriad aspects of PFC-associated toxicities in experimental animal models have been published. These include mammary gland development, disruption of various hormones, reproductive endpoints, diabetes and other metabolic disorders, serum lipids and cardiovascular diseases, liver and kidney function and disease, and behavioral outcomes. These toxicities support the body of evidence that exposure to PFCs leads to adverse health outcomes in a variety of experimental animal models, wildlife species, and humans.

VIII.7 Detailed Supported Opinion – Other PFCs Relevant in the State of Minnesota

As mentioned above, Järnberg and van Bavel (2007) estimated from published literature that the total number of described synthetic PFCs exceeds 10,000 individual compounds. Industry is demonstrably capable of devising new PFCs faster and in greater volume, and is doing so at a rate faster than the scientific community can study them. Thus, there are not sufficient studies and data for a wide-scale comprehensive assessment of all of these individual compounds similar to what has occurred for PFOA and PFOS. However, sufficient toxicological evidence does exist concerning three other PFCs of concern in Minnesota—PFHxS, PFBA, and PFBS—that suggest that these compounds may pose a risk to human health.

VIII.7.a PFHxS

PFHxS is a six-carbon chain PFC. It is considered by the U.S. EPA as a long-chain PFC, so is subject to the same guidelines and restrictions as PFOA and PFOS. Like PFOA and PFOS, it has a long serum half-life in humans, up to 8.5 years by some estimates (Olsen et al., 2007). Like many of the PFCs other than PFOA and PFOS, peer-reviewed publications are limited and are largely limited to studies conducted by or in cooperation with scientists from the 3M Company. An exploratory 28-day study of PFBS and PFHxS in rats commissioned by 3M in 1999 revealed that PFHxS exposure was associated with a decline in total cholesterol, increased liver weight, and liver hypertrophy in rats dosed at 10 mg/kg (3MA00760311). In a 2006 report on the effects of several PFCs in APOE3Leiden mice, a high dose of PFHxS had to be stopped because of overt toxicity to the mice, as manifested by reduced food intake and decreased body weight (3MA01507211). Exposure to PFHxS was also associated with a robust decrease in cholesterol and triglycerides (3MA01507211).

In the publicly available peer-reviewed scientific literature, a 2009 publication authored by scientists from the Medical Department of the 3M Company (Butenhoff et al., 2009a), indicated that it was the first article to report on the biological response of experimental animal models exposed to PFHxS, despite that studies were conducted on this compound as early as 1999. In 2012, a peer-reviewed paper on the pharmacokinetics of PFHxS in rats, mice, and monkeys was published by three of the four 3M Company scientists from the 2009 paper in collaboration with scientists from two U.S. universities and a laboratory in Sweden (Sundström et al., 2012). In 2013, from a university laboratory in Sweden, a study indicating that a single neonatal exposure to PFHxS was sufficient to alter levels of proteins in the brain critical for neuronal development was published (Lee and Viberg, 2013). Epidemiological studies of PFC-exposed humans have associated liver damage (Gleason et al., 2015) and decreased antibody responses to vaccines with PFHxS serum concentrations (Grandjean et al., 2012). Given the long half-life of PFHxS and the published toxicological findings (although relatively few in number in comparison to PFOA and PFOS), exposure to PFHxS also poses a present or potential hazard to human health. Dr. Deanna Luebker, Global Regulatory Manager of 3M's Separation and Purification Sciences Division stated that "…if they [chemicals] can readily degrade and break down, so things like carbon and oxygen, hydrogen, they typically don't cause any problems. So it's nice when they break down and kind of go away" (Luebker Depo. Tr. 35:11-14). The opposite supposition being that if chemicals do not readily degrade and break down, they do not go away, and do cause problems.

VIII.7.b PFBA and PFBS

Studies of PFBA and PFBS, while limited in number relative to PFOA and PFOS, show certain toxicities, which is particularly noteworthy given that certain of these studies were undertaken by scientists funded by the 3M Company.

In a study of PFBA given to male and female SD rats in drinking water for 28- or 90-days, authored by scientists from both the U.S. EPA and the 3M Company (Butenhoff et al., 2012b), the authors identified several statistically significant changes in the weights of various organs. The authors attempted to dismiss these results as "spurious" or not "toxicologically significant" as they did not show progression with dose, were not consistent between 28-day and 90-day studies, and lacked histological findings. For example, mean absolute (not corrected for body

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weight of the animals) thyroid gland weights in male rats given 6 or 30 mg/kg/day of PFBA for 28-days were elevated by approximately 100% compared to the control group; a 150 mg/kg/day dose group did not have a statistical elevation in thyroid gland weights, but was approximately 55% greater in weight compared to the control group. The authors stated that these weight changes were not toxicologically significant. Moreover, these studies demonstrated that PFBA lowered total and free T4 in rats exposed for 28-days at a concentration of 150 mg/kg/d and 90-days at a concentration of 30 mg/kg/d (Butenhoff 2012b). Similar thyroid hormone lowering effects have been observed in experimental animal model studies using PFOS and PFOA.

But the statistically significant results should not be so dismissed. As mentioned above, for some agents, the occurrence of adverse health outcomes does not always follow a "standard" dose-response curve. Some dose-response curves are U-shaped or inverse-U-shaped, indicating that lower and higher doses produce responses that differ from moderate doses. Moreover, while a three-week recovery period (evaluated in separate groups of rats that were treated and then euthanized three weeks after cessation of treatment) demonstrated that thyroid weights returned to control levels, the long-term effects of a short-term increase in thyroid weight cannot simply be discounted as spurious, especially when it occurred in two dose groups and had such a large effect size. Increases in thyroid gland weight may reflect changes in circulating TH, which are exquisitely controlled via positive and negative feedback among the hypothalamus, anterior pituitary gland, and the thyroid gland. Increases in thyroid gland weight also may reflect inflammation in the thyroid gland. Some of the male animals with increased thyroid gland weights had signs of thyroid follicular epithelial hypertrophy/hyperplasia, which often accompanies hepatocellular hypertrophy (NTP, 2017). Hepatocellular hypertrophy also was observed in male animals given 30 mg/kg/day of PFBA.

In a developmental study of PFBA in CD-1 mice (Das et al., 2008), authored by scientists from both the U.S. EPA and the 3M Company, statistically significant delays in eye opening and onset of puberty in offspring were noted in several of the PFBA dose groups. The authors concluded that while developmental effects were detectable, developmental exposure to PFBA did not produce adverse developmental effects at the same profound level that had been reported in this strain of mouse following exposure to PFOA or PFOS. However, the authors also noted that early pregnancy loss at high doses may represent a common feature of PFAAs. It is also notable that delayed sexual maturation is an effect also seen in offspring of PFOA dosed female rats, and that a delay in eye opening has been observed in offspring of PFOS dosed female rats. Therefore, while the authors believed that PFBA was not as developmentally toxic as PFOA or PFOS, PFBA still produced meaningful adverse toxicological outcomes, some of which have also been observed in PFOA and PFOS reproductive toxicity studies.

The authors of the last-mentioned study (Das et al., 2008) did not describe in great detail the statistically significant and toxicologically meaningful findings of delayed eye opening and onset of puberty observed in their study. But there is reason to hypothesize that thyroid effects and developmental effects are related. In experimental rodent models, thyroid hormones play a role in reproductive tract development, maturation, and function; both hypo- and hyperthyroid (decreased and increased thyroid hormones) conditions have been associated with delayed vaginal opening and onset of puberty (Choksi et al., 2003). Similarly, hypo- and hyperthyroid conditions have been associated with changes in reproductive system development, maturation, and function in humans (Choksi et al., 2003). Therefore, TH status should be evaluated when

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changes are observed in reproductive tract development, maturation, and function following exposure to an exogenous agent, especially when the database suggests such linkages. A recently published study (Feng et al., 2017) evaluated these linkages; however, it concerned PFBS rather than PFBA.

The toxicological database of peer-reviewed published manuscripts for PFBS contains even fewer studies than for PFBA. In addition to the Lieder et al. (2009a) study in adult rats used by the MDH for the PFBS HRL, Lieder et al. (2009b) also published a study on the developmental effects of PFBS. Otherwise, no other peer-reviewed published studies concerning PFBS toxicity appear to exist, although several unpublished reports are on the U.S. EPA public docket (York, 2003a,b). Regardless, the Feng et al. (2017) study noted reports of effects of PFOS and other PFCs on fetal growth, development, and adult reproductive function as well as thyroid hormone status and decided to investigate the linkages between PFBS exposure and these endpoints. The Feng et al. (2017) study demonstrated that when given to pregnant ICR mice from GD1-20 at doses of 200 or 500 mg/kg/day, PFBS induced permanent hypothyroid with deficits in perinatal growth, pubertal onset, and reproductive organ development in female mice. Thus, this particular publication adds to the body of evidence that short-chain compounds, such as PFBA and PFBS, pose a substantial potential hazard to human health, especially to susceptible developing organisms.

PFBS and other short-chain compounds have been touted by industry and industry trade representatives as having "favorable toxicological profiles." For example, in a recent press release by the FluroCouncil, a Global Industry Council for FluoroTechnology, the language "improved health and environmental profiles" is used to compare the newer, "approved" chemistries to the "older" fluorinated chemistry (FluroCouncil, 2017a). In an earlier News Update, also by the FluroCouncil (FluroCouncil, 2017b), the following is provided:

> "…the current PFAS chemistries used in these applications, known as short-chain fluorinated polymers, are well studied, and data from these studies have been provided to regulators globally as part of their chemical review processes. The science shows these new short-chain chemistries are not bioaccumulative and offer significantly improved toxicological profiles over the chemistries they replaced. Short-chain fluorinated polymers have been approved for use by the EPA and other regulators around the world."

I would like to dissect this paragraph with respect to short-chain compounds:

1) Short-chain compounds are well studied and data from these studies have been provided to regulators globally as part of their chemical review processes. It may be true that industry scientists have performed copious studies with short-chain PFCs and provided the results of these studies to regulators across the globe. However, the reality is that if these industry studies are not part of the publicly available peer-reviewed literature, then they are likely limited to only those studies that are required for chemical review processes. These required studies do not evaluate all possible toxicological effects. For example, testing for developmental immunotoxicity is not a requirement under TSCA within the U.S., but it is well accepted that the developing immune system is highly susceptible to the disruptive effects of chemical agents (Dietert and DeWitt, 2010). Therefore, the term "well studied" is

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misleading as it likely only refers to a limited number of required studies performed by industry scientists or research laboratories contracted by PFC-producing industries. This same situation occurred with the legacy PFCs, PFOA and PFOS. Studies evaluating the toxicity of PFOA and PFOS were performed for many years by industry scientists and their contractors or grantees. As described in section VII.5, above, 3M was conducting PFC toxicology studies by 1949 and as early as 1963, had sufficient information on the basic toxicity of various fluorochemical surfactants to provide LD50s in adult rats and mice in a technical bulletin along with a statement that "Due care should be exercised in handling these materials until further information is available on their physiological properties" (3M Company, 1963). Although one of the earliest studies on the toxicity of PFCs in experimental animal models was published in 1980 (Griffith and Long, 1980), published studies did not explode in number until the 2000s, more than two decades after these early studies. The growth in the number of studies occurred after the 3M Company announced that it was phasing out the perfluorooctanyl chemistry used to make PFOS and after PFOS and PFOA were reported as widespread environmental contaminants by various environmental chemistry studies (for example Giesy and Kannan, 2001). While it is possible to speculate about the timeline, papers authored by 3M Company scientists on the toxicity of PFCs were published in the 2000s and beyond and were based, in some cases, on studies performed in the 1980s and 1990s. Therefore, the 3M Company had data about the toxicity of legacy compounds that may have been shared with regulators, but was not part of the publicly available peer-reviewed literature that is vitally important for the advancement of scientific knowledge and for regulators and policy makers at the local and state level. The same may be true of the short-chain chemistries.

2) These short-chain chemistries are not bioaccumulative. Bioaccumulation is a term that describes the net uptake of chemicals from the environment by any or all of the possible routes and from any source where the chemicals are present (Spacie et al., 1995). The presence of a chemical in an organism alone is not sufficient to induce an adverse health outcome, but depends on the response of an organism to the presence of the chemical (Spacie et al., 1995). Therefore, judgments about adverse health outcomes must arise from what is know about dose-response relationships and the factors associated with toxicity rather than just the magnitude of the bioaccumulation (Spacie et al., 1995). Short-chain PFCs enter living organisms from the environment via the same putative pathways as long-chain PFCs. The few publicly available studies on these short-chain PFCs, for example PFBA and PFBS, indicate that these compounds are excreted from humans in days rather than years (PFBA: 3-4 days; Chang et al., 2008. PFBS: ~25 days; Olsen et al., 2008). However, PFHxS, which has a shorter chain length than PFOS, is known to have a longer half-life than PFOS. Thus, it may not uniformly be the case that a shorter chain length equates to a shorter half-life in serum. Therefore, while these short-chain PFCs do not remain in the body as long as the long-chain PFCs, because they are in the environment, they can, and do, bioaccumulate. In a study to evaluate the bioaccumulation of various PFCs from the environment, Pérez et al. (2013) demonstrated the presence of 21 different PFCs of varying chain lengths, including PFBA and PFBS, in five human tissues (bone, brain, kidney, liver, lung) collected from 20 subjects at autopsy in Catalonia, Spain. PFBA had the highest mean concentration of any PFC in the lung and the kidney and was approximately equivalent in concentration to PFOA in the liver (Pérez et al., 2013). PFBS, although low relative to other PFCs, was detectable in all tissues but brain. Although this is a single study and did not evaluate potential differences

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in exposure scenarios among subjects, it demonstrates that short-chain PFCs do indeed bioaccumulate. Further, to the extent that PFCs accumulate in human tissue, measuring the half-life of these compounds in serum may not fully account for the presence of PFCs in the human body and their elimination therefrom.

3) These new short-chain chemistries offer significantly improved toxicological profiles over the chemistries they replaced. The phrase "significantly improved toxicological profiles" is entirely unclear and subjective. Based on what toxicological measures? Death? Cancer endpoints? Organ damage? By definition, toxicology is the study of the adverse health effects of exogenous agents on living organisms, therefore, the presence of a toxicological profile implies the presence of adverse health effects in living organisms.

4) Short-chain fluorinated polymers have been approved for use by the EPA and other regulators around the world. Approval for use does not imply safety. Approved for use by regulatory agencies typically is associated with caveats such as use restrictions, waste capture requirements, limits on emissions to environmental media, etc. Approval for use in no way implies that the compounds in question are safe for human or wildlife exposure.

Regarding this final point on approval for use, I note that according to Rodricks and Levy (2013), who summarized a 2009 National Research Council (NRC) advisory report on human health risk assessment (Science and Decisions: Advancing Risk Assessment), assumptions that are not yet certain may be required in order to assess emerging problems. *The authors assert that an implicit regulatory assumption that compounds for which no significant toxicity data exist carry no risk is a troubling default assumption for which solutions are critical*. Therefore, the authors acknowledge that the toxicological community must offer the best scientific support for moving risk assessment forward, even where there is a degree of uncertainty. I agree with this assertion and further assert that while the scientific database on PFCs is far from complete, it would be unethical, particularly when there are proven toxicities, to move forward under the assumption that there are no other toxicities beyond those that have been proven. It is better to assume that similar compounds are likely to show similar toxicities, until that is disproven.

Given the toxicities shown already in the limited studies concerning PFBA, PFBS, and other short-chain PFCs designed to replace the long-chain PFCs, given that they bioaccumulate in human organs as shown by Pérez et al., (2013), and given their similar physicochemical structure to better-studied PFCs such as PFOA and PFOS, it is my opinion that PFBA, PFHxS, and other short-chain PFCs pose a present or potential hazard to human health

IX. Use of Toxicology Studies to Develop Protective Health Guidelines

As described at various points in this report, toxicology studies are regularly utilized by regulators and government agencies to develop protective human health guidelines for various chemicals, including PFCs. These values are developed through an evaluation of the body of established toxicological literature for a particular chemical at a particular point in time. As such, these protective health guidelines may not account for new or novel findings that post-date their establishment, and revisions in these health guidelines may lag behind the leading scientific research. This is likely to be especially true for chemicals like PFCs, for which the scientific literature is growing at a rapid pace.

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While protective health guidelines are used to establish a level at which there is an acceptably low risk of adverse health effects, they should not be understood to reflect a chemical concentration at which there is *no* risk. As the below description of the development of PFC health-based levels by Minnesota and the EPA illustrate, health guidelines considered to be adequately protective at one point in time may be revealed to be insufficiently protective as the scientific literature on a chemical advances.

The MDH has developed and issued health risk limits (HRLs) for four PFCs commonly detectable in Minnesota: PFOA (MDH, 2009a), PFOS (MDH, 2009c), PFBA (MDH, 2011a), and PFBS (MDH, 2011b). Based on its similarity to PFOS and its long half-life in humans, they have also determined that the HRL for PFOS is appropriate for PFHsX (MDH, 2009b). These initial HRLs represented levels of these chemicals in drinking water that the MDH then considered safe for people, including sensitive subpopulations, to consume over the course of a lifetime and were based on the available information at the time of issuance. The HRL developed for PFOA and PFOS was 0.3 µg/L and was 7 µg/L for PFBA and PFBS. Concentrations in drinking water above the HRLs were believed to pose human health risks.

