Highlights from Day 1: Tuesday, October 17th, 2023

Nancy Beck, Hunton Andrews Kurth LLP., The State of Risk Assessment, Regulation, and Peer Review at EPA: A Case Study of EPA's Priority Actions on PFAS

1. EPA Risk Assessment and Peer Review Process: Risk assessment involves scoping, problem formulation, assessing the science, dose-response modeling, and toxicity evaluation. The peer review process is described as "fit for purpose" and may involve backup peer reviewers for highly influential information. It also involves seeking input from the National Academy of Sciences (NAS) for significantly controversial or high-visibility products. Important aspects of peer review include consideration of (1) Multiple perspectives and balanced points of view (2) Diversity in work sector (3) Avoiding conflicts of interest (4) Public/stakeholder involvement (5) Transparency. The talk emphasized the importance of peer-review charge questions, meaning the "right questions = right answers."

2. Challenges in Measuring PFAS: While thousands of PFAS substances exist, the ability to measure them is limited. The talk highlighted that only a fraction of these substances can be measured in different media, such as food, drinking water, surface water, and air. The ability to measure PFAS varies across media types. For example, 16 PFAS can be reliably measured in human blood, 30 PFAS in food, and zero PFAS in ambient air.

3. Complexity of PFAS Health Effects: The health effects of PFAS were discussed, with the acknowledgment that almost every health effect has been alleged, and the science and academic literature on the topic are continuously evolving. PFAS have a wide range of applications and industry uses (including Healthcare, Military, Automotive, and Alternative Energy) and can be found in various aspects of daily life. The DoD extensively uses PFAS, and "losing access to PFAS… would greatly impact national security and DoD's ability to fulfill its mission."

4. EPA PFAS Assessments and Proposed Values: The EPA has proposed Reference Doses (RfD) for PFOA and PFOS, which are significantly lower than previous values. The proposed RfD value for PFOA is in parts per trillion and is 140,000-fold lower than Health Canada's advisory.

5. SAB Panel and Hazard Assessment Approach: The SAB charge was robust and over 20 pages long. The panel incorporated 2016 assessments into the 2021 document, and not all studies were evaluated similarly. The SAB did not have a protocol or follow the ORD IRIS handbook. Different groups wrote different chapters in the document. The panel was composed of 16 members with diverse scientific backgrounds: the panel lead was a physicist, two members were from state health departments, and most worked in academia. Two of the 16 members had experience in risk assessment, one had consulting experience, and no industry members, or clinicians were on the panel.

6. Key recommendations to the EPA: (1) The evidence identification methodology should be supplemented with "additional transparency and completeness… including development of a protocol with clear intrusion/extrusion criteria and study evaluation approaches". (2) The 2016 health effects summary should be considered as heavily as more recent studies. (3) A consistent framework and descriptors should be used for evidence synthesis and integration. (4) The time constraints on the EPA suggest that the agency should focus on health outcomes with the most substantial evidence, including liver disease, immune system dysfunction, serum lipid aberration, impaired fetal growth, and cancer. (5) Stronger justification is necessary for BMRs chosen to define decreased antibody response and other factors.
7. Federal regulatory activity: Beck included an introductory state of the science regarding PFAS exposure and a brief timeline of events related to PFAS regulation. PFAS has been a priority since 2019, yet PFAS blood levels have decreased over the past two decades due to the voluntary phase-out in 2006. The EPA proposed enforceable MCLs for drinking water is 4 PPT. In 2022, the EPA proposed listing PFOA and PFOS as CERCLA "Hazardous Substances." The cost of cleanup and enforcement following this potential ruling is likely underestimated and impractical, with implications reaching far beyond industry producers. The EPA intends to use "enforcement discretion" to pursue PFAS enforcement targets (PFAS manufacturers, federal facilities, and parties who release significant amounts of PFAS into the environment); the final rule is expected in February 2024. Other regulations discussed include required reporting of almost all industry PFAS use in the past 11 years (finalized October 2023, due in 2025) and removing the 100-pound threshold for reporting PFAS.
8. State regulatory activity: State governments have taken action to regulate PFAS. Twelve states have laws to ban PFAS in various products; 8 states have reporting requirements. Business owners voluntarily ban PFAS in their products due to public pressure and consumer group testing. There are few consistencies in PFAS regulation across states (definition, bans against selling or distribution, etc.), but many more inconsistencies (such as what constitutes “intentionally added” PFAS, which products are to be regulated, etc.).
9. Costs/Implications: The Final PFAS reporting rule passed in 2023 is estimated to cost $845 million, with no net benefits quantified. The Chamber of Commerce estimates the proposed CERCLA rule to cost 17.4 billion, also with no net benefits quantified. The proposed MCL of 4 ppb will likely cost 771 million, with $461 million in net benefits accrued.