The MDH HRL for PFOA (MDH, 2009a) was based on a RfD of 0.000077 mg/kg/day identified from a chronic non-cancer study of Cynomologus monkeys published by Butenhoff et al. (2002). Monkeys were given oral doses of APFO for six months and a LOAEL (although Butenhoff et al. refer to this as the lowest observable effect level or LOEL) of 3 mg/kg/day was identified based on increases in liver weight (no NOAEL was identified). It is also notable that a monkey dosed at 3 mg/kg/d became ill and was humanely sacrificed during the course of the study, and a compound-related cause of death could not be definitively ruled out. Using the BMD approach, the MDH identified a serum concentration of 23 mg/L as the POD, which when adjusted to a HED, was 0.0023 mg/kg/day. The MDH applied a total uncertainty factor of 30 based on an uncertainty factor of three for interspecies extrapolation for potential differences in toxicodynamics and 10 for intraspecies variability, which brought the RfD to 0.000077 mg/kg/day. The MDH applied standard metrics for converting this to a drinking water consumption rate to determine the 0.3 µg/L HRL.

The MDH HRL for PFOS (MDH, 2009c) was based on a RfD of 0.00008 mg/kg/day identified from a subchronic non-cancer study of Cynomologus monkeys published by Seacat et al. (2002). Monkeys were given oral doses of PFOS for 182 days and a NOAEL of 0.15 mg/kg/day was identified even though, at the 0.15 mg/kg/d dose, decreases in serum cholesterol (as high density lipoprotein) and total triiodothyronine (T3), and increased thyroid stimulating hormone (TSH) were observed. It is also notable that, at the next highest dose level, 0.75 mg/kg/d, two dosed monkeys died of compound-related causes. Thus, in this study, there was not a significant gap between the NOAEL and a level at which PFOS induced mortality in monkeys. Using the BMD approach, the MDH identified a serum concentration of 35 mg/L as the POD, which when adjusted to a HED, was 0.0025 mg/kg/day. The MDH applied a total uncertainty factor of 30 based on an uncertainty factor of three for interspecies extrapolation for potential differences in toxicodynamics and a 10 for intraspecies variability, which brought the RfD to 0.00008 mg/kg/day. The MDH applied standard metrics for converting this to a drinking water consumption rate to determine the 0.3 µg/L HRL.

The MDH HRL for PFBA (MDH, 2011a) was based on a RfD of 0.0038 mg/kg/day identified from a subacute study of SD rats performed for the 3M Company by NOTOX (2007a). Rats were given PFBA in drinking water for 28-days and using a BMD approach (provided by Dr. Butenhoff from the 3M Company to the MDH via email correspondence) 3.01 mg/kg/day was identified as the POD, which when adjusted to a HED, was 0.38 mg/kg/day. This value was based on the critical effect of decreased cholesterol. The MDH applied a total uncertainty factor of 100 based on an uncertainty factor of three for interspecies toxicodynamic differences, 10 for intraspecies variability, and three for database insufficiencies, which brought the RfD to 0.0.0038 mg/kg/day. The MDH applied standard metrics for converting this to a drinking water consumption rate to determine the 7 µg/L HRL. The MDH calculated subchronic and chronic HRLs, also from NOTOX (2007b) studies of rats given PFBA in drinking water for 90-days, which were 8 and 10 µg/L, respectively. A value 7 µg/L was selected as the HRL for all exposure durations.

The MDH HRL for PFBS (MDH, 2011b) was based on a RfD of 0.0014 mg/kg/day identified from a chronic study of SD rats performed by Lieder et al. (2009a). Rats were given PFBS via oral gavage for 90-days and a NOAEL of 60 mg/kg/day was identified for male rats based on decreased hemoglobin and hematocrit and histological changes in the kidney. Using the BMD approach, the MDH calculated a HED of 0.42 mg/kg/day by dividing the NOAEL by a half-life adjustment factor of 142 for extrapolation from male rats to humans. The MDH applied a total uncertainty factor of 100 based on an uncertainty factor of three for interspecies extrapolation for potential differences in toxicodynamics, 10 for intraspecies variability, and three for database insufficiencies, which brought the RfD to 0.0042 mg/kg/day. The MDH applied standard metrics for converting this to a drinking water consumption rate to determine the 7 µg/L HRL. The MDH calculated a subchronic HRL, also from Lieder et al. (2009a), which was 9 µg/L.

Similarly, the U.S. EPA established HALs for PFOA and PFOS of 0.07 µg/L in 2016 (U.S. EPA, 2016a,b). RfDs for PFOA and PFOS were 0.00002 mg/kg/day based on the Lau et al. (2006) developmental toxicity study for PFOA and a study of the developmental toxicity of PFOS by Luebker et al. (2005). The PFOS RfD for the drinking water health advisory differs from the RfD used in the Health Effects Document for Perfluorooctane Sulfonate (U.S. EPA, 2016d), but only by 0.00001 mg/kg/day (0.00003 mg/kg/day compared to 0.00002 mg/kg/day for the HAL). According to the U.S. EPA, the goal of the HAL was to protect the most sensitive populations, which they identified as fetuses during pregnancy and breastfed infants (U.S. EPA, 2016a,b). Even though the RfD values used by the MDH prior to 2017 and the U.S. EPA are similar (0.00008 mg/kg/day for the MDH and 0.00002 mg/kg/day for the U.S. EPA), the final values differ (0.3 µg/L for the MDH compared to 0.07 µg/L for the U.S. EPA) based on correction factors applied by the MDH to adjust mg to µg (i.e, a factor of 1,000) and by the chronic intake rate (0.049 L/kg/day for the MDH and 0.054 L/kg/day for the U.S. EPA).

In the spring of 2017, the MDH released HBVs for PFOA (MDH, 2017f), PFOS (MDH, 2017g), and PFBA (MDH, 2017e). According to the MDH (2017a), the release of the 0.07 µg/L HAL for chronic exposure to PFOA and PFOS in drinking water by the U.S. EPA prompted the MDH to reassess the MDH HALs issued in 2009. These updated guidance values apply to short periods of time during pregnancy and breastfeeding as well as over a lifetime of exposure and are health recommendations to local officials operating public water supplies and to private well owners in areas with PFCs in groundwater (MDH, 2017b).

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The MDH used the same basic methodology as they previously used for establishment of HRLs, but used a different toxicokinetic model (with input from an external peer review panel) designed to protect developing organisms (MDH, 2017a). In the updated toxicokinetic model, additional exposure parameters were included for placental transfer, breastmilk transfer, and breastmilk intake, to take into account exposure scenarios for formula-fed and breastfed infants (MDH, 2017a). One key difference between this model and models used by the U.S. EPA in the creation of their HAL was that the MDH used different volume of distribution (Vd) values for both PFOA and PFOS for infants that included an early-life stage Vd adjustment factor to account for the higher water content in bodies of infants compared to older children and adults (MDH, 2017a). In addition, the MDH considered two scenarios for reasonable maximum exposures (RMEs; maximum exposure reasonably expected to occur): 1) an infant fed exclusively with formula reconstituted with contaminated water starting at birth and then followed by lifetime consumption of contaminated water and 2) an infant exclusively breastfed for 12 months and then followed by lifetime consumption of contaminated water (MDH, 2017a). Another key difference is that the MDH used a relative source contribution (RSC; the percentage of a person's exposure attributed to drinking water) of 0.5 whereas the U.S. EPA used a value of 0.2. A value of 0.2 indicates that 20% of a person's exposure to a particular chemical comes from drinking water (MDH, 2017a). The U.S. EPA Exposure Decision Tree allows for one of three values to be chosen, the default 20% value, a value of 50%, or a maximum value of 80% (Krishnan and Carrier, 2013). The value of 0.5 (or 50%) used by the MDH is based on evidence from MDH's biomonitoring studies (MDH, 2008; 2010) that demonstrated that drinking water in the East Metro area is a major source of PFCs. MDH's use of an RSC of 50% is less conservative than the EPA's decision to use a default value of 20%.

Using the revised toxicokinetic model, the value derived for short-term, subchronic, and chronic exposures for PFOA was 0.035 µg/L and for PFOS was 0.027 µg/L. The PFOA HBV was based on a RfD of 0.0053 mg/kg/day derived from the Lau et al. (2006) developmental toxicity study of PFOA. The PFOS HBV was based on a RfD of 0.0051 mg/kg/day derived from the Luebker et al. (2005) developmental toxicity study of PFOS. While the critical studies identified for both compounds for derivation of the HBVs were based on developmental endpoints, the MDH determined that these HBVs also would be protective for health effects in the liver, immune system, and thyroid gland, and for PFOA, effects on the kidneys. The MDH determined that due to the long half-lives of these compounds, a single HBV was most appropriate for short-term, subchronic, and chronic exposures.

The MDH retained the value of 7 µg/L for the PFBA HBV (MDH, 2017e).

The MDH also lists PFHxS in the human health-based water guidance table, band utilizes that HBV for PFOS as a surrogate. Based on the limited toxicological evidence available regarding PFHxS, and its long half-life in human beings, there appear to be sufficient similarities between PFHxS and PFOS to support MDH's decision.

In summary, the MDH HBVs for PFCs are: PFOA = 0.035 µg/L. PFOS = 0.027 µg/L. PFBA = 7 µg/L. PFBS (HRL) = 7 µg/L. PFHxS = 0.027 ug/L (based on the PFOS HBV).

In Ex. 148 (3MN_MN00042206, Estimation of "Safe" Reference Level of PFOS in Plasma), Dr. John Butenhoff goes through a series of calculations to estimate a reference level for PFOS in

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human plasma, which would be comparable to a RfD. A breakdown and assessment of Dr. Butenhoff's approach is found in Appendix B. Dr. Butenhoff estimated a RfD of 0.000005 mg/kg/day, based on a LOAEL of 0.5 mg/kg/day in a 90-day Rhesus monkey study with PFOS. The HAL or HBV that could be calculated from this RfD is about 0.035 ug/L (see Appendix B), which is on the order of magnitude as the HAL calculated by the U.S. EPA and the HBV calculated by the MDH. Dr. Butenhoff made some calculations to estimate that the human plasma concentration associated with this exposure level would be about 1.05 µg/L. I would like to point out here that this is *lower* than average human concentrations for the general U.S. population for PFOS and *lower* than the average human concentrations measured in the East Metro study in 2014, which were just under 20 ug/L (MDH, 2015). As early as the late 1990s, a toxicologist working for the 3M Company estimated that safe human serum concentrations for PFOS were *lower* than reported human serum concentrations in the general U.S. population at the time and at the present.

In June of 2017, the MDH informed the City of Cottage Grove, MN, a city in MN where the 3M Company operates a production facility, of a Notice of Health Risk Advisory for Cottage Grove Well Nos. 2-8 and 10. At this 3M Company facility, PFC production began in the late 1940s and was phased out at the end of 2002 (ATSDR, 2005), but PFCs are still detectable in waters in and around this facility. The MDH based this advisory on combined levels of PFOA, PFOS, PFBA, PFBS, and PFHxS measured in Cottage Grove Community Wells. According Minnesota Administrative Rules section 4717.7880, when a combination of PFOA, PFOS, PFHxS, PFBA, or PFBS are found in drinking water, a health risk index (HRI) is calculated to determine if the combined health risk exceeds a level of concern (MDH, 2017c). The HRI calculated by first creating a ratio that is the groundwater concentration of the chemical to the HBV for that chemical and then adding the ratios of the individual chemicals together (MDH, 2017c). An HRI that is greater than one is considered an exceedance of the HBV. This is a typical approach for site-specific characterization of risks (U.S. EPA, 1989). Based on this approach, the MDH determined that PFC concentrations in eight out of the 11 community wells in Cottage Grove contained combined levels of PFCs that exceeded the HBVs or HRLs. The MDH recommended that the City of Cottage Grove take action to reduce the levels of PFCs to below the HBV for PFOA and/or the HRI of 1.0 (MDH, 2017c). Also in June of 2017, the MDH informed individual well owners/users that (a) samples from their wells indicated exceedances of HBVs or HRIs for PFCs, (b) well water should not be used for drinking or cooking on a long-term basis, and (c) bottled water and installation of a granular activated carbon filter system (or connection to city water, if available) were available at no cost (MDH, 2017h). These were, in my opinion, reasonable actions to take to protect the public from exposure to PFCs above the HBVs and HRLs.

X. Affirmation

I affirm under penalty of perjury that the foregoing is a true and correct statement of my opinions in this matter and the grounds for those opinions.

Jamie C. DeWitt
September 22, 2017

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Appendix A

Curriculum Vitae (CV) of Jamie C. DeWitt

Jamie C. DeWitt

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Brody School of Medicine
East Carolina University,
6S-10 Brody Building, 600 Moye Blvd., Greenville, NC 27834
Phone: 252-744-2474
Email: dewittj@ecu.edu

Environmental toxicologist who employs principals from immunotoxicology, neurotoxicology, and developmental toxicology to understand how exposure to emerging environmental contaminants, such as per- and polyfluoroalkyl substances (PFASs), geogenic dusts, and pharmaceutical and personal care product pollutants, affect health and contribute to human diseases and disorders.

EDUCATION

Ph.D., Environmental Science and Neural Science
School of Public and Environmental Affairs and Program in Neural Science
Indiana University, Bloomington, IN, 2004
Concentrations: Environmental and developmental neurotoxicology and risk assessment
Dissertation title: Developmental intoxication of dioxins and polychlorinated biphenyls in an avian model: Correlations of brain asymmetry, behavior, and related developmental effects

B.S., Environmental Science and Biology
Lyman Briggs College
Michigan State University, East Lansing, MI, 1992

PROFESSIONAL EXPERIENCE

Associate Professor of Pharmacology and Toxicology
Department of Pharmacology and Toxicology, Brody School of Medicine, East Carolina University, Greenville, NC.
July 2015-present.

Adjunct Associate Professor of Public Health
Department of Public Health, Brody School of Medicine, East Carolina University, Greenville, NC.
July 2015-present.

Adjunct Assistant Professor of Public Health
Department of Public Health, Brody School of Medicine, East Carolina University, Greenville, NC
July 2012-July 2014.

Affiliated Member
The Harriet and John Wooten Laboratory for Alzheimer's and Neurodegenerative Disease Research, East Carolina University, Greenville, NC.
July 2011-present.

Assistant Professor of Pharmacology and Toxicology
Department of Pharmacology and Toxicology, Brody School of Medicine, East Carolina University, Greenville, NC.
July 2008-July 2015.

Postdoctoral Trainee in Immunotoxicology
University of North Carolina at Chapel Hill in cooperation with the U.S. Environmental Protection Agency (Training Agreement CT829472), National Health and Environmental Effects Research Laboratory, Experimental Toxicology Division, Immunotoxicology Branch, Research Triangle Park, NC (Advisor: Dr. Robert Luebke). Evaluation of immune function and exploration of immunotoxic mechanisms, including use of knock-out models and molecular techniques, of various xenobiotics (organotins and perfluoroalkyl acids) in rodent models.
June 2004-June 2008.

Postdoctoral Research Associate in Environmental and Ecotoxicology
Developmental Neurobiology and Environmental Toxicology Laboratory, School of Public and Environmental Affairs, Indiana University, in cooperation with the U.S. Fish and Wildlife Service Bloomington Ecological Services Field Office, Bloomington, IN (Advisors: Dr. Diane Henshel and Daniel Sparks). Cardiotoxic effects in wild passerine birds developmentally exposed to polychlorinated biphenyls.
September 2003-May 2004.

Research Assistant in Environmental and Ecotoxicology
Developmental Neurobiology and Environmental Toxicology Laboratory, School of Public and Environmental Affairs, Indiana University, Bloomington, IN (Advisor: Dr. Diane Henshel). Toxicological effects of dioxin and polychlorinated biphenyls after developmental exposure in an avian model, wild birds, and wild fish.
August 1995-August 2003.

Field Assistant in Limnology
Lake Lemon Conservancy District, Unionville, IN. Canada goose control, littoral zone revegetation, and monitoring of native and exotic aquatic plant populations.
June 2000-May 2003.

Field Assistant in Ecotoxicology
U.S. Fish and Wildlife Service-Bloomington Ecological Services Field Office, Bloomington, IN. Wild bird and macroinvertebrate population monitoring in a metal-contaminated lake, including assessment of fertile eggs for embryonic abnormalities.
April 1997-October 1997.

Research Associate in Entomology
Landscape Entomology Division, Department of Entomology, Michigan State University, East Lansing, MI. Research and efficacy tests for forest, ornamental and turf entomological studies for the Michigan Department of Agriculture and Turf Foundation.
September 1992-August 1995.

Research Assistant in Entomology
Medical Entomology Division, Department of Entomology, Michigan State University, East Lansing, MI. Assessment of Lyme disease prevalence in deer and dog ticks collected from a Lyme disease endemic area in Michigan.
May 1992-May 1993.

PUBLICATIONS

Peer-Reviewed Manuscripts

vonderEmbse AN, Hu Q, and **DeWitt JC.** 2017. Developmental toxicant exposure in a mouse model of Alzheimer's disease induces differential sex-associated microglial activation and increased susceptibility to amyloid accumulation. *Journal of Developmental Origins of Health and Disease.* 2:1-9.

Meadows JR, Parker C, Gilbert KM, Blossom SJ, and **DeWitt JC**. 2017. A single dose of trichloroethylene given during development does not substantially alter markers of neuroinflammation in brains of adult mice. *Journal of Immunotoxicology.* 14:95-109.

DeWitt JC, Buck BJ, Goossens D, Teng Y, Pollard J, McLaurin B, Gerads R, and DE Keil. 2017. Health effects following subacute exposure to geogenic dust collected from active drainage surfaces (Nellis Dunes Recreation Area, Las Vegas, NV). *Toxicology Reports*. 4:19-31.

Rushing BR, Hu Q, Franklin JN, McMahen R, Dagnino S, Higgins CP, Strynar MJ, and **DeWitt JC**. 2017. Evaluation of the immunomodulatory effects of 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoate in C57BL/6 mice. *Toxicological Sciences*. Epub ahead of print: doi: 10.1093/toxsci/kfw251.

Keil DE, Buck B, Goossens D, Teng Y, Pollard J, McLaurin B, Gerads R, **DeWitt JC**. 2016. Health effects from exposure to atmospheric mineral dust near Las Vegas, NV, USA. *Toxicology Reports*. 3:785-795.

Jusko TA, Oktapoda M, Murinová LP, Babjaková J, Verner M-A, **DeWitt JC**, Babinská, Thevenet-Morrison K, Conka K, Drobná B, Thurston SW, Lawrence BP, Dozier AM, Jarvinene-Seppo KM, Patayová H, Trnovec T, Legler J, Hertz-Picciotto I, and Lamoree MH. 2016. Demographic, reproductive, and dietary determinants of perfluorooctane sulfonic (PFOS) and perfluooctanoic acid (PFOA) concentrations in human colostrum. *Environmental Science and Technology*. 50:7152-7162.

DeWitt JC, Buck B, Goossens D, Hu Q, Chow R, David W, Young S, Teng Y, Leetham-Spencer M, Murphy L, Pollard J, McLaurin B, Gerads R, and Keil D. 2016. Health effects following subacute exposure to dusts from arsenic-rich sediment at the Nellis Dunes Recreation Area, Las Vegas, NV. *Toxicology and Applied Pharmacology*. 304:79-89.

Leetham M, **DeWitt J**, Buck B, Goossens D, Teng Y, Pollard J, McLaurin B, Gerads R, and Keil D. 2016. Oxidative stress and lung pathology following geogenic dust exposure. *Journal of Applied Toxicology*. 36:1276-1283.

Keil D, Buck B, Goossens D, Teng Y, Spencer M, Murphy L, Pollard J, Eggers M, Gerards R, and **DeWitt J**. 2016. Immunotoxicological and neurotoxicological profile of health effects following subacute exposure to geogenic dust from sand dunes at the Nellis Dunes Recreation Area, Las Vegas, NV. *Toxicology and Applied Pharmacology,* 291:1-12.

DeWitt JC, Williams W, Creech NJ, and RW Luebke. 2016. Suppression of antigen-specific antibody responses in mice exposed to perfluorooctanoic acid: Role of PPARα and B cell targeting. *Journal of Immunotoxicology*. 13:38-45.

Jiang Q, Ma W, Wu J, Wingard CJ, and **DeWitt JC**. 2016. Perfluorooctanoic acid-induced toxicity in primary cultures of chicken embryo cardiomyocytes. *Environmental Toxicology*. 31:1580-1590.

Khalil N, Chen A, Lee M, Czerwinski SA, Ebert JR, **DeWitt JC**, and Kannan K. 2016. Association of perfluoroalkyl substances, bone mineral density, and osteoporosis in the US population in NHANES 2009-2010. *Environmental Health Perspectives*. 124:81-87.

Wambaugh JF, Setzer W, Pitruzzello AM, Liu J, Reif D, Kleinstreuer N, Ching N, Wang Y, Sipes N, Martin M, Das K, **DeWitt J**, Strynar M, Judson R, Houck K, and Lau C. 2013. Dosimetric anchoring of in vivo and in vitro studies for perfluorooctanoate and perfluorooctanesulfonate. *Toxicological Sciences*. 136:308-327.

Jiang Q, Lust R, and **DeWitt JC**. 2013. Perflurooctanoic acid induced-developmental cardiotoxicity: Are peroxisome proliferator activated receptor α (PPARα) and bone morphorgenic protein 2 (BMP2) pathways involved? *Journal of Toxicology and Environmental Health Part A*. 76:635-650.

Hu Q, Franklin JN, Bryan I, Morris E, Wood A, and **DeWitt JC**. 2012. Does developmental exposure to perflurooctanoic acid (PFOA) induce immunopathologies commonly observed in neurodevelopmental disorders? *NeuroToxicology*. 33:1491-1498.

Jiang Q, Lust R, Strynar MJ, and **DeWitt JC**. 2012. Perflurooctanoic acid induces developmental cardiotoxicity in chicken embryos and hatchlings. *Toxicology*. 293:97-106.

Fair PA, Stavros H-C, Mollenhauer MAM, **DeWitt JC**, Henry N, Kannan K, Mitchum G, Y SH, Bossart GD, Keil DE, and Peden-Adams MM. 2012. Immune function in female B6C3F1 mice is modulated by DE-71, a commercial polybrominated diphenyl ether mixture. *Journal of Immunotoxicology*. 9:96-107.

Hu Q, Strynar MJ, and **DeWitt JC**. 2010. Are developmentally exposed C57BL/6 mice insensitive to suppression of TDAR by PFOA? *Journal of Immunotoxicology*. 7:344-349.

DeWitt JC, Copeland CB, and Luebke RW. 2009. Suppression of humoral immunity by perfluorooctanoic acid is independent of elevated serum corticosterone concentration in mice. *Toxicological Sciences*. 109:106-112.

Peden-Adams MM, Stuckey JE, Gaworecki K, Berger-Ritchie J, Bryant K, Jodice PG, Scott TR, Boone S, McGuinn WD, **DeWitt JC**, and Keil DE. 2009. Developmental toxicity in white leghorn chickens following in ovo exposure to perfluorooctane sulfonate (PFOS). *Reproductive Toxicology*. 27:307-318.

Whalen MM, **DeWitt JC**, Luebke RW. 2008. Serum supplementation modulates the effects of dibutyltin on human natural killer cell function. *Toxicological Sciences*. 104:312-319.

DeWitt JC, Copeland CB, Strynar MJ, and Luebke RW. 2008. Perflurooctanoic acid-induced immunomodulation in adult C57BL/6J or C57BL/6N female mice. *Environmental Health Perspectives*. 116:644-650.

DeWitt JC, Copeland CB, and Luebke RW. 2008. An organotin mixture found in polyvinyl chloride (PVC) pipe is not immunotoxic to adult Sprague-Dawley rats. *Journal of Toxicology and Environmental Health Part A*. 71:276-282.

DeWitt JC, Copeland CB, and Luebke RW. 2007. Immune function is not impaired in Sprague-Dawley rats exposed to dimethyltin dichloride (DMTC) during development or adulthood. *Toxicology.* 232:303-310.

Lim J, **DeWitt JC**, Sanders RA, Watkins JB III, and Henshel DS. 2007. Suppression of endogenous anti-oxidant enzymes by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-Induced oxidative stress in chicken liver during development. *Archives of Environmental Contamination and Toxicology.* 52:590-595.

DeWitt JC, Copeland CB, and Luebke RW. 2006. Developmental exposure to 1.0 or 2.5 mg/kg of dibutyltin dichloride does not impair immune function in Sprague-Dawley rats. *Journal of Immunotoxicology*. 3:245-252.

DeWitt JC, Millsap DS, Yeager RL, Heise SS, Sparks DW, and Henshel, DS. 2006. External heart deformities in passerine birds exposed to environmental mixtures of polychlorinated biphenyls during development. *Environmental Toxicology and Chemistry.* 25:541-551.

DeWitt JC, Copeland CB, and Luebke RW. 2005. Immune responses in Sprague-Dawley rats exposed to dibutyltin dichloride in drinking water as adults. *Journal of Immunotoxicology*. 2:151-160.

DeWitt JC, Meyer EB, and Henshel DS. 2005. Environmental toxicity studies using chickens as surrogates for wildlife: Effects of vehicle volume. *Archives of Environmental Contamination and Toxicology*. 48:260-269.

DeWitt JC, Meyer EB, Watkins JB, and Henshel DS. 2005. Environmental toxicity studies using chickens as surrogates for wildlife: Effects of day of injection. *Archives of Environmental Contamination and Toxicology*. 48:270-277.

Stanton B, **DeWitt J**, Henshel D, Watkins S, and Lasley B. 2003. Fatty acid metabolism in neonatal chickens (*Gallus domesticus*) treated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) or 3,3',4,4',5-pentachlorobiphenyl (PCB-126) *in ovo*. *Comparative Biochemistry and Physiology C - Pharmacology and Toxicology,* 136(1):73-84.

Henshel DS, **DeWitt JC**, and Troutman, A. 2002. Using chicken embryos for teratology studies. In: *Current Protocols in Toxicology* (M.D. Maines, L.G. Costa, E. Hodgson, D.J. Reed, and I.G. Sipes, Eds.), Supplement 14, pp. 13.4.1-13.4.19.

Henshel DS, Martin JW and **DeWitt JC**. 1997. Brain asymmetry as a potential biomarker for developmental TCDD intoxication: A dose-response study. *Environmental Health Perspectives*. 105:718-725.

Henshel DS, Martin JW, Norstrom RJ, Elliot J, Cheng KM and **DeWitt JC**. 1997. Morphometric brain abnormalities in double-crested cormorant chicks exposed to polychlorinated dibenzo-*p*-dioxins, dibenzofurans, and biphenyls. *Journal of Great Lakes Research*. 23:11-26.

Walker ED, Smith TW, **DeWitt J**, Beaudo DC, McLean RG. 1994. Prevalence of *Borrelia burgdorferi* in host-seeking ticks (Acari: Ixodidae) from a Lyme disease endemic area in northern Michigan. *Journal of Medical Entomology*. 31(4):524-8.

Review Articles

Wang Z, **DeWitt JC**, Higgins CP, and Cousins IT. 2017. A never-ending story of per- and polyfluoroalkyl substances (PFASs)? *Environmental Science & Technology*. 51:2508-2518.

Hessel EVS, Ezendam J, van Broekhuizen FA, Hakkert B, **DeWitt JC**, Granum B, Guzylack L, Lawrence BP, Penninks A, Rooney AA, Piersma AH, and van Loveren H. 2016. Assessment of recent developmental immunotoxicity studies with bisphenol A in the context of the 2015 EFSA t-TDI. *Reproductive Toxicology*. 65:448-456.

Corsini E, Luebke RW, Germolec DR, and **DeWitt JC**. 2014. Perfluorinated compounds: emerging POPs with potential immunotoxicity. *Toxicology Letters*, 230:263-270.

DeWitt J, Peden-Adams M, Keller J, and Germolec D. 2012. The immunotoxicity of perfluorinated compounds: Recent developments. *Toxicologic Pathology,* 40:300-311.

DeWitt J, Peden-Adams M, Keil D, and Dietert R. 2012. Current status of developmental immunotoxicity: Early-life patterns and testing. *Toxicologic Pathology*, 40:230-236.

Dietert RR, Dietert J, and **DeWitt JC**. 2011. Environmental risk factors for autism. *Emerging Health Threats Journal* (invited review). 4:7111.

Dietert RR, **DeWitt JC**, Germolec DR, and Zelikoff JT. 2010. Breaking patterns of environmentally influenced disease for health risk reduction: Immune perspectives. *Environmental Health Perspectives* 118:1091-1099.

DeWitt JC, Shnyra A, Badr MZ, Loveless SE, Hoban D, Frame SR, Cunard R, Anderson SE, Meade BJ, Peden-Adams MM, Luebke RW, and Luster MI. 2009. Immunotoxicity of perfluorooctanoic acid and perfluorooctane sulfonate and the role of peroxisome proliferator activated receptor alpha. *Critical Reviews in Toxicology* 39:76-94.

Edited Books

DeWitt JC (ed). 2015. *Toxicity of Perfluoroalkyl and Polyfluoroalkyl Substances*. Springer Science + Business Media, LLC (Invited).

Book Chapters

DeWitt JC and Keil DE. 2017. Current issues in developmental immunotoxicity. In: *Immunopathology in Toxicology and Drug Development* (Parker GA, ed). Springer International Publishing, Switzerland.

DeWitt JC, Germolec DR, Luebke RW, and Johnson, VJ. 2016. Associating changes in the immune system with clinical diseases for interpretation of risk assessment. In: *Current Protocols in Toxicology*. 67:18.1.1-18.1.22.

DeWitt JC, Peden-Adams MM, and Keil DE. 2015. Immunotoxic effects of perfluoroalkylated compounds: Mechanisms of action. In: *Molecular Immunotoxicology* (Corsini E and van Loveren H, eds). Wiley-VCH GmbH & Co., Weinheim.

DeWitt JC and Dietert RR. 2014. Immunotoxicity in autism spectrum disorders. In: *The Comprehensive Guide to Autism* (Patel VB, Martin CR, Preedy V, and Preedy VR, eds). Springer Reference, New York, NY.

Dietert RR, **DeWitt JC**, and Luebke RW. 2012. Reducing the prevalence of immune-based chronic disease. In: *Immunotoxicity, Immune Dysfunction, and Chronic Diseases* (Dietert RR and Luebke RW, eds), Molecular and Integrative Toxicology, Springer Science + Business Media, LLC. pp 419-440.

DeWitt J, Peden-Adams M, Keil D, and Dietert R. 2012. Developmental immunotoxicity (DIT): Assays for evaluating effects of exogenous agents on development of the immune system. In: *Current Protocols in Toxicology*. Chapter 18: Unit 18.15.

Luebke RW, **DeWitt JC**, Germolec DR, Salazar KD, and Kerkvliet NI. 2012. Immunomodulation by persistent organic pollutants. In: *Dioxins and Health, Including Other Persistent Organic Pollutants and Endocrine Disruptors, 3rd Edition* (Schecter A, ed), John Wiley and Sons, Inc., Hoboken, NJ. pp 171-192.

DeWitt JC and Dietert RR. Postnatal immune dysfunction and its impact on growth parameters. 2012. In: *Handbook of Growth and Growth Monitoring in Health and Disease* (Preedy VR, ed), Springer, New York, NY. pp 741-755.

DeWitt JC and Luebke RW. 2010. Immunological Aging. In: *Comprehensive Toxicology*, 2nd Edition, Volume 5 (Lawrence D, ed), Elsevier Limited, Oxford, UK. pp 455-465.

Dietert RR and **DeWitt J**. 2010. Developmental immunotoxicity (DIT): The why, where and how of DIT testing. In: *Immunotoxicity Testing: Methods and Protocols* (Dietert RR, ed), Methods in Molecular Biology. Humana Press, Inc., Totowa, NJ. 598:17-25.

Luebke RW, Beamer CA, Bowman C, **DeWitt JC**, Gowdy K, Johnson VJ, Shepherd DM, and Germolec DR. 2009. Immunotoxicology (developmental immunotoxicology section). In: *General and Applied Toxicology*, 3rd Edition (Marrs T, Ballantyne B, Syversen T, eds.), John Wiley & Sons, Ltd., Chichester, UK, pp 1561-1583.

Other Scholarly Contributions

Portier CJ et al. (90+ co-authors). 2016. Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA). *Journal of Epidemiology and Community Health*. 70:741-745.

DeWitt JC and Luebke RW. 2014. Immunological Aging. *Online Reference Database Biomedical Science*.

Benbrahim-Tallaa L, Lauby-Secretan B, Loomis D, Guyton KZ, Grosse Y, El Ghissassi F, Bouvard V, Guha N, Mattock H, and Straif K *on behalf of the International Agency for Research on Cancer Monograph Working Group* (**DeWitt JC**, Mechanisms Subgroup Member). 2014. Carcinogenicity of perfluorooctanoic acid, tetrafluoroethylene, dichloromethane, 1,2-dichloropropane, and 1,3-propane sultone. *The Lancet Oncology*. 15:924-925.

IARC. 2014 Perfluoro-octanoic acid, Tetrafluoroethylene, Dichloromethane, 1,2-Dichloropropane, and 1,3-Propane sultone. *IARC Monogr Eval Carcinog Risks Hum* (**DeWitt JC**, Mechanisms Subgroup Member). *Monograph 110*.

DeWitt JC and Dietert RR. 2011. Response to "Theoretical aspects of autism: Causes - a review" by Ratajczak, HV (*Journal of Immunotoxicology* 8:68-79, 2011). *Journal of Immunotoxicology.* 8:195-197.

Non-Refereed Articles

"Toxicant induced brain asymmetry: More than just a bird-brained scheme?" Learned Discourses, *SETAC Globe*, Jan/Feb 2001 (invited).

RESEARCH FUNDING

Brody Brothers Endowment Foundation 1 year
Immunomodulatory Effects of Aqueous Film Forming Foam (AFFF): An Effective Fire Suppressant or a Persistent Environmental Contaminant with Unknown Health Consequences?
Role on project: Principal Investigator
Status: Award notification November 2016. Direct costs: $20,000

Center for Human Health and Environment at NCSU Pilot Project Program 1 year
Discovery of Biomarkers of Effect following Environmentally-Relevant Exposure to Pharmaceutical Pollutants
Role on project: Co-Principal Investigator
Status: Award notification August 2015. Direct costs: $25,000

Brody School of Medicine Internal Seed/Bridge Grant Program 1 year
Post-translational Modifications to Potassium Channels in Alzheimer's Disease: Triggers of Onset and Progression?
Role on project: Co-Principal Investigator
Status: Award notification August 2015. Direct costs: $25,000.