Dennis Paustenbach, David Brew, and Careen Khachatoorian, Dioxins vs. PFOA/PFAS: Similarities and Differences

1. Historical Perspective on Dioxins: Review of the history of dioxins, including notable incidents such as the Nitro incident in West Virginia in 1949 and the use of Agent Orange

in Vietnam from 1962 to 1970. The talk also mentions the Kociba et al. rat study in 1976, which identified cancer risks associated with low-dose dioxin exposure. Studies from 1985-2005 suggest various possible health effects, regardless of dose and species.

2. Historical Perspective on PFOA/PFAS: The history of per- and polyfluoroalkyl substances (PFAS) is discussed, highlighting the production of PFAS by 3M in 1947 and the mixed results in toxicology studies from the 1960s to the 1980s. Concerns about developmental effects, cancer risks, and various claims of health effects are mentioned, irrespective of dose or species. A 2012 Faroe Island study suggests that elevated PFAS exposure is associated with decreased effectiveness in vaccinations (but within normal limits)

3. Environmental and Biological Persistence: Dioxins and PFAS are described as environmentally and biologically persistent compounds. They are referred to as "the most toxic man-made compound" and "forever chemicals," respectively. The study of dioxin and PFAS in humans has suggested that the biological half-life is eight and a half years for dioxins, an estimated three years for PFOA, and three to four years for PFOS.

4. Toxicity and Lethal Doses: The presentation discussed toxicity and lethal doses for both dioxins and PFAS. While dioxins are known for their extreme toxicity in animals, it is noted that the substances have never killed a human (even in cases of intentional poisoning), and the LD_{50} for humans is believed to be much higher than in animals. Similar claims are made for other chemicals like DDT, PCB, Deca BDE, and HCBD. The talk highlights that these chemicals have no known lethal dose and show no clear increased cancer risk for humans.

5. Cancer and Disease Incidence: PFAS is commonly discussed as a multi-system toxicant, yet there is little acknowledgment of dose, species, and epidemiology. The talk emphasized that few chemicals at commonly encountered human doses affect numerous target organs. While animal studies with dioxin suggested that it is carcinogenic, no human study has clearly shown the chemical to be carcinogenic at any dose. Animal studies with PFOA/PFOS have demonstrated instances of liver cancer at high doses but are not statistically significant when compared to controls. No human epidemiology studies have indicated that PFOA/PFOS causes an increased risk of any cancer. PFAS and Dioxins are described as similar chemicals, with shared characteristics including uneven acute toxicity across species, long biological half-life, wasting syndrome at high doses in animals, very weak to no signal for human carcinogenicity, and a lack of clear genotoxicity.

6. Regulatory and Legal Aspects: The regulatory history of dioxins and PFAS and their associated legal and personal injury claims is discussed the threat of regulation and personal injury claims have resulted in public agencies going into action against PFAS with inconclusive data. The press and legal system have played a role in Dioxin and PFAS public opinion and, subsequently, the filing and distribution of billions in personal injury claims. It was suggested that the precautionary principle may override risk

assessment and the scientific method in the face of public outcry, with the result being increased focus on the allocation of resources to achieve low regulatory water goals. The talk also raises questions about whether the costs and allocation of resources for stringent regulation, which could reach hundreds of billions of dollars, are justified when compared to other societal needs.