The Harriet and John Wooten Laboratory for Alzheimer's and Neurodegenerative Disease Research 1 year
Microglia as a Target of Environment x Gene Interactions Part II: Digging into the Biochemistry of Alzheimer's Disease
Role on project: Principal Investigator
Status: Award notification November 2014. Direct costs: $12,000

Interdisciplinary Research Collaboration Award (East Carolina University) 6 months
Pharmaceutical and Personal Care Product Contaminants in Fresh Water
Role on Project: Corresponding Faculty PI
Status: Award notification August 2014. Direct costs: $23,000

Alzheimer's North Carolina 1 year
A Multidisciplinary Approach to Fight Senior Dementia
Role on Project: Co-Investigator
Status: Award notification February 2014. Direct costs: $50,000

East-West Research Collaboration Award (East Carolina University) 6 months
Pharmaceutical and Personal Care Product Contaminants in Fresh Water
Role on Project: Corresponding Faculty PI
Status: Award notification December 2013. Direct costs: $23,000

The Harriet and John Wooten Laboratory for Alzheimer's and Neurodegenerative Disease Research 1 year
Microglia as a Target of Environment x Gene Interactions: Exacerbation of Alzheimer's Pathology by Early-life Exposure to Lead
Role on project: Principal Investigator

Status: Award notification April 2013. Direct costs: $12,000

Bureau of Land Management 3 years
Nellis Dunes Recreation Area Dust Exposure and Human Health Risk Assessment
Role on project: Co-Principal Investigator
Status: Award notification March 2011. Direct costs: $105,699

Department of Defense 1 year
Immunopathogenesis in autism: Regulatory T cells and autoimmunity in neurodevelopment
Role on project: Principal Investigator
Status: Award notification December 2009. Direct costs: $75,000.
School of Public and Environmental Affairs, Indiana University. Ph.D. Student Travel Award and Graduate Student Organization Travel Award. 2001. Funded amount: $500.00.

Ohio Valley Chapter of the Society of Environmental Toxicology and Chemistry. Student Travel Grant. 1997, 1998, 2001. Funded amounts: $300.00 each year.

EDITORIAL BOARDS/AD HOC MANUSCRIPT REVIEWER

Editorial Board Member, *Environmental Health Perspectives*. 2017-
Series co-Editor (with Sarah Blossom), *Molecular and Integrative Toxicology*. 2016-
Associate Editor, *Toxicology and Applied Pharmacology*. 2016-
Editorial Board Member, *Journal of Toxicology and Environmental Health Part A*. 2013-
Editorial Board Member, *Journal of Immunotoxicology*. 2010-
Ad Hoc Reviewer:

Advances in Physiology Education
Archives of Toxicology
Chemosphere
Drug and Chemical Toxicology
Environment International
Environmental Research
Environmental Science & Technology
Food and Chemical Toxicology
Human & Experimental Toxicology
International Immunopharmacology
International Journal of Tropical Biology
Journal of Immunotoxicology
NeuroToxicology
PLoS One
Reproductive Toxicology
Southeastern Naturalist
Toxicology Letters
Toxicological Sciences
Archives of Environmental Contamination & Toxicology
Chemical Research in Toxicology
Environmental Health Perspectives
Environmental Pollution
Environmental Science & Pollution Research
Epidemiology
GENE
International Aquatic Research
Journal of Environmental Immunology & Toxicology
Journal of Toxicology & Environmental Health
Pharmacological Research
Regulatory Toxicology & Pharmacology
Science of the Total Environment
Toxicology & Applied Pharmacology
Toxicology Reports

GRANT REVIEWER

Department of Defense Congressionally Directed Medical Research Programs, 2013-2016
Graduate Women in Science Graduate Fellowships, 2011, 2014-2017
CDC-NIOSH, 2010, 2013, 2016

EXTERNAL REVIEWER

ATSDR, 2017 (manuscript and Toxicological Profile)

New York State Department of Public Health, 2017 (Cancer incidence investigation: Village of Hoosick Falls, Rensselaer County, New York)

ORAL PRESENTATIONS (Invited)

"Not Seeing the Forest for the Trees: How the Complexity of the Immune System Challenges Policies for Environmental Health Protection." *Department of Pathobiology Annual Retreat*, Brown University, Providence, RI. 2017.

"The Science behind GenX." *Water Wednesday*, Clean Cape Fear, Wilmington, NC. 2017.

"Is it Possible to Untangle Underlying Developmental Susceptibilities from Exogenous Triggers in ASD?" *Autism Think Tank*, Autism Research Institute, Dallas-Fort Worth, TX. 2017.

"Urgent Research Needs for Better Understanding the Toxicity of PFASs." *Northeast Superfund Research Program Meeting*, Northeastern University, Boston, MA. 2017.

"Emerging Toxicological Knowledge and Data Gaps for "Novel" PFASs." *Public Workshop on Perfluoroalkyl and Polyfluoroalkyl Substances (PFASs) in Carpets, Rugs, Indoor Upholstered Furniture, and Their Care and Treatment Products*, Safer Consumer Products Program, Department of Toxic Substances Control, California Environmental Protection Agency, Sacramento, CA. 2017.

"Pharmaceuticals and Personal Care Products as Emerging Pollutants in Coastal Waters (with Dr. Siddhartha Mitra). *Science on the Sound Symposium*, Coastal Studies Institute, Wanchese, NC. 2017.

"Emerging Aquatic Contaminants and Health: Finding Solutions with Transdisciplinary Teams." Coastal Health Initiative, East Carolina University, Greenville, NC. 2016.

"Water Pollution: Is seeing believing?" *Love a Sea Turtle Second Annual Environmental Symposium*, River Park North, Greenville, NC. 2016.

"Developmental Immunotoxicology." *Middle Atlantic Reproduction and Teratology Association*, Covance Research Products, Inc., Denver, PA. 2015.

"A Little Bit of this and a Little Bit of that…How do we Understand Risks of Agents in just a Drop of Water?" *Love a Sea Turtle First Annual Environmental Symposium*, River Park North, Greenville, NC. 2015.

"Updates on Alzheimer's Disease Research in the DeWitt Lab at East Carolina University" (with Annalise vonderEmbse). *Senior Services Community Health Program*, Vidant Medical Center, Greenville, NC. 2015.

"Immunomodulatory Effects of Perfluoroalkyl Substances in Rodents and Humans." *Immunotoxicology in Food and Ingredient Safety Assessment: Approaches and Case Studies, SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety*, Washington, DC. 2015.

"Updates on Alzheimer's Disease Research in the DeWitt Lab at East Carolina University" (with Annalise vonderEmbse). *Alzheimer's Professional Partnership-Greenville*, Greenville, NC. 2015.

"From Sink to Sea: Evaluating Health Impacts of Pills and Perfumes after we Wash them away" (with Krista MCoy). *FaculTea Seminar*, East Carolina University, Greenville NC. 2014.

"Better Living through Chemistry: A Tale of Two Toxicants." *Department of Chemistry Seminar*, East Carolina University, Greenville, NC. 2014.

"The Nuts and Bolts of Interdisciplinary Toxicological Research" (with Christie Sayes). *Western Carolina University Department of Biology Spring Seminar Series*. Cullowhee, NC. 2014.

"Alzheimer's Disease and Neurodegenerative Disorders Research at East Carolina University" (with Annalise vonderEmbse). *Alzheimer's Professional Partnership-Goldsboro*, Goldsboro, NC. 2015.

"Endocrine Disruption of the Neuro-immune Interface." *The Collaborative on Health and the Environment Partnership Call* (Teleseminar). 2014

"Contaminated Drinking Water: A Case Study of Perfluorinated Compounds." *Coastal Water Resources Center*, East Carolina University, Greenville, NC. 2013.

"Villains and Heroes in the Battle for Clean Water" (with Siddhartha Mitra and Anthony Cannon). *STEM at Starlight*, Greenville, NC. 2013.

"The Nuts and Bolts of Alzheimer's Disease Research at East Carolina University." *Senior Services Community Health Program*, Vidant Medical Center, Greenville, NC. 2013.

"Alzheimer's Disease and Neurodegenerative Disorders Research at East Carolina University." *Alzheimer's Professional Partnership-Greenville*, Greenville, NC. 2013.

"A Neuroimmune Investigation of an Endocrine-Disrupting Compound". *Department of Biology Seminar*, East Carolina University, Greenville, NC. 2013.

"A Neuroimmune Investigation of an Endocrine-Disrupting Compund: How Bisphenol A may Disrupt Learning and Memory through Immunomodulation." *Endocrine Disrupting Chemicals Forum*, Research Triangle Park, NC. 2013.

"Undecafluoro-2-methyl-3-oxahexanoic Acid Versus Perfluorooctanoic Acid: Is Polyfluorination a Less Immunotoxic Option than Perfluorination?" *Department of Environmental and Molecular Toxicology Seminar*, North Carolina State University, Raleigh, NC. 2013.

"Early Life Triggers of Developmental Immunotoxicity." *Society for Toxicologic Pathology*, Annual Meeting, Denver, CO. 2011.

"Is the Pathway to Autism Paved with Environmental Chemicals?" *Department of Comparative Medicine seminar*. East Carolina University, Greenville, NC. 2011.

"PPAR Involvement in PFAA Immunotoxicity." *U.S. EPA PFAA Days III Workshop*, U.S. Environmental Protection Agency, Research Triangle Park, NC. 2010.

"Are Environmental Contaminants (Developmental) Immunotoxicants? A Case Study of a Fluorinated Compound." *Department of Microbiology and Immunology Seminar*, East Carolina University, Greenville, NC. 2010.

"Developmental Immunotoxicity of PFOA, an Emerging Contaminant." *Department of Biology Seminar*, East Carolina University, Greenville, NC. 2009.

"The Immunotoxicity of Perfluorooctanoic Acid (PFOA)." *Department of Physiology Seminar*, Brody School of Medicine, East Carolina University, Greenville, NC. 2008.

"Immunotoxic Potentials of PFOA." *U.S. EPA PFAA Days II Workshop*, U.S. Environmental Protection Agency, Research Triangle Park, NC. 2008.

"Chasing Down the Mechanism of Perfluorooctanoic Acid-Induced Immunomodulation: Knock-outs and Adrenalectomies." *National Health and Environmental Effects Research Laboratory Work in Progress*, U.S. Environmental Protection Agency, Research Triangle Park, NC. 2007.

"Wildlife Immunotoxicology." Immunotoxicology course. College of Veterinary Medicine, North Carolina State University. 2006.

"Immunotoxicity of Individual Organotin Compounds in Sprague-Dawley Rats." *Society for Risk Analysis* 25th Annual Meeting, Orlando, FL. 2005.

"Immune Function in Rats Exposed to Organotins as Adults or During Development." *National Health and Environmental Effects Research Laboratory Work in Progress*, U.S. Environmental Protection Agency, Research Triangle Park, NC. 2005.

"Brain Asymmetry in Domestic Hatchling Chickens Developmentally Exposed to TCDD: A Histological Examination." *Society of Environmental Toxicology and Chemistry* 24th Annual Meeting, Austin, TX. 2003.

"Service Learning and Scientific Research." Indiana University Community Outreach and Partnerships in Service-Learning Workshop, Indiana University, Bloomington, IN. 2004.

"Toxic Effects of Mercury." Clean Air Indiana Speak out on the Clear Skies Initiative, Indiana University, Bloomington, IN. 2003.

"Environmental Health Concerns for Toxics in Indiana Superfund Sites." Indiana Public Interest Research Group (INPIRG) Teach-In on Indiana Superfund Issues, Indiana University, Bloomington, IN. 2002.

"Introduction to Environmental Toxicology." Techniques in Environmental Science and Environmental and People courses. School of Public and Environmental Affairs, Indiana University-Bloomington. 2000, 2001, 2003.

"Bioaccumulation and Biomagnification of Environmental Chemicals in Colonial Fish-eating Waterbirds." Introduction to Environmental Sciences course. School of Public and Environmental Affairs, Indiana University-Bloomington. 2000 and 2001.

"Women in the Sciences: Abolishing Gender Apartheid." IU Skills for Leadership Conference, Office of Women's Affairs, Indiana University, Bloomington, IN. 1999.

ORAL PRESENTATIONS

"Perspectives from the AAMC Mid-Career Women Faculty Professional Development Seminar "MIDWIMS"). *Brody Women Faculty Committee*. Greenville, NC. 2017.

"Immunopathogenesis in Autism: Regulatory T Cells and Markers of Autoimmunity in Mice Developmentally Exposed to Perflurooctanoic Acid (PFOA). *27th Annual NeuroToxicology Conference*, Annual Meeting, Durham, NC. 2011.

"PFOA-induced Immunomodulation in mice: An Overview." *Society of Toxicology* 48th Annual Meeting, Baltimore, MD. 2009.

"Pathways of PFOA-mediated Immunosuppression." *Society of Toxicology* 48th Annual Meeting, Baltimore, MD. 2009.

"Dose-response of Perfluorooctanoic Acid-Induced Immunomodulation in Adult C57BL/6 Mice." *Society of Toxicology* 46th Annual Meeting, Charlotte, NC. 2007.

"Immune Function in Rats Developmentally Exposed to Dibutyltin Dichloride." *Society of Toxicology* 45th Annual Meeting, San Diego, CA. 2006.
"Neurotoxic Effects in Avian Species: Implications for Human and Ecological Health." School of Public and Environmental Affairs *2nd Annual Young Researchers Conference*, Indiana University, Bloomington, IN. 2002.

"TCDD-Induced Brain Asymmetry and Behavior: What do Individual Chicks Have to Say?" *Ohio Valley Chapter of the Society of Environmental Toxicology and Chemistry*, Hueston Woods State Park, College Corner, OH. 2000.

"Behavioral and Morphological Changes in Domestic Chicks Exposed to TCDD or PCB-126 at Embryonic Day 0 or Embryonic Day 4." *Ohio Valley Chapter of the Society of Environmental Toxicology and Chemistry*, Indiana University, Bloomington, IN. 1997.

"Behavioral Changes in Domestic Hatchling Chicks Exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) *in ovo*." *Conference on Chlorine in the Environment*, Massachusetts Institute of Technology, Boston, MA. 1996.

"Behavioral Assessment of Hatchling Chicks Exposed to TCDD *in ovo*: Preliminary Results." *Great Lakes Bioeffects Workgroup*. Wright State University, Dayton, OH and *Ohio Valley Chapter of the Society of Environmental Toxicology and Chemistry*, Eastern Kentucky University, Richmond, KY. 1996.

CONTINUING EDUCATION COURSES

Stress as a Confounding Factor in Toxicology Studies
Rodent Pathology (Immunopathology)
Basic Embryology and Developmental Toxicology
Grants 101: Professional Grant Writing Workshop
Immunology for Toxicologists
Risk Communication for the General Public
Estrogen Mimics in Health and Disease
Methods for Assessment of Neurotoxicity

PROFESSIONAL ORGANIZATIONS

2009-Present	Carolinas Society of Environmental Toxicology and Chemistry
2005-Present	Society of Toxicology (SOT)
2005-Present	North Carolina Chapter of the Society of Toxicology

1997-Present	Society of Environmental Toxicology and Chemistry (SETAC)
1996-2004	Ohio Valley Chapter of the Society of Environmental Toxicology and Chemistry
1996-2004	Great Lakes Bioeffects Workgroup

AWARDS AND HONORS

- *The Faculty Mentor Award*, East Carolina University Honors College. 2017.
- *Outstanding Young Investigator Award*, Immunotoxicology Specialty Section, Society of Toxicology. 2013.
- *Outstanding Teaching Award*, School of Public and Environmental Affairs, Indiana University. 1999 and 2002.
- *Future Faculty Teaching Fellowship*, Preparing Future Faculty program, Indiana University. 2002.
- *Marian Vinegar Award*, Outstanding Student Presentation at the annual meeting, Ohio Valley Chapter of the Society of Environmental Toxicology and Chemistry. 2000.
- *Outstanding Educational Volunteer*, Monroe County Humane Association, Bloomington, IN. 2000.
- *Outstanding Student Poster Award*, Society of Environmental Toxicology and Chemistry 19th Annual Meeting (3rd place). 1998.
- *Teaching Excellence Recognition Award*, School of Public and Environmental Affairs, Indiana University. 1998.

PROFESSIONAL PRACTICE

Workshop Participant, Is the European Food Safety Authority (EFSA) standard for bisphenol A sufficiently protective of the immune system and should the Dutch government consider a different standard? Organized by representatives of RIVM (National Institute for Public Health and the Environment), Amsterdam, The Netherlands. September, 2015.

- Provided immunotoxicological guidance for regulatory consideration of bisphenol A (BPA).

Consultant, CZR Incorporated, Wilmington, NC. May-July, 2014-present.

- Provided toxicological interpretation of stream water quality monitoring data for heavy metals.

Technical Advisor, Office of Health Assessment and Translation (OHAT), National Toxicology Program, National Institute of Environmental Health Sciences. March 2013. March 2015. April 2016.