Nick Fletcher, Food Safety Australia/New Zealand

1. Role and Function of FSANZ: FSANZ, a statutory agency within the Australian Government Health portfolio, is responsible for developing and administering the Australia New Zealand Food Standards Code. This code is a legislative instrument enforced by state and territory laws. FSANZ itself is not responsible for enforcement.
2. Hazard Assessment for PFOS, PFOA, and PFHxS: FSANZ was requested by the Department of Health in June 2016 to recommend Health-Based Guidance Values (HBGVs) for PFOS, PFOA, and PFHxS. This initiated a hazard assessment for these substances in 2017 using the US EPA PBPK model and an assessment of dietary exposure to PFOS, PFOA, and PFHxS.
3. Toxicological Assessment of PFOA: The assessment of perfluorooctanoic acid (PFOA) by FSANZ involved a substantial toxicological database, including acute and short-term toxicity studies in rodents, subchronic and chronic studies in monkeys and rodents, and developmental and reproduction studies in mice and rats. Three studies were identified as suitable for determining an HBGV and included the Cynomolgus monkey study of Butenhoff et al. (2002), the Perkins et al. rat study (2004), and the mouse developmental study of Lau et al. (2006). The serum PFOA data was used for pharmacokinetic modeling to derive HEDs. The primary effects observed in lab rodents were peroxisome proliferation-mediated hepatomegaly, reproductive, and developmental effects. Animals experience a much shorter half-life for PFOA (days) than humans (years). Among animals, the half-life varies extensively across species and gender.
4. Derivation of the TDI for PFOA: Three studies were identified as suitable for determining an HBGV; these included the Cynomolgus monkey study of Butenhoff et al. (2002), the Perkins et al. rat study (2004), and the mouse developmental study of Lau et al. (2006). The serum PFOA data from these studies was used for pharmacokinetic modeling to derive HEDs. The NOAEL for each study was identified, and a TDI of 26 ng/kg bw/day was recommended based on a NOAEL for fetal toxicity in a mouse development and reproductive study.
5. Immunomodulation review and epidemiological evidence: The presentation discussed how, at sufficiently high dosage and duration, "PFOA causes atrophy and changed cellularity of immune system organs in mice but not in rats." At a 4 mg/kg/d (LOEL) dose, PFOA was reported to suppress humoral responses to inoculated antigens. While epidemiology studies have shown associations between PFOS and PFOA serum

concentrations and compromised antibody production, no evidence suggests an increased incidence of infectious disease due to PFOA/PFOS effects on the immune system. No agencies established an HBGV based on epidemiological evidence in 2017, and there had been inconsistent health findings and uncertain biological significance in epidemiological studies. The evidence was most substantial for an association between exposure, increased serum cholesterol, and decreased birth weight, yet FSANZ could not determine whether PFOA is responsible for the alleged health effects.

6. Australian Total Diet Study on PFAS: The 27th Australian Total Diet Study (ATDS) investigated the levels of per- and polyfluoroalkyl substances (PFAS), including PFOS and PFOA, in various everyday foods and beverages. PFOS was the only substance detected, found in low levels in less than two percent of all samples. The overall dietary exposure to PFOS and PFOA for the general Australian population was lower than the established Tolerable Daily Intake (TDI), indicating no public health and safety concerns related to these substances in the food supply.

Michael Dourson, PFOA: A North American Perspective

1. Differences in Safe Doses: There are significant variations in the safe doses of PFOA proposed by different regulatory authorities across North America due to differences in the choice of PFOA's critical effect, the use of animal-based PBPK models instead of human-based data, and alternative choices of uncertainty factors. The range of safe doses spans from 0.0000015 to 0.02 µg/kg-day, resulting in a substantial discrepancy between the recommendations.

2. ATSDR 2021 Approach: ATSDR's 2021 assessment is highlighted for its use of the Koskela et al. 2016 study, which identified a safe dose of 0.003 µg/kg-day by measuring the effects of developmental exposure to PFOA on skeletal and neurological development, with a human dose of 0.821 ug/kg-day. However, concerns are raised about the statistical methods used and the study's design to provide a singular dose to only six pregnant mice.

3. Canada's Approach: Canada's 2018 assessment relies on the Perkins et al. 2004 study that exposed male rats to a daily dose of PFOA and measured hepatocellular hypertrophy, which determined a safe dose of 0.02 µg/kg-day with a human dose of 0.52 ug/kg-day. Concerns are raised about the study's relevance to humans due to activation of a receptor important to liver response in rats that is not applicable to humans and the inability to account for non-linear kinetics. In April 2021, the Canadian government published their intent to reduce their current guidelines of 200 ppt of PFAS chemicals in drinking water with 30 ppt.

4. EPA 2022 and 2023 Approaches: EPA's 2022 interim and 2023 draft assessments use different studies and propose safe doses of 0.0000015 µg/kg-day and 0.00003 µg/kg-day

for PFOA, respectively. Concerns were raised about using observational cohorts and the assumption that developmental effects are related to the area under the curve (AUC).