- Evaluated OHAT protocol for evaluation of PFOS-PFOA immunotoxicity.

External Peer Reviewer, U.S. Environmental Protection Agency, External peer review of EPA's Draft Health Effects Documents for Perfluorooctanoic acid (PFOA) and Perfluorooctane Sulfonate (PFOS). 2014.

- Scientific peer reviewer of the health effects documents. Nominated and selected.

Working Group Member, International Agency for Research on Cancer (IARC), IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 110: Perfluorooctanoic acid, Tetrafluoroethylene, Dichloromethane, 1,2-Dichloropropane, and 1,3-Propane sultone. 2014.

- Member of Mechanistic and Other Relevant Data Working Group for perfluorooctanoic acid and tetrafluoroethylene. Invited.

Consultant, Constella Group, LLC, Durham, NC. October 2004-December 2005.

- Summarized immunotoxicology of atrazine for the National Toxicology Program's Report on Carcinogens.

Consultant, Henshel EnviroComm, Bloomington, IN. June 1999-May 2004.

- Representative of the Restoration Advisory Board for Jefferson Proving Ground (Department of Defense) through the Technical Assistance for Public Participation program.
- Interpreted risk assessment documents associated with base clean-up for the general public.

Consultant, Dinosaur Inc., Bloomington, IN. June 2000-September 2000.
- Summarized the potential health and environmental effects of land-applied paper mill sludge.

Consultant, Integrated Pest Management in Schools and Childcare Centers, School of Public and Environmental Affairs Information Clearinghouse, Bloomington, IN. April 2000-September 2000.
- Summarized the potential health effects of pesticides commonly used in schools and childcare centers.

Co-Director, *Summer Program for Exploration of Complex Issues in Environmental Science for Teachers (SPECIES-Teachers)* and *Environmental Education 99*, School of Public and Environmental Affairs, Indiana University, Bloomington, IN. Summer 1999 and 2001.
- Directed hands-on environmental science summer field workshop for Indiana teachers.

Consultant, Brownstown Elementary Fourth Grade, Brownstown, IN. September 1999-May 2000.
- Served as environmental science expert during weekly videoconferences in a "students as environmental scientists" program.

Associate Director, *Research Experience for High School Students*, College of Arts and Sciences, Indiana University, Bloomington, IN. February 1999-October 1999.
- Mentored high school students participating in research in university laboratories, provided weekly counseling, and oversaw development of final research reports and presentations.

Co-Director, *Environment 98* and *Environment 99*, School of Public and Environmental Affairs, Indiana University, Bloomington, IN. Summer 1998 and 1999.
- Directed hands-on environmental science summer field workshop for Indiana students.

Chemical Safety Assistant, Office of Radiation, Chemical and Biological Safety, Michigan State University, East Lansing, MI. August 1993-June 1995.
- Developed Michigan State University's Chemical Hygiene Plan, performed university-wide laboratory safety inspections, and trained new science employees in chemical and laboratory safety.

TEACHING EXPERIENCE

Instructor, East Carolina University

- Practical Problems in Biometry. Graduate (course director).
- General Toxicology. Graduate (co-course director).
- Advanced Toxicology. Graduate (co-course director)
- Medical Pharmacology. Graduate physician assistant students (topical: endocrine pharmacology, toxicology).
- Medical Pharmacology. Second year medical students (topical: endocrine pharmacology, toxicology).
- Pharmacology Mini-Course. First and second year dental students (topical: toxicology, management of poisoned patients, endocrine pharmacology).
- Foundations of Medicine/Problem Based Learning Mini-Course. First and second year medical students.

- Foundations of Medicine/PirateMD. First and second year medical students.

Instructor, Indiana University

- Analytical Problem Solving (statistics). Undergraduate, honors, 2 semesters.
- Environment and People. Undergraduate (co-instructor), 1 semester.
- Introduction to Statistical Techniques. Undergraduate, 1 semester.
- Introduction to Environmental Sciences. Undergraduate, 1 semester.
- Environmental Risk Analysis. Graduate, 1 semester.
- Outdoor Environmental Awareness (Public land management). Undergraduate recruitment course, 6 semesters.
- Introduction to Risk Assessment and Risk Communication. Undergraduate, 1 semester.
- Environmental Toxicology. Combined undergraduate/graduate, 1 semester.
- Techniques in Environmental Science (field/lab techniques). Undergraduate, 3 semesters.

Teaching Assistant/Coordinator, Indiana University

- Aquatic Habitat Analysis (field techniques). Combined undergraduate/graduate, 3 semesters.
- Terrestrial Habitat Analysis (field techniques). Combined undergraduate/graduate, 3 semesters.
- Environmental Toxicology. Undergraduate and graduate, 3 semesters.
- Teaching Assistant and Undergraduate Teaching Intern Training Workshop. Combined undergraduate and graduate, 6 sessions.

Laboratory Mentor, East Carolina University

High school students

- Sunnie Li and Alex Reulbach, Summer Ventures Program (high school laboratory research). Project: Neuroinflammation in a rodent model of Gulf War Illness. 2017.
- Matthew Clayton, high school laboratory research for the NC Science Fair. Project: Developmental effects of pharmaceutical pollutants in an avian model. 2016.
- Virginia Billings, Summer Ventures Program (high school laboratory research). Project: Developmental effects of pharmaceutical pollutants in an avian model. 2016.
- Jaein Yoon, Medical Honors Program (high school laboratory research). Project: Developmental effects of pharmaceutical pollutants in an avian model. 2015-2016.
- Chevonne Parker, Summer Ventures Program (high school laboratory research). Project: Neuronal T-cell infiltration following developmental trichloroethylene exposure. 2015.
- Catherine Taylor and Jessi Zhou, Medical Honors Program (high school laboratory research). Project: Microglial responses in an Alzheimer's mouse model developmentally exposed to lead. 2014-2015.
- Janelle Neal, Summer Ventures Program (high school laboratory research). Project: Microglial responses following inhalation exposure to natural dusts. 2014.
- Brian Alloway, Medical Honors Program (high school laboratory research). Project: Peroxisome proliferation in livers of C57BL/6 mice exposed to undecafluoro-2-methyl-oxahexanoic acid (U2M3-OHxA) gavage. 2013-2014.
- Kortney Wager, Summer Ventures Program (high school laboratory research). Project: Developmental effects of BPA on immune responses. 2013.
- Brian Ennis and Jonathan Reed, Medical Honors Program (high school laboratory research). Project: Teratogenicity of PFOS in early chicken embryos. 2012-2013.
- Willa Chen, Summer Ventures Program (high school laboratory research). Project: Developmental effects of PFOA in primary cardiomyocyte cultures from chickens. 2012.
- Elizabeth Fox and Samantha Rouse, Medical Honors Program (high school laboratory research). Project: Teratogenicity of PFOS in early chicken embryos. 2011-2012.

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- Pranavi Sanka, Summer Ventures Program (high school laboratory research). Project: Developmental effects of PFOS: T cell infiltration into mouse brains. 2011.
- Erin Morris and Andrew Wood, Medical Honors Program (high school laboratory research). Project: Developmental effects of PFOA on T cell infiltration and myelin basic protein levels in mouse brains. 2010-2011.
- Jillian Loftis, Summer Ventures Program (high school laboratory research). Project: Developmental effects of PFOA on glycogen deposition in a chicken model. 2010.
- Clarissa Morrissey, Medical Honors Program (high school laboratory research). Project: Teratogenicity of PFOA in early chicken embryos. 2009-2010.
- Taylor Brundage, Summer Ventures Program (high school laboratory research). Project: Developmental teratogenic effects of PFOA in a chicken model. 2009.
- Ian Bryan, Medical Honors Program (high school laboratory research). Project: Developmental effects of PFOA on liver glucocorticoid receptor levels, and pancreatic alpha and beta cells in a mouse model. 2008-2009.

Undergraduate students

- Robert Strickland, General Studies/Program in Neuroscience (undergraduate laboratory research). Project: Neuroinflamamtion in a rodent model of Gulf War Illness. 2017-
- Chastity Ward, Summer Biomedical Research Program (undergraduate laboratory research). Project: Immunotoxic effects of AFFF in a rodent model. 2017.
- Christopher Hamby, Mutidisciplinary Studies Program in Neuroscience (undergraduate laboratory research/senior thesis advisor). Project: Microglial morphology in a rodent model of Gulf War Illness. 2016-2017.
- Ishmael Gomez, Summer Biomedical Research Program (undergraduate laboratory research). Project: DAP12 microglial signaling in a rodent model of Alzheimer's disease. 2016.
- Brianna Davidson, Multidisciplinary Studies Program in Neuroscience (undergraduate laboratory research). Project: Synaptic degeneration in a rodent model of Alzheimer's disease. 2016.
- Samuel Vance, Mutidisciplinary Studies Program in Neuroscience (undergraduate laboratory research/senior thesis advisor). Project: Project: Post-translational modifications and Alzheimer's pathology. 2015-2017.
- Waeya Lin, Summer Biomedical Research Program (undergraduate laboratory research). Project: Exacerbation of Alzheimer's pathology by prenatal exposure to lead; Dystrophic microglia. 2015.
- Giovana Fernanda Cosi Bento, Brazil Scientific Mobility Program (undergraduate laboratory research). Project: Exacerbation of Alzheimer's pathology by prenatal exposure to lead; Synaptosomes. 2015.
- Zoe Hinton, Mutidisciplinary Studies Program in Neuroscience (undergraduate laboratory research/senior thesis advisor). Project I: Exacerbation of Alzheimer's pathology by prenatal exposure to lead; Synaptosomes. 2015. Project II: Microglial morphology in a rodent model of Gulf War Illness. 2016-2017.
- Andrew Wood, Biology (undergraduate honors thesis advisor). Project: Exacerbation of Alzheimer's pathology by prenatal exposure to lead; Measurement of amyloid beta. 2014-2015.
- Dakota Johnson, Biology (undergraduate honors thesis advisor). Project: Exacerbation of Alzheimer's pathology by early-life exposure to lead; Measurement of amyloid beta. 2013-2014.
- Sydney Henry, Summer Biomedical Research Program (undergraduate laboratory research). Project: Neurotoxic effects of dust collected from the Nellis Dunes Recreation Area. 2014.
- Andrew Wood, Biology undergraduate student. Project: Developmental effects of BPA on serum IL-4 and IgG. 2013.
- Dominique Baldwin, Biology undergraduate student. Project: Neurotoxic effects of dust collected from the Nellis Dunes Recreation Area. 2013.

- Megan Biller, Summer Biomedical Research Program (undergraduate laboratory research). Project: Microglia in Alzheimer's-prone triple transgenic mice. 2013.
- Blake Rushing, Summer Biomedical Research Program (undergraduate laboratory research). Project: Blood distribution, urinary excretion, and T cell-dependent immunotoxicity of undecafluoro-2-methyl-oxahexanoic acid (U2M3-OHxA) in C57BL/6 mice exposed via gavage. 2012.
- Alvin-Ming-Yun Tsang, Psychology (undergraduate honors thesis advisor). Project: Developmental effects of nanoparticles in a rodent model. 2011-2012.
- Nick Creech, Summer Biomedical Research Program (undergraduate laboratory research). Project: Immunological effects of PFOA on a T-cell independent antigen (DNP-Ficcol) in an adult mouse model. 2010-2011.
- Hatel Patel, Biochemistry undergraduate student. Project 1: Developmental effects of PFOA on liver peroxisomes proliferation in a chicken model. Project 2: Effects of PFOA on myelin basic protein levels in the brains of developmentally-exposed mice. 2009.
- Ian Bryan, Biology and Chemistry undergraduate student. Project: Developmental effects of PFOA and PROS in a chicken model, including early embryo teratogenesis and hatchling glycogen levels. 2009-2012.

Master's students

- Carmen Davis, Environmental Health Master's Student. Project: Developmental effects of Triclosan in an avian model. 2015-2016.
- Cory Boles, Biomedical Sciences Master's Student. Project: Exacerbation of Alzheimer's pathology by early-life exposure to lead. 2013-2015.
- Annalise vonderEmbse, Biomedical Sciences Master's Student. Project: Exacerbation of Alzheimer's pathology by early-life exposure to lead; Effects on microglia. 2012-2014.

Doctoral students

- Jacqueline Meadows, Pharmacology and Toxicology Ph.D. Student. Project: Developmental effects of pharmaceutical pollutants in an avian model. 2015-
- Annalise vonderEmbse, Pharmacology and Toxicology Ph.D. Student. Project: Exacerbation of Alzheimer's pathology by early-life exposure to lead; Effects on microglia. 2014-2017.
- Jason Franklin, Pharmacology and Toxicology Ph.D. Student. Project: Developmental neuroimmunotoxicity of bisphenol a in a rodent model. 2010-2014.
- Qixiao Jiang. Pharmacology and Toxicology Ph.D. Student. Project: Developmental cardiotoxicity of perfluorinated compounds in an avian model. 2009-2013.

Medical students

- Amie McPherson and Danesh Ghiassi, Medical students. Project: Isolation and stimulation of regulatory T cells from spleens of PFOA-exposed mice. 2009.

Advisory, East Carolina University

- Khoa Do, Biomedical Sciences Master's Student (Thesis committee; Advisor: Hu Huang). 2016-2017.
- John Atkinson, Biology Master's Student (Thesis committee; Advisor: David Rudell). 2015-2016.
- Blake Rushing, Pharmacology and Toxicology Ph.D. Student (Dissertation committee; Advisor: Mustafa Selim). 2015-
- Ahmed Aldhafiri, Pharmacology and Toxicology Ph.D. Student (Dissertation committee; Advisor: Ken Soderstrom). 2014-
- Jason Hoggard, Biomedical Sciences Master's Student (Thesis committee; Advisor: Lance Bridges). 2014-2015.

- Matthew Edwards, Biology Master's Student (Thesis committee; Advisor: Krista McCoy). 2014-2015.
- Bevin Blake, Biology Master's Student (Thesis committee; Advisor: Krista McCoy). 2013-2015.
- Anastasia Weeks, Microbiology and Immunology Master's Student (Thesis committee; Advisor: Mark Mannie). 2013-2017.
- Samar Rezq, Pharmacology and Toxicology Ph.D. Student (Dissertation committee; Advisor: Abdel Abdel-Rahman). 2013-2016.
- Partha Nagchowdhuri, Pharmacology and Toxicology Ph.D. Student (Dissertation committee; Advisor: Brian McMillen). 2013-
- Suelen Demor, Biology Ph.D. Student (Dissertation committee; Advisor: David Chalcraft). 2013-2017.
- Tessa Holland, Pharmacology and Toxicology Ph.D. Student (Dissertation committee; Advisor: Ken Soderstrom). 2013-
- Samantha Sellers, Anatomy and Cell Biology Ph.D. Student (Dissertation committee). 2013.
- Alvin Ming-Yun Tsang, Psychology Undergraduate Student (Honors Thesis Advisor). 2011-2012.
- Abdullah Aldossari, Pharmacology and Toxicology Ph.D. Student (Dissertation committee; Advisor: Jared Brown). 2011-.
- Michael Smith, Biology Master's Student (Thesis committee; Advisor: Xiaoping Pan). 2010-2011.
- Pranita Katwa, Pharmacology and Toxicology Ph.D. Student (Dissertation committee; Advisor: Jared Brown). 2009-2012.

COMMUNITY SERVICE

Scientific Community

- Member, Society of Toxicology Specialty Section Collaboration and Communication Group. 2017-present.
- Vice-President, Society of Toxicology Immunotoxicology Specialty Section. 2017-present.
- Program Planning Committee, Volunteers Sub-committee, 2017 Annual Meeting, Society of Environmental Toxicology and Chemistry. 2016-2017.
- Vice-President Elect, Society of Toxicology Immunotoxicology Specialty Section. 2016-2017.
- Program Committee Member, Society of Toxicology Immunotoxicology Specialty Section. 2015-2016.
- Moderator for Toxicology, Epidemiology, and Human Health section, FLUOROS 2015 meeting, Golden, CO. 2015.
- Program Planning Committee, 2015 Annual Meeting, Society of Environmental Toxicology and Chemistry. 2014-2015.
- Senior Councilor, Immunotoxicology Specialty Section Society of Toxicology. 2014-2015.
- Past-President, North Carolina Society of Toxicology. 2014-2015.
- Junior Councilor, Immunotoxicology Specialty Section Society of Toxicology. 2013-2014.
- President, North Carolina Society of Toxicology. 2013-2014.
- Appointed Member, Research Funding Committee, Society of Toxicology. 2012-2014.
- Vice President, North Carolina Society of Toxicology. 2012-2013.
- Vice President-Elect, North Carolina Society of Toxicology. 2011-2012.
- Program Committee Member, Society of Toxicology Immunotoxicology Specialty Section. 2010-2011.
- Councilor, North Carolina Society of Toxicology. 2009-2011.
- Workshop co-chair and organizer, "Is Modulation of the Immune System by Perfluoroalkyl Acids a Human Health Concern?" Society of Toxicology 48th Annual Meeting, Baltimore, MD. 2009.
- Symposium co-chair and organizer, "Immune Biomarkers in Alternative Species: Implications for Risk Assessment," Society of Toxicology 46th Annual Meeting, Charlotte, NC. 2007.

- Platform session co-chair, "Immunotoxicology: Immune Modulation and Cell Specific Responses," Society of Toxicology 46th Annual Meeting, Charlotte, NC. 2007.
- Postdoctoral Representative and Program Committee member, Immunotoxicology Specialty Section of the Society of Toxicology. 2005-2007.
- Mentor, Association of Women in Science Program (WISP) Mentoring Project, Office of Women's Affairs, Indiana University, Bloomington, IN. 2000-2002.
- Student Board Member, Ohio Valley Chapter of Environmental Toxicology and Chemistry. 2000-2001.

Workplace Community

- Department of Comparative Medicine Promotion and Tenure Committee, Brody School of Medicine, East Carolina University, 2017-present.
- Committee member, Coastal Strategic Planning Committee, East Carolina University, 2016-2017.
- BSOM Promotion and Tenure Committee, Brody School of Medicine, East Carolina University, 2015-present.
- Secretary/Treasurer, Brody Women Faculty Committee. 2015-2017.
- Committee member, Planning committee for the joint PhD program in Integrated Coastal and Marine Sciences, East Carolina University. 2015-present
- Committee member, School of Dental Medicine Admissions Committee, East Carolina University, 2014-present.
- Committee member, BSOM Sustainability Committee, Brody School of Medicine, East Carolina University, 2014-2016.
- Committee member, BSOM Research Committee, Brody School of Medicine, East Carolina University. 2014-2015.
- Five-Year Review Committee for Dean Paul Cunningham, Dean of the Brody School of Medicine (appointed by the Vice Chancellor for Health Sciences). 2014.
- Committee member, Institutional Animal Use and Care Committee. 2013-present.
- M1 Curriculum Committee member, Brody School of Medicine, East Carolina University. 2013-2016.
- Master Educator Committee member, Brody School of Medicine, East Carolina University. 2012-2016.
- Chair, Brody Women Faculty Committee. 2012-2013.
- Group member, Brody Vision, Innovation, Achievement (VIA) group. 2011-2015.
- Undergraduate Research and Creative Activity Biomedical Sciences Grant Review Committee. 2011-present.
- Chair-elect, Brody Women Faculty Committee. 2011-2012.
- Committee member, Coastal Maritime Council, East Carolina University. 2010-present.
- Five-Year Review Committee for Dr. David Taylor, Chair of the Department of Pharmacology and Toxicology (appointed by the Dean of the School of Medicine). 2010.
- Committee member, Shared Resources Committee, Brody School of Medicine, East Carolina University. 2008-2012.
- Faculty of the Interdisciplinary Doctoral Program in Biological Sciences, East Carolina University. 2009-present.
- Committee member, Brody Women Faculty Committee, East Carolina University. 2008-present.
- Graduate Faculty, Division of Research and Graduate Studies, East Carolina University. 2008-present.
- Vice-President and at-large member, EPA RTP Networking and Leadership Training Organization, USEPA. 2004-2008.
- Organizing committee member, 2007 NIEHS Biomedical Career Fair. 2006-2007.

- Executive committee member/Vice-chair, Environmental Science program representative, Association of SPEA Ph.D. Students, School of Public and Environmental Affairs, Indiana University. 2001-2002.
- Environmental Science program representative, Dean's Student Advisory Committee, School of Public and Environmental Affairs, Indiana University. 1997-2002.

Other

- Science Event Co-Coordinator, "ADdMe to Tox Town," Girl Scouts TechnoQuest Event. 2017.
- Science Event Co-Coordinator, "Biometry in Action," Brody Girl's STEM Day. 2016.
- Science Event Coordinator, "The Water Cycle," Youth Ocean Conservation Summit. 2016.
- STEM volunteer, various events, Love a Sea Turtle. 2015-present.
- Science Event Coordinator, "Marshmallow Genetics" and "DNA Necklaces," ECU Girl's STEM Day. 2014-2016.
- Scientific Expert, Alzheimer's North Carolina fundraising walk, Washington, NC. 2014-2016.
- Über Judge, Blue Heron Bowl, Regional Competition for the National Ocean Sciences Bowl. 2012.
- Judge, North Carolina Region 1 Science and Engineering Fair. 2010. 2011.
- North Carolina Estuarium Docent. 2009-present.

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Appendix B

Estimating "Safe" PFOS Doses, an Example and Comments

Estimating "Safe" PFOS Doses, an Example and Comments.

Dr. John Butenhoff derived a plasma PFOS reference level of 1.05 ppb (µg/L), to his best recollection, in 1997 or 1998 (3M_MN00042160. Butenhoff Depo. Tr. October 27, 2006; 59-70). In this derivation, Dr. Butenhoff did the following (adopted from Ex.148. 3M_MN00042206):

LOAEL in Rhesus monkeys = 0.5 mg/kg/day over 90 days.

Safety factors:

10 for LOAEL to NOAEL

10 for sub-chronic to chronic

100 for interspecies extrapolation

10 for exposure of children (Food Quality Safety Act and Water Act)

Applying a 100,000-fold safety factor (product of four safety factors, above) to the LOAEL = 0.5 mg/kg/day divided by 100,000 = 0.000005 mg/kg/day or 0.005 µg/kg/day. Dr. Butenhoff adjusted this value for the default 70 kg body weight for a human calculate a value of 0.35 µg/day.

Comment – Reference doses typically are expressed in mg/kg/day as it is the LOAEL or NOAEL divided by uncertainty factors (U.S. EPA, 1989). Alternatively, a human equivalent dose (HED) can be used. For PFOS, the U.S. EPA (U.S. EPA, 2016d) scaled serum concentrations (typically in mg/L) for the NOAEL or LOAEL identified in an experimental animal study to clearance of PFOS in humans. The HED also expressed in mg/kg/day. It is therefore somewhat confusing as to why Dr. Butenhoff multiplied the 0.005 µg/kg/day by the default human body weight value.

Dr. Butenhoff then adjusted this 0.35 µg/day value by 90 days, which was the duration of the Rhesus monkey study that identified the LOAEL of 0.5 µg/kg/day. He expressed this as a total dose of 31.5 µg, which appears to be his estimate of the potential total mass of PFOA in the plasma of the Rhesus monkeys after 90 days of exposure to 0.35 µg.

Finally, Dr. Butenhoff adjusted the 31.5 µg value by 10% as this was his assumption that 10% of this mass would be in the plasma of the Rhesus monkeys. He then assumed that an average human has 3 liters of plasma and calculated 1.05 µg/L (3.15 µg divided by 3 L).

Comment – Again, this approach is somewhat confusing as it does not exactly follow approaches used by the U.S. EPA to derive RfDs or HALs even though Dr. Butenhoff indicates that "…it follows the approach used by federal agencies" (Ex.148. 3M_MN00042206). As a reminder, RfDs are expressed in mg/kg/day whereas HALs are expressed in µg/L (or mg/L) of drinking water and reflect RfDs adjusted by body weight and the drinking water intake (U.S. EPA, 2016d).

Comment – If we use the LOAEL from the Rhesus monkey study as a starting point and adjust it by the uncertainty factors used by Dr. Butenhoff, the RfD is 0.000005 mg/kg/day. Using

formulas consistent with the U.S. EPA for PFOS (U.S. EPA, 2016d), the following calculations can be made:

$$\frac{0.000005 \text{ mg/kg/day}}{0.054 \text{ L/kg/day*}} = 9.3 \times 10^{-5} \text{ mg/L (DWEL; drinking water equivalent level)}$$

*drinking water intake rate

Lifetime health advisory = DWEL x RSC =

9.3×10^{5} mg/L x 0.2 (value used by U.S. EPA) = 0.000016 mg/L or 0.016 µg/L

If we do the same calculations, but use values of the MDH for drinking water intake rate (0.049 L/kg/day) and RSC (0.5), the calculations are as follows:

$$\frac{0.000005 \text{ mg/kg/day}}{0.049 \text{ L/kg/day}} = 1.02 \times 10^{-4} \text{ mg/L (DWEL; drinking water equivalent level)}$$

Lifetime health advisory = DWEL x RSC =

1.02×10^{-4} mg/L x 0.5 (value used by U.S. EPA) = 0.000051 mg/L or 0.051 µg/L

Comment – The "safe" PFOS dose calculated by Dr. Butenhoff in the late 1990s was therefore more conservative than the U.S. EPA 2016 HAL (0.07 µg/L) and on the same order of magnitude as the MDH HBV (0.027 µg/L).

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11/17/2017 7:13 PM
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Appendix C

List of References

3M Company. 1963. Technical Information for 3M Brand Fluorochemical Surfactants.

3M_MN00042160. Butenhoff Depo. Tr. October 27, 2006.

3M_MN01663513. Fluorad Fluorochemical Surfactant FC-95. 90-day subacute rhesus monkey toxicity study (International Research and Development Corporation). Dated January 2, 1979.

3M_MN01663537. Fluorad Fluorochemical Surfactant FC-95. Ninety day subacute rat toxicity study (International Research and Development Corporation). Dated November 10, 1978.

3M_MN02330325. Memo regarding two-year toxicity/carcinogenicity study of fluorochemical FC-143 in rats from Charles Reinhardt (DuPont) to Greg Sykes.

3M_MN02343342. Final report: 26-week capsule toxicity study with ammonium perfluorooctanoate (APFO) in cynomolgus monkeys (Covance Study Number: 6329-231; Authored by Peter J. Thomford, PhD). Dated December 18, 2001 (as study completion date).

3M_MN02483163. See Olsen et al., 2001a.

3M_MN03095624. See Luebker et al., 2005.

3M_MN03112178 at 3M_MN03112393. Fluorocarbons and human health: Studies in an occupational cohort. Dr. Gilliland's 1992 doctoral thesis.

3M_MN03278834. Final report: 26-week capsule toxicity study with perfluorooctane sulfonic acid potassium salt (PFOS: T-6295) in cynomolgus monkeys (Covance 6329-223; Authored by Peter J. Thomford, PhD). Dated January 11, 2002 (as study completion date).

3M_MN05305661. Results of toxicity tests in mice given heptafluorobutyric acid by intraperitoneal injection or inhalation. Dates of work noted as Jan. 25-Feb. 14, 1949.

3MA00027126. Two year oral (diet) toxicity/carcinogenicity study of fluorochemical FC-143 in rats (RIKER Experiment No. 0281CR0012). Volume 1 of 4. Conducted during April, 1981-May, 1983.

3MA00248385. C-8 gavage: Embryo-fetal toxicity and teratogenicity study in the rat. MR-4130-001 (Haskell Laboratory Report No. 1-82). Dated January 14, 1982.

3MA00326722. Experiment No. 0680TR0010. Oral teratology study of FM-3422 in rats (Safety Evaluation Laboratory, RIKER Laboratories, Inc. St. Paul, Minnesota). Dated 2/18/81.

3MA00356530. Experiment No. 0680TR0008. Oral teratology study of FC-95 in rats (Safety Evaluation Laboratory, RIKER Laboratories, Inc. St. Paul, Minnesota). Signed 12/17/80.

3MA00360639. Lamprecht EG. Fetal rat lens artifact – Summary of developments to date. Memo regarding study files of Riker experiments nos. 0680TR0008, 0680TR0010 0680TR0020, 0681TR0095, 0681TR0110, and 0680RR0018. Dated November 6, 1981.

3MA00417473. See Alexander 2001a.

3MA00593073. FC-95, FC-143 and FM-3422 – 90 day subacute toxicity studies conducted at IRDC - Review of final reports and summary.

3MA00593233. Two year oral (diet) toxicity/carcinogenicity study of fluorochemical FM-3924 in rats (RIKER Experiment No 02281CR0012). Volume 1 of 5. Conducted during April, 1981-May, 1983.

3MA00631764. See Gilliland and Mandel, 1993.

3MA00760311. Report: Exploratory 28-day oral toxicity study with telomere alcohol, telomere acrylate, PFBS, PFHS and PFOS (positive control) by daily gavage in the rat followed by a 14/28-day recovery period. NOTOX Project 242933.

3MA00812492. Final report: 104-week dietary carcinogenicity study with narrow range (98.1%) N-ethyl perfluorooctanesulfonamido ethanol in rats (Covance 6329-212; Peter J. Thomford, PhD). Dated December 31, 2001.

3MA01405733. Draft report: Two year oral (diet) toxicity/carcinogenicity study of fluorochemical FC-143 in rats (RIKER Experiment No. 0281CR0012). Conducted during April, 1981-May, 1983.

3MA01472304. See Alexander, 2001b.

3MA01507211. TNO report: The effect of 3 perfluorinated alkyl sulphonated on cholesterol/bile acid metabolism in 15%-fat fed E3-Leiden transgenic mice in vivo and on fatty acid conversion into cholesterol in rat hepatocytes in vitro. Project/study number: 031.10074/3M-02 (TNO Quality of Life, TNO Life Sciences for Food and Pharma, Authored by: Cohen LH, Pieterman EJ, and Hoegee-de Nobel E). Dated 18 October 2006.

3MA01508403. Experiment No. 0681TR0110. Oral teratology study of T-2998CoC in rats (Safety Evaluation Laboratory, RIKER Laboratories, Inc. St. Paul, Minnesota). Signed 12-15-81.

3MA01797217. Fluorad Fluorochemical FC-143. Ninety day subacute rhesus monkey toxicity study (International Research and Development Corporation). Dated November 10, 1978.

3MA02543911. Olsen unpublished draft of an epidemiological study of fluorochemical production employees of the 3M plant in Cottage Grove.

3MA02557439. See Lundin and Alexander, 2007.

3MA10008766. Experiment No. 0681TR0362. Special lens oral teratology study of T-2999CoC in two strains of rats (Safety Evaluation Laboratory, RIKER Laboratories, Inc. St. Paul, Minnesota). Signed 7-16-82.

3MA10014327. Phone conversation report: Review of FC-143 final report: Leydig cell tumor incidence. 12/09/1987.

3MA10025147. Pathology review of reported tumorigenesis in a two year study of FM-3924 in rats (Pathology Associates International). Dated November 25, 1998.

3MA10065004. Fluorad Fluorochemical Surfactant FC-95. Ninety-day subacute rhesus monkey toxicity study (International Research and Development Company). Dated December 18, 1978.

3MA10069722. See Olsen et al., 1998.

3MB00012976. Experiment No. 0680TR0020. Special lens oral teratology study of T-2999CoC in rats (Safety Evaluation Laboratory, RIKER Laboratories, Inc. St. Paul, Minnesota). Signed 12/22/81.

3MB00040027. Final report: 104-week Dietary chronic toxicity and carcinogenicity study with perfluorooctane sulfonic acid potassium salt (PFOS: T-6295) in rats (Covance 6329-183; Authored by Peter J. Thomford, PhD). Dated January 2, 2002 (as study completion date).

Abbott BD, Wolf CJ, Schmid JE, Das KP, Zehr RD, Helfant L, Nakayama S, Lindstrom AB, Styrnar MJ, and Lau C. 2007. Perfluorooctanoic acid-induced developmental toxicity in the mouse is dependent on expression of peroxisome proliferator-activated receptor-alpha. *Toxicological Sciences* 98:571–581.

Abdellatif A, Al-Tonsy AH, Awad ME, Roberfroid M, and Khan MN. 2003. Peroxisomal enzymes and 8-hydroxydeoxyguanosine in rat liver treated with perfluorooctanoic acid. *Disease Markers* 19:19–25.

Abdellatif AG, Preat V, Taper HS, and Roberfroid M. 1991. The modulation of rat liver carcinogenesis by perfluorooctanoic acid, a peroxisome proliferator. *Toxicology and Applied Pharmacology* 111:530–7.

Abdellatif AG, Preat V, Vamecq J, Nilsson R, and Roberfroid M. 1990. Peroxisome proliferation and modulation of rat liver carcinogenesis by 2,4-dichlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid, perfluorooctanoic acid and nafenopin. *Carcinogenesis* 11:1899–902.

Alexander BH. 2001a. Final report: Mortality study of workers employed at the 3M Cottage Grove Facility. Division of Environmental Health Sciences, University of Minnesota, School of Public Health.

Alexander BH. 2001b. Final report: Mortality study of workers employed at the 3M Decatur Facility. Division of Environmental Health Sciences, University of Minnesota, School of Public Health.

AR-226. 2017. ChemView database on chemical health and safety data received by EPA and EPA's assessments and regulatory actions for specific chemicals under the Toxic Substances Control Act. Accessed May 2017. https://java.epa.gov/chemview.

ATSDR. 2005. Health Consultation: 3M Chemolite, Perfluorochemical releases at the 3M-Cottage Grove facility, City of Cottage Grove, Washington County, Minnesota. http://www.health.state.mn.us/divs/eh/hazardous/sites/washington/3mcg0205.pdf.

ATSDR. 2015. Draft toxicological profile for perfluoroalkyls. Accessed May 2017. https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf.

ATSDR. 2017. Toxic substances portal – perfluoroalkyls. Accessed May 2017. https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=1117&tid=237.

Barry V, Winquist A, and Steenland K. 2013. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. *Environmental Health Perspectives* 121:1313–1318.

Benninghoff AD, Orner GA, Bucher CH, Hendricks JD, Duff AM, and Williams DE. 2012. Promotion of hepatic carcinogenesis by perfluoroalkyl acids in rainbow trout. *Toxicological Sciences* 125:69–78.

Biegel LB, Hurtt ME, Frame SR, O'Conner JC, and Cook JC. 2001. Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. *Toxicological Sciences* 60:44–55.