5. Faroe Islands studies: The EPA's study, Grandjean et al., 2012, found that higher concentrations of PFOA were correlated with lower serum antibody concentrations for vaccinations in young children. A similar study by Grandjean et al., 2017 predicted lower serum antibody concentrations in five-year-olds from estimated PFAS exposure during infancy. The conclusions drawn by these studies were influential on the EPA's 2022 interim decision to update the safe dose of PFOA to 0.0000015 ug/kg-day. The Heilman et al., 2006 study, which investigated a similar relationship between vaccine antibodies and polychlorinated biphenyls (PCBs) in a cohort of children in the Faroe Islands, suggested reduced vaccine antibody concentrations in children with elevated blood levels of PCBs. PCBs may be a confounding variable to the alleged association between PFOA levels and vaccine antibodies. While the EPA study chose a relevant critical effect, criticism is drawn by using a human observational cohort that other authorities had rejected. One panelist pointed out that Grandjean and colleagues acknowledge the inability to causally attribute associated effects to PFOA:
    - Grandjean et al. (2012) state, “Although all of the 5 PFCs measured showed negative associations with antibody levels, the overlapping confidence intervals and the lack of comparative toxicology studies prevent inference in regard to causal attribution...”
    - The more recent Grandjean et al. (2017a) study states, “Owing to the intercorrelations between the serum PFAS concentrations, further analysis of the possible role of individual PFASs was not pursued, and the observed associations may reflect the effects of the PFAS mixtures.”
    - Similarly, Grandjean et al. (2017b) state, “The close correlations prevented meaningful adjustment for concomitant PFAS exposures.”

   Agencies should consider the implications of these and other study author-cited limitations for use of associated PFOA data for quantitative risk assessment and derivation of toxicity factors for PFOA.

6. Harmonization and Cooperation: Dourson emphasized the need for North American regulatory authorities to work together to establish a single safe dose or a reasonable range for PFOA. Understanding the relationship between PFOA isomers and clearance is a critical issue for determining the half-life of PFOA. A therapeutic trial for the administration of PFOA (1200 mcg once per week) for cancer treatment suggests a human half-life estimation of 0.5 to 1.5 years. Additionally, the appropriate critical effect for PFOA needs to be established. It was recommended to conduct additional clearance studies and consider newly available human data for harmonization. The talk emphasizes using the best science to determine safe ranges and converge on one correct human half-life for PFOA.

Highlights from Day 2: Wednesday, October 18th, 2023

Daniel Dietrich & Helmut Greim, Universität Konstanz, "World Health Organization (WHO) and European Food Safety Authority (EFSA) Risk Evaluations" TDI and tolerable drinking-water levels derived by Germany, EFSA, ECHA and WHO

1. European Activities on PFAS: The author's described various European activities related to per- and polyfluoroalkyl substances (PFAS), including the German drinking water commission's standard, European Food Safety Agency's Tolerable Daily Intake (EFSA's TDI), for PFAS in food, ECHA's proposal for restrictions on PFAS, and the recent proposal by five member states to restrict approximately 10,000 PFAS chemicals. They noted that based on the POP regulation (EC regulation 2019/1021) of very persistent and very bioaccumulative compounds, under which PFOS, PFOA and PFHxS have been placed, the derivation of DNELs/DMELs is not considered relevant, since PFASs should be treated as non-threshold substances for the purposes of risk assessment like PBT/vPvB substances under REACH (ECHA 2023, Wollin et al 2023).
2. German Drinking Water Commission: The German Drinking Water Commission established Health-Based Values (HBVs) based on a TDI for total PFAS, resulting in a drinking water standard of 0.1 microgram per liter. The TDI is derived from a NOAEL for reproductive toxicity in rats, with various extrapolation factors applied to humans (Wilhelm et al. 2010). The TDI for this agency was based on rodent data only, not epidemiologic data.
3. ECHA's Approach: ECHA's approach involves using rat data with adjustment factors for subacute, subchronic, and chronic exposure to determine DNELs (Derived No Effect Levels) for PFAS. DNEL values are calculated for long-term, systemic effects via various routes of exposure (rat, subacute, rat subchronic, and rat chronic). This agency used only rodent data and not epidemiologic studies. Due to the difference in pathophysiology, human relevance of thyroid effects in rats is questionable.
4. EFSA's Risk Assessment: EFSA's risk assessment relies on epidemiological studies, which provide evidence of associations between PFAS exposure in food and increased serum levels of cholesterol and liver enzyme alanine transferase. However, it raises questions about the significance of some associations, especially regarding birth weight and reduced antibody response to vaccination. The literature the birth weight association is based on is highly contradictory, and no mode of action by PFAS has been established for either immunotoxicity or birth weight health effects. It was readily apparent that in the EU, there was no consensus about whether to rely on animal data or human epi data. Further, it was apparent that the endpoint of interest varied with each agency and that there was no consensus about the endpoint which drives the safe dose. For example, some chose cancer, others chose changes in cholesterol, while others chose changes in liver enzymes.