Biegel LB, Liu RCM, Hurtt ME, and Cook JC. 1995. Effects of ammonium perfluorooctanoate on Leydig cell function: In vitro, in vivo, and ex vivo studies. *Toxicology and Applied Pharmacology*. 134:18–25.

Boobis AR, Cohen SM, Dellarco V, McGregor D, Meek ME, Vickers C, Willcocks D, and Farland W. 2006. IPCS framework for analyzing the relevance of a cancer mode of action for humans. *Critical Reviews in Toxicology*. 36:781–792.

Boobis AR, Doe JE, Heinrich-Hirsch B, Meek ME, Munn S, Ruchirawat M, Schlatter J, Seed J, and Vickers C. 2008. IPCS framework for analyzine the relevance of a noncancer mode of action for humans. *Critical Reviews in Toxicology*. 38:87–96.

Bonefeld-Jørgensen EC, Long M, Fredslund SO, Bossi R, and Olsen J. 2014. Breast cancer risk after exposure to perfluorinated compounds in Danish women: a case-control study nested in the Danish National Birth Cohort. *Cancer Causes & Control*. 25:1439–1448.

Buck RC, Franklin J, Berger U, Conder JM, Cousins IT, de Voogt P, Jensen AA, Kannan K, Mabury SA, van Leeuwen SP. 2011. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. *Integrated Environmental Assessment and Management*. 7:513–541.

Burdan F, Szumiło J, Dudka J, Klepacz R, Błaszczak M, Solecki M, Korobowicz A, Chałas A, Klepacki J, Palczak M, Zuchnik-Srona A, Hadała-Kiś A, Urbanowica Z, and Wójtowica Z. 2005. Morphological studies in modern teratological investigations. *Folia Morphologica* 64:1–8.

Butenhoff JL. Depo. Tr. September 8, 2017.

Butenhoff JL, Bjork JA, Change SC, Ehresman DJ, Parker GA, Das K, Lau C, Lieder PH, van Otterdijk FM, and Wallace KB. 2012b. Toxicological evaluation of ammonium perfluorobutyrate in rats: twenty-eight day and ninety-day oral gavage studies. *Reproductive Toxicology* 33:513–530.

Butenhoff JL, Chang S-C, Ehreshman DJ, and York RG. 2009a. Evaluation of potential reproductive and developmental toxicity of potassium perfluorohexanesulfonate in Sprague Dawley rats. *Reproductive Toxicology*. 27:331–341.

Butenhoff J, Costa G, Elcombe C, Farrar D, Hansen K, Iwai H, Jung R, Kennedy G, Lieder P, Olsen G, and Thomford P. 2002. Toxicity of ammonium perfluorooctanoate in male cynomolgus monkeys after oral dosing for 6 months. *Toxicological Sciences* 69:244–257.

Butenhoff JL, Dhresman DJ, Chang S-C, Parker GA, and Stump DG. 2009b. Gestational and lactational exposure to potassium perfluorooctanesulfonate (K^+PFOS) in rats: Developmental neurotoxicity. *Reproductive Toxicology* 27:319–330.

Butenhoff JL, Kennedy GL Jr, Chang S-C, and Olsen GW. 2012a. Chronic dietary toxicity and carcinogenicity study with ammonium perfluorooctanoate in Sprague-Dawley rats. *Toxicology* 298:1–13.

Butenhoff JL, Kennedy GL Jr, Frame SR, O'Connor JC, and York RG. 2004. The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. *Toxicology* 196:95–116.

C8 Science Panel. 2012. C8 Probable Link Reports. Accessed May 2017. http://www.c8sciencepanel.org/index.html.

CAS (Chemical Abstracts Service). 2017. CAS Registry and CAS Registry Number FAQs. CAS, A division of the American Chemical Society. Accessed August 2017. https://www.cas.org/content/chemical-substances/faqs.

Caverly-Rae JM, Frame SR, Kennedy GL, Butenhoff JL, and Change S-C. 2014. Pathology review of proliferative lesions of the exocrine pancreas in two chronic feeding studies in rats with ammonium perfluorooctanoate. *Toxicology Reports* 1:85–91.

Chang S-C, Das K, Ehresman DJ, Ellefson ME, Gorman GS, Hart JA, Noker PE, Tan Y-M, Lieder PH, Lau C, Olsen GW, and Butenhoff JL. 2008. Comparative pharmacokinetics of perfluorobutyrate in rats, mice, monkeys, and humans and relevance to human exposure via drinking water. *Toxicological Sciences*. 104:40–53.

Chang S-C, Thibodeaux JR, Eastvold ML, Ehresman DJ, Bjork JA, Froehlich JW, Lau CS, Singh RJ, Wallace KB, and Butenhoff JL. 2007. Negative bias from analog methods used in the analysis of free thyroxine in rat serum containing perfluorooctanesulfonate (PFOS). *Toxicology* 234:21–33.

Chatterjee S. 2014. Artefacts in hitopathology. *Journal of Oral and Maxillofacial Pathology* 18:S111–S116.

Choksi NY, Jahnke GD, St. Hilaire C, and Shelby M. 2003. Role of thyroid hormones in human and laboratory animal reproductive health. *Birth Defects Research Part B, Developmental and Reproductive Toxicology* 68:479–491.

Cook JC, Murray SM, Frame RS, and Hurtt ME. 1992. Induction of Leydig cell adenomas by ammonium perfluorooctanoate: A possible endocrine-related mechanism. *Toxicology and Applied Pharmacology*. 113:209–217.

Cooper DS and Ladenson PW. 2011. The thyroid gland. In *Greenspan's Basic & Clinical Endocrinology* (Gardner DG and Shoback D, eds), 9th edition, chapter 7. New York, NY: McGraw-Hill.

Curran I, Hierlihy SL, Liston V, Pantazopoulos P, Nunnikhoven A, Tittlemier S, Barker M, Trick K, and Bondy G. 2008. Altered fatty acid homeostasis and related toxicologic sequelae in rats exposed to dietary potassium perfluorooctanesulfonate (PFOS). *Journal of Toxicology and Environmental Health Part A* 71:1526–1541.

Das KP, Grey BE, Zehr RD, Wood CR, Butenhoff JL, Chang S-C, Ehresman DJ, Tan Y-M, and Lau C. 2008. Effects of perfluorobutyrate exposure during pregnancy in the mouse. *Toxicological Sciences* 105:173–181.

Das KP, Grey BE, Rosen MB, Wood CR, Tatum-Gibbs KR, Zehr RD, Strynar MJ, Lindstrom AB, and Lau C. 2015. Developmental toxicity of perfluorononanoic acid in mice. *Reproductive Toxicology* 51:133–144.

DeWitt JC, Copeland CB, and Luebke RW. 2009a. Suppression of humoral immunity by perfluorooctanoic acid is independent of elevated serum corticosterone concentration in mice. *Toxicological Sciences* 109:106–112.

DeWitt JC, Copeland CB, Strynar MJ, and Luebke RW. 2008. Perfluorooctanoic acid- induced immunomodulation in adult C57BL/6J or C57BL/6N female mice. *Environmental Health Perspectives* 116:644–650.

DeWitt JC, Germolec DR, Luebke RW, and Johnson VJ. 2016a. Associated changes in the immune system with clinical diseases for interpretation in risk assessment. *Current Protocols in Toxicology*. 67:18.1.1–18.1.22.

DeWitt JC and Keil DE. 2017. Current issues in developmental immunotoxicity. In *Immunopathology in Toxicology and Drug Development* (Parker GA, ed), chapter 13. Switzerland: Springer International Publishing.

DeWitt JC, Shnyra A, Badr MZ, Loveless SE, Hoban D, Frame SR, Cunard R, Anderson SE, Meade BJ, Peden-Adams MM, Luebke RW, and Luster MI. 2009b. Immunotoxicity of perfluorooctanoic acid and perfluorooctane sulfonate and the role of peroxisome proliferator activated receptor alpha. *Critical Reviews in Toxicology* 39:76–94.

DeWitt JC, Williams WC, Creech J, and Luebke RW. 2016b. Supression of antigen- specific antibody responses in mice exposed to perfluorooctanoic acid: Role of PPARα and T- and B-cell targeting. *Journal of Immunotoxicology* 13:38–45.

Dietert RR and DeWitt J. 2010. Developmental immunotoxicity (DIT): the why, when, and how of DIT testing. *Methods in Molecular Biology*. 598:17-25.

Dietert RR, DeWitt JC, Germolec DR, and Zelikoff JT. 2010. Breaking patterns of environmentally influenced disease for health risk reduction: Immune perspectives. Environmental Health Perspectives. 118:1091–1099.

Dong BJ and Greenspan S. 2015. Thyroid and antithyroid drugs. In *Basic and Clinical Pharmacology* (Katzung BG and Trevor AJ, eds.) 13th edition, chapter 38. New York, NY: McGraw-Hill.

Eaton DL. 2003. Scientific judgement and toxic torts – A primer in toxicology for judges and lawyers. *Journal of Law and Policy* 12:5–42.

Eriksen KT, Sørensen M, McLaughlin JK, Lipworth L, Tiønneland A, Overvad K, and Raaschou-Nielsen O. 2009. Perfluorooctanoate and perfluorooctanesulfonate plasma levels and risk of cancer in the general Danish population. *Journal of the National Cancer Institute* 101:605–609.

Ex.148. 3M_MN00042206. Estimation of "Safe" Reference Level of PFOS in Plasma. Palmver v 3M Company. Dated 10-27-06. Exhibit 148.

Fei C, McLaughlin JK, Tarone RE, and Olsen J. 2008. Fetal growth indicators and perfluorinated chemicals: a study in the Danish National Birth Cohort. *American Journal of Epidemiology* 168:66–72.

Feng X, Cao X, Zhao S, Wang X, Hua X, Chen L, and Chen L. 2017. Exposure of pregnant mice to perfluorobutanesulfonate causes hypothyroxinemia and developmental abnormalities in female offspring. *Toxicological Sciences* 155:409–419.

Filgo AJ, Auist EM, Hoenerhoff MJ, Brix AE, Kissling GE, and Fenton SE. 2015. Perfluorooctanoic acid (PFOA)-induced liver lesions in two strains of mice following developmental exposures: PPARα is not required. *Toxicologic Pathology* 43:558–568.

FluoroCouncil. 2017a. Press Release: FluoroCouncil addresses recent reports about fluorinated chemistries and water issues. June 9, 2017.

FluoroCouncil. 2017b. News Update: Experts to California regulators: Diverse fluorinated substances, tested and approved by government agencies, important to key products used by consumers. February 8, 2017.

Giannini EG, Testa R, and Savarino. 2005. Liver enzyme alteration: A guide for clinicians. *CMAJ*. 172:367–379.

Gilliland FD and Mandel JS. 1993. Mortality among employees of a perfluorooctanoic production plant. *Journal of Occupational Medicine* 35:950–954.

Gilliland FD. 1992. See 3M_MN03112178.

Gleason JA, Post GB, and Fagliano JA. 2015. Associations of perfluorinated chemical serum concentrations and biomarkers of liver function and uric acid in the US population (NHANES), 2007-2010. *Environmental Research*. 136:8–14.

Grandjean P, Anderson EW, Budtz-Jorgensen E, Nielsen F, Molbak K, Weihe P, Heilmann C, 2012. Serum vaccine antibody concentrations in children exposed Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. *JAMA*. 307:391–397.

Granum B, Haug LS, Namork E, Stolevik SB, Thomsen C, Aaberge IS, van Loveren H, Lovik M, and Nygaard UC. 2013. Pre-natal exposure to perfluoroalkyl substances may be associated with altered vaccine antibody levels and immune-related health outcomes in early childhood. *Journal of Immunotoxicology* 10: 373–379.

Gregus Z. 2015. Mechanisms of toxicity. In *Casarett & Doull's The Basice Science of Poisons* (Klaassen CD, ed), 8th edition, chapter 3. New York, NY: McGraw-Hill.

Griffith FD and Long JE. 1980. Animal toxicity studies with ammonium perfluorooctanoate. *American Industrial Hygiene Association Journal* 41:576–83.

Gupta V and Lee M. 2011. Central hypothyroidism. *Indian Journal of Endocrinology and Metabolism* 15:99–106.

Hall AP, Elcombe CR, Foster JR, Harada T, Kaufmann W, Knippel A, Küttler K, Malarkey DE, Maronpot RR, Nishikawa A, Nolte T, Schulte A, Strauss V, and York MJ. 2012. Liver hypertrophy: A review of adaptive (adverse and non-adverse) changes – conclusions from the 3rd International ESTP Expert Workshop. *Toxicologic Pathology*. 40:971–994.

Hardell E, Kärrman A, van Bavel B, Boa J, Carlberg M, and Hardell L. 2014. Case-control study on perfluorinated alkyl acids (PFAAs) and the risk of prostate cancer. *Environment International* 63:35–39.

Heinrich-Hirsch B, Madle S, Oberemm A, and Gundert-Remy U. 2001. The use of toxicodynamics in risk assessment. *Toxicology Letters* 120:131–141.

Houtz EF, Higgins CP, Field JA, and Sedlak DL. 2013. Presistence of perfluoroalkyl acid precursors in AFFF-impacted groundwater and soil. *Environmental Science & Technology* 47:8187–8195.

Hu Q, Strynar MJ, and DeWitt JC. 2010. Are developmentally exposed C57BL/6 mice insensitive to suppression of TDAR by PFOA? *Journal of Immunotoxicology* 7:344–349.

Hu W, Jones PD, Upham BL, Trosko JE, Lau C, and Giesy JP. 2002. Inhibition of gap junctional intercellular communication by perfluorinated compounds in rat liver and dolphin kidney epithelial cells lines *in vitro* and Sprague-Dawley rats *in vivo*. *Toxicological Sciences*. 68:429–436.

Hu XC, Andrews DQ, Lindstrom AB, Bruton TA, Schaider LA, Grandjean P, Lohmann R, Carignan CC, Blum A, Balan SA, Higgins CP, and Sunderland EM. 2016. Detection of poly- and perfluoroalkyl substances (PFASs) in U.S. drinking water linked to industrial sites, military fire training areas, and wastewater treatment plants. *Environmental Science & Technology Letters* 3:344–350.

HESI. 2017. What we do. Accessed May 2017. http://hesiglobal.org/whatwedo/.

IARC. 2006. IARC monographs on the evaluation of carcinogenic risks to humans: Preamble. *World Health Organization* Lyon, France.

IARC. 2012. Monograph 100A: Pharmaceuticals. IARC monographs on the evaluation of carcinogenic risks to humans. *World Health Organization* Lyon, France.

IARC. 2016. Monograph 110: Some chemicals used as solvents and in polymer manufacture. IARC monographs on the evaluation of carcinogenic risks to humans. *World Health Organization* Lyon, France.

Jacquet N, Maire MA, Rast C, Bonnard M, and Vasseur P. 2011. Perfluorooctanoic acid (PFOA) acts as a tumor promoter on Syrian hamster embryo (SHE) cells. *Environmental Science and Pollution Research International* 19:2537–2549.

Järnberg U and van Bavel B. 2007. Perfluoroalkylated acids and related compounds (PFAS) in the Swedish environment. Chemistry Sources Exposure Report.

Karls B. 2017. Monitoring data for municipal drinking water wells relevant to the East Metro area. Provided by Bob Karls of The Antea Group.

Keenan C, Elmore S, Francke-Carroll S, Kemp R, Kerlin R, Peddada S, Pletcher J, Rinke M, Schmidt SP, Taylore I, and Wolf DC. 2009. Best practices for use of historical control data of proliferative rodent lesions. *Toxicologic Pathology* 37:679–693.

Keller DA, Juberg DR, Catlin N, Farland WH, Hess FG, Wolf DC, and Doerrer NG. 2012. Identification and characterization of adverse effects in 21st century toxicology. *Toxicological Sciences* 126:291–297.

Kennedy GL, Butenhoff JL, Olsen GW, O'Connor JC, Seacat AM, Perkins RG, Biegel LB, Murphy SR, and Farrar DG. 2004. The toxicology of perfluorooctanoate. *Critical Reviews in Toxicology*. 34:351–384.

Kennedy GL, Hall GT, Brittelli MR, Barnes JR, and Chen HC. 1986. Inhalation toxicity of ammonium perfluorooctanoate. *Food and Chemical Toxicology* 24:1325–1329.

Klaunig JE. 2015. Chemical carcinogenesis. In *Casarett & Doull's The Basice Science of Poisons* (Klaassen CD, ed), 8th edition, chapter 8. New York, NY: McGraw-Hill.

Krishnan K and Carrier R. 2013. The use of exposure source allocation factor in the risk assessment of drinking-water contaminants. *Journal of Toxicology and Environmental Health, Part B, Critical Reviews*. 16:39–51.

Lau C, Anitole K, Hodes C, Lai D, Pfahles-Hutches A, and Seed J. 2007. Perfluoroalkyl acids: A review of monitoring and toxicological findings. *Toxicological Sciences*. 99:366–394.

Lau C, Thibodeaux JR, Hanson RG, Rogers JM, Grey BE, Stanton ME, Butenhoff JL, and Stevenson LA. 2003. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. II: Postnatal evaluation. *Toxicological Sciences* 74:382–5392.

Lau C, Thibodeaux JR, Hanson RG, Narotsky MG, Rogers JM, Lindstrom AB, and Strynar MJ. 2006. Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. *Toxicological Sciences* 90:510–518.

Lee I and Viberg H. A single neonatal exposure to perfluorohexane sulfonate (PFHxS) affects the levels of important neuroproteins in the developing mouse brain. *NeuroToxicology*. 37:190–196.

Lieder PH, Chang SC, York RG, and Butenhoff JL. 2009a. Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Sprague-Dawley rats. *Toxicology* 255:45–52.

Lieder PH, York RG, Hakes DC, Chang SC, and Butenhoff JL. 2009b. A two-generation oral gavage reproduction study with potassium perfluorobutanesulfonate (K+PFBS) in Sprague Dawley rats. *Toxicology* 259:33–45.

Loveless, S. E., Hoban, D., Sykes, G., Frame, S. R., and Everds, N. E. 2008. Evaluation of the immune system in rats and mice administered linear ammonium perfluorooctanoate. *Toxicological Sciences* 105:86–96.

Luci S, Giemsa B, Hause G, Kluge H, and Eder K. 2007. Clofibrate treatment in pigs: Effects on parameters critical with respect to peroxisome proliferator-induced hepatocarcinogenesis in rodents. *BMC Pharmacology* 7:6.

Luebker DJ. Depo. Tr. August 29, 2017.

Luebker DJ, Case MT, York RG, Moore JA, Hansen KJ, and Butenhoff JL. 2005. Two-generation reproduction and cross-foster studies of perfluorooctanesulfonate (PFOS) in rats. *Toxicology* 215:126–148.

Lundin JI and Alexander BH. 2007. Final report: Mortality of employees of an ammonium perfluorooctanoate production facility. Division of Environmental Health Sciences, University of Minnesota, School of Public Health.

Luster MI, Portier C, Pait DG, White KL Jr, Gennings C, Munson AE, and Rosenthal GJ. 1992. Risk assessment in immunotoxicity. I. Sensitivity and predictability of immune tests. *Fundamental and Applied Toxicology* 18:200–210.

MDH 2007. Perfluorochemicals Past, present and future actions. Accessed September 2017. https://www.pca.state.mn.us/sites/default/files/gp5-18.pdf.

MDH 2008. East Metro PFC biomonitoring pilot project. Accessed August 2017. http://www.health.state.mn.us/divs/hpcd/tracking/biomonitoring/projects/eastmetropfc2008.html.

MDH. 2009a. Toxicological summary for perfluorooctanoic acid (PFOA) and salts. http://www.health.state.mn.us/divs/eh/risk/guidance/gw/pfoa2010.pdf.

MDH. 2009b. Toxicological summary for perfluorohexane sulfonate (PFHxS). http://www.health.state.mn.us/divs/eh/risk/guidance/gw/pfhxs.pdf.

MDH. 2009c. Toxicological summary for perfluorooctane sulfonate (PFOS) and salts. http://www.health.state.mn.us/divs/eh/risk/guidance/gw/pfos2010.pdf.

MDH. 2010. East Metro PFC biomonitoring follow-up project. Accessed August 2017. http://www.health.state.mn.us/tracking/biomonitoring/projects/eastmetropfc.html.

MDH. 2011a. Toxicological summary for perfluorobutyrate (PFBA). http://www.health.state.mn.us/divs/eh/risk/guidance/gw/pfba.pdf.

MDH. 2011b. Toxicological summary for perfluorobutane sulfonate (PFBS). http://www.health.state.mn.us/divs/eh/risk/guidance/gw/pfbs.pdf.

MDH. 2015. East Metro PFC3 biomonitoring project. December 2015 report to the community. Accessed September 2017. http://www.health.state.mn.us/divs/hpcd/tracking/biomonitoring/projects/PFC3CommunityReport.pdf.

MDH. 2016. 3M – Oakdale disposal site. June 2016. http://www.health.state.mn.us/divs/eh/hazardous/sites/washington/oakdale/oakdaledump.html. Accessed September 2017.

MDH. 2017a. Background document: Toxicokinetic model for perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) and its use in the derivation of human health-based water guidance values.

MDH. 2017b. MDH response to EPA health advisory for PFOS and PFOA. http://www.health.state.mn.us/divs/eh/hazardous/topics/pfcs/current.html. Last accessed August, 2017.

MDH. 2017c. Memorandum to City of Cottage Grove regarding Notice of Health Risk Advisory for Perfluorochemicals (PFCs).

MDH. 2017d. Perfluorochemicals (PFCs) in Minnesota: PFC contaminated sites in Minnesota. Accessed August 2017. http://www.health.state.mn.us/divs/eh/hazardous/topics/pfcs/sites.html.

MDH 2017e. Toxicological summary for perfluorobutyrate (PFBA). http://www.health.state.mn.us/divs/eh/risk/guidance/gw/pfba2summ.pdf.

MDH. 2017f. Toxicological summary for perfluorooctanoic acid (PFOA) and salts. http://www.health.state.mn.us/divs/eh/risk/guidance/gw/pfoa.pdf.

MDH. 2017g. Toxicological summary for perfluorooctane sulfonate (PFOS) and salts. http://www.health.state.mn.us/divs/eh/risk/guidance/gw/pfos.pdf.

MDH. 2017h. Sample letter to well owners concerning drinking water advisory for PFCs.

MDH. 2017i. Evaluating concurrent exposures to multiple chemicals. http://www.health.state.mn.us/divs/eh/risk/guidance/gw/additivity.html.

Muggleton-Harris AL, Festing MF, and Hall M. 1987. A gene location for the inheritance of the cataract Fraser (CatFr) mouse congenital cataract. *Genetic Research* 49:235–2238.

NCBI. 2017. TGFA transforming growth factor alpha [*Homo sapiens* (human)]. Gene ID: 7039. Accessed September 2017. https://www.ncbi.nlm.nih.gov/gene/7039.

Nelles JL, Hu W-Y, and Prins GS. 2011. Estrogen action and prostate cancer. *Expert Reviews in Endocrinology and Metabolism.* 6:437–451.

Nilsson R, Beije B, Préat V, Erixon K, and Ramel C. 1991. On the mechanism of the hepatocarcinogenicity of peroxisome proliferators. *Chemico-Biological Interactions* 78:235–250.

NJ DWQI (New Jersey Drinking Water Quality Institute). 2017. Maximum contaminant level recommendation for perfluorooctanoic acid in drinking water: Basis and background. http://www.nj.gov/dep/watersupply/pdf/pfoa-recommend.pdf.

NOTOX. 2007a. Repeated dose 28-day oral toxicity study with MTDID-8391 by daily gavage in the rat, followed by a 21-day recovery period. Project 470677 Final Report.

NOTOX. 2007b. Repeated dose 90-day oral toxicity study with MTDID 8391 by daily gavage in the rat followed by a 3-week recovery period. Project 484492 Final Report.

NRC (National Research Council). 2004. Values and limitations of animal toxicity data. In *Intentional Human Dosing Studies for EPA Regulatory Purposes: Scientific and Ethical Issues*, appendix A. Washington, DC: National Academies Press.

NTP. 2015. OHAT systematic review. Accessed May 2017. https://ntp.niehs.nih.gov/pubhealth/hat/noms/index-2.html.

NTP. 2016. Monograph on immunotoxicity associated with exposure to perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). Research Triangle Park, NC: National Toxicology Program. http://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/pfoa_pfosmonograph_508.pdf.

OECD (Organisation for Economic Co-Operation and Development). 2012. Appendix I. Collection of working definitions. Testing of Chemicals, Accessed August 2017. http://www.oecd.org/chemicalsafety/testing/49963576.pdf.

Olsen unpublished draft. 2008. Corresponds to 3MA02543911.

Olsen GW, Burlew MM, Burris JM, and Mandel JH. 2001. Final report: Epidemiology, 220-3W-05: A longitudinal analysis of serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) levels in relation to lipid and hepatic clinical chemistry test results from male employee participants of the 1994/95, 1997, and 2000 fluorochemical medical surveillance program.

Olsen GW, Burris JM, Ehresman DJ, Froehlich JW, Seacat AM, Butenhoff JL, and Zobel LR. 2007. Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. *Environmental Health Perspectives*. 115:1298-1305.

Olsen GW, Burris JM, Mandel JH, and Zobel LR. 1998. An epidemiological investigation of clinical chemistries, hematology and hormones in relation to serum levels of perfluorooctane

sulfonate in male fluorochemical production employees. Report or manuscript dated April 22, 1998.

Olsen GW, Chang S-C, Noker PE, Gorman GS, Ehresman DJ, Lieder PH, and Butenhoff JL. 2008. A comparison of pharmacokinetics of perfluorobutanesulfonate (PFBS) in rats, monkeys, and humans. *Toxicology*. 256:65–74.

Pérez F, Nadal M, Navarro-Ortega A, Fàbrega F, Domingo JL, Barceló D, and Farré M. 2013. Accumulation of perfluoroalkyl substances in human tissues. *Environment International*. 59:354–362.

Raleigh KK, Alexander BH, Olsen GW, Ramachandran G, Morey SZ, Church TR, Logan PW, Scott LLF, and Allen EM. 2014. Mortality and cancer incidence in ammonium perfluorooctanoate production workers. *Occupational Environmental Medicine* 0:1–7.

Rappazzo KM, Coffman E, and Hines EP. 2017. Exposure to perfluorinated alkyl substances and health outcomes in children: A systematic review of the epidemiological literature. *International Journal of Environmental Research and Public Health*. 14:691.

Rodricks JV and Levy JI. 2013. Science and decisions: advancing toxicology to advance risk assessment. *Toxicological Sciences* 131:1–8.

Rogers JM. 2015. Developmental toxicology. In *Casarett & Doull's The Basice Science of Poisons* (Klaassen CD, ed), 8th edition, chapter 10. New York, NY: McGraw-Hill.

Seacat AM, Thomford PJ, Hansen KJ, Olsen GW, Case MT, and Butenhoff JL. 2002. Subchronic toxicity studies on perfluorooctanesulfonate potassium salt in cynomolgus monkeys. *Toxicological Sciences* 68:249–264.

Selgrade MK. 2007. Immunotoxicity: the risk is real. *Toxicological Sciences*. 100:328–332.

Silins I and Högberg J. 2011. Combined toxic exposures and human health: Biomarkers of exposure and effect. *International Journal of Research in Public Health*. 8:629–647.

Sundström M, Chang S-C, Noker PE, Gorman GS, Har JA, Ehresman DJ, Bergman A, and Butenhoff JL. Comparative pharmacokinetics of perfluorohexanesulfonate (PFHxS) in rats, mice, and monkeys. *Reproductive Toxicology*. 33:441–451.

SOT. 2008. Toxicology concepts. Accessed May 2017. www.toxicology.org/education/docs/IntroToxSlides26-50.ppt.

Spacie A, McCarty LS< and Rand GM. 1995. Bioaccumulation and bioavailability in multiphase systems. In *Fundamentals of Aquatic Toxicology: Effects, Environmental Fate, and Risk Assessment* (Rand GM, ed), 2nd edition, chapter 16. Philadelphia, PA: Taylor & Francis.

Steenland K, Zhao L, and Winquist A. 2015. A cohort incidence study of workers exposed to perfluorooctanoic acid (PFOA). *Occupational and Environmental Medicine*. 72:373–380.

Steenland K and Woskie S. 2012. Cohort mortality study of workers exposed to perfluorooctanoic acid. *American Journal of Epidemiology* 176:909–917.

Stein CR, McGovern KJ, Pajak AM, Maglione PJ, and Wolff MS. 2016. Perfluoroalkyl and Polyfluoroalkyl Substances and Indicators of Immune Function in Children Aged 12 - 19 years: National Health and Nutrition Examination Survey. *Pediatric Research* 79: 348–357.

Thibodeaux JR, Hanson RG, Rogers JM, Grey BE, Barbee BD, Richards JH, Butenhoff JL, Stevenson LA, and Lau C. 2003. Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse: I: maternal and prenatal evaluations. *Toxicological Sciences* 74:369–381.

Tyagi S, Gupta P, Saini AS, Kaushal C, and Sharma S. 2011. The peroxisome proliferator-activated receptor: A family of nuclear receptors role in various diseases. *Journal of Advanced Pharmacological Technology and Research* 2:236–240.

Ubel FA, Sorenson SD, and Roach DE. 1980. Health status of plant workers exposed to fluorochemicals – a preliminary report. *American Industrial Hygiene Association Journal*. 41:584–590.

Upham BL, Deocampo ND, Wurl B, and Trosko JE. 1998. Inhibition of gap junctional intercellular communication by perfluorinated fatty acids is dependent on the chain length of the fluorinated tail. *International Journal of Cancer*. 78:491–495.

Upham BL, Park J-S, Babica P, Sovadinova I, Rummel AM, Trosko JE, Hirose A, Hasegawar R, Kanno J, and Sai K. 2009. Structure-activity-dependent regulation of cell communication by perfluorinated fatty acids using *in vivo* and *in vitro* model systems. *Environmental Health Perspectives*. 117:545–551.

U.S. EPA. 1989. Risk Assessment Guidance for Superfund, Volume I, Human Health Evaluation Manual (Part A). https://www.epa.gov/sites/production/files/2015-09/documents/rags_a.pdf.

U.S. EPA. 1993. Reference dose (RfD): Description and use in health risk assessments; background document 1A. Accessed May 2017. https://www.epa.gov/iris/reference-dose-rfd-description-and-use-health-risk-assessments.

U.S. EPA. 2012. Benchmark dose technical guidance. *Risk Assessment Forum* US Environmental Protection Agency.

U.S. EPA. 2016a. Drinking water health advisory for perfluorooctanoic acid (PFOA). *U.S. Environmental Protection Agency, Office of Water, Health and Ecological Criteria Division*. Washington, DC.

U.S. EPA. 2016b. Drinking water health advisory for perfluorooctane sulfonate (PFOS). *U.S. Environmental Protection Agency, Office of Water, Health and Ecological Criteria Division.* Washington, DC.

U.S. EPA. 2016c. Health effects support document for perfluorooctanoic acid (PFOA). *U.S. Environmental Protection Agency, Office of Water, Health and Ecological Criteria Division.* Washington, DC.

U.S. EPA. 2016d. Health effects document for perfluorooctane sulfonate (PFOS). *U.S. Environmental Protection Agency, Office of Water, Health and Ecological Criteria Division.* Washington, DC.

U.S. EPA. 2017a. Memorandum on Laboratory PFAS Results for NC DEQ Cape Fear Watershed Sampling: Preliminary Non-Targeted Analysis. National Exposure Research Laboratory. Issued August 31, 2017.

U.S. EPA. 2017b. Per- and polyfluoroalkyl substances (PFASs) under TSCA. Accessed May 2017. https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/and-polyfluoroalkyl-substances-pfass-under-tsca.

Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR Jr, Lee DH, Shioda T, Soto AM, vom Saal FS, Welshons WV, Zoeller RT, and Myers JP. 2012. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. *Endocrine Reviews* 33:378–455.

Vieira VM, Hoffman K, Shin H-M, Weinberg JM, Webster TF, and Fletcher T. 2013. Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: a geographic analysis. *Environmental Health Perspectives* 121(3): 318–323.

Wang Z, DeWitt JC, Higgins CP, and Cousins IT. 2017. A never-ending story of per- and polyfluoroalkyls substances (PFASs)? *Environmental Science & Technology* 51:2508–2518.

Winkens K, Vestergren R, Berger U, and IT Cousins. 2017. Early life exposure to per- and polyfluoroalkyl substances (PFASs): A critical review. *Emerging Contaminants*. In press: http://dx.doi.org/10.1016/j.emcon.2017.05.001.

Wolf CJ, Fenton SE, Schmid JE, Calafat AM, Kuklenyik Z, Bryant XA, Thibodeaux J, Das KP, White SS, Lau CS, and Abbott BD. 2007. Developmental toxicity of perfluorooctanoic acid in the CD-1 mouse after cross-foster and restricted gestational exposure. *Toxicological Sciences* 95:462–473.

York RG. 2003a. Oral (gavage) repeated dose 90-day toxicity study of potassium perfluorobutane sulfonate (PFBS) in rats.Argus Research Protocol Number 418-026.

York RG. 2003b. Oral (gavage) two-generation (one litter per generation) reproduction study of perfluorobutane sulfonate (PFBS) in rats. Argus Research Protocol Number 418-021.

Yu WG, Liu W, and Jin YH. 2009a. Effects of perfluorooctane sulfonate on rat thyroid hormone biosynthesis and metabolism. *Environmental Toxicology and Chemistry* 28:990–996.

Yu WG, Liu W, Jin YH, Liu XH, Wang FQ, Liu L, Nakayama SF. 2009b. Prenatal and postnatal impact of perfluorooctane sulfonate (PFOS) on rat development: a cross-foster study on chemical burden and thyroid hormone system. *Environmental Science & Technology* 43:8416–8422.

Yu WG, Liu W, Liu L, and Jin YH. 2011. Perfluorooctane sulfonate increased hepatic expression of OAPT2 and MRP2 in rats. *Archives of Toxicology* 85:613–621.

Zartarian VG, Ott WR, and Duan N. 2006. Basic concepts and definitions of exposure and dose. In *Exposure Analysis* (Ott WR, Steinmann AC, and Wallace LA, eds.), pp 33–64. Boca Raton, FL: CRC Press.