5. EFSA's Immunotoxicity study: Effects of PFAS on the immune system were considered the most critical, with children showing an association between serum levels of PFOA (as well as the sum of PFOA, PFNA, PFHxS and PFOS, and vaccine antibody titers (Abraham et al, 2020). Based on the results of this study, a TWI of 4.4 ng/kg bw per week was established. Some of the European population exceeds this TWI. Despite the association, "the study revealed no influence of PFOA and PFOS on infections during the first year of life and on levels of cholesterol… the negative associations of PFAS levels and parameters of immune response observed in other epidemiological studies [was confirmed] … but for PFOA only." Moreover, EFSA, despite the lack of an association of PFOS with reduced antibody titers, equated all PFAS groups evaluated (PFOA, PFNA, PFHxS and PFOS) to PFOA and argued that the reduced antibody titer effects were transposable to all PFAS irrespective of the evidence to the contrary and derived a TDI of 0.63ng/kg day.

6. ESFA's Key Assumptions and Remaining Questions: The ESFA assumed equal activity of PFOS, PFOA, PFNA and PFHxS, despite there being no effect observed for PFOS on antibody titer in the Abraham et al., 2020 study. Additionally, no MOA or biological relevance has been proposed for the common critical endpoints: increased cholesterol and liver weights (rodents), decreased body weight (infants, and reduced antibody response to infectious agents. It remains unanswered whether the reduced antibody response is sufficient to cause increased infections or immune system dysfunction. It is important to discern the immunotoxicity of individual PFAS substances, as the Bil et al (2023) study assumes that all PFAS induce immunotoxicity, which was not supported by the findings of the Abraham et al (2020) study.

7. The World Health Organization (WHO) and PFAS: the WHOs PFOS and PFOA minimal risk levels (based on ASTDR (2021) minimal risk levels and WHO default parameters) allow for PFOS drinking water values of 12 ng/L for adults and 3 ng/L for children. For PFOA, the values are 18 ng/L for adults and 4 ng/L for children. Intermediate (15-364 days) MRLs were calculated for PFAS in the ATSDR 2021 report and were as follows: PFOA- MRL 0.000003 mg/kg, with a critical endpoint of skeletal effects in mice; LOAEL 0.821 ug/kg bw, AF 300. PFOS- MRL 0.000002 mg/kg, with a critical endpoint of delayed eye opening, decreased pup weights in rats; NOAEL 0.515 ug/kg bw, AF 300. PFHxS- MRL 0.00002 mg/kg, with a critical endpoint of thyroid follicular epithelial hypertrophy/hyperplasia in rats; NOAEL 4.7 ug/kg bw, AF 300. PFNA- 0.000003 mg/kg, with a critical endpoint of decreased body weight and developmental delays in mice; NOAEL 1 ug/kg bw, AF 300. It should be noted that the transferability of the PFHxS study to humans is questionable, as thyroid hyperplasia in rats is not relevant to humans. Critical issues with the WHO studies include its reliance on MRLs based on animal studies and criticism of PBPK data and derived half-lives. Provisional Guidance proposed for individual PFAS was 0.1 ug/L for PFOS and PFOA, and 0.5 ug/L for summary PFAS. These provisional guidance values were derived with "significant uncertainties and absence of consensus with identifying the critical health endpoint to calculate a HBGV".

8. Differing Conclusions and Data Gaps: The authors highlighted the apparent absence of sufficient consideration of the biological causality and relevance in determining health guidance values for PFAS. They emphasized the need for improved experimental designs, better communication of uncertainties, and taking responsibility for appropriate communication to close important data gaps. It also underscored the importance of understanding that statistically significant findings especially when the original experimental design was questionable, may not always be clinically significant.

Tamar Berman, PhD, Israeli Ministry of Health, Setting Guideline Values for PFAS in Drinking Water: Decision Making Process in Israel

1. Adoption of Regulatory Standards from Other Countries: Israel considered adopting regulatory requirements implemented in other countries, specifically looking at the global landscape. Health Canada's 2018 standards for PFOA (0.6 ug/L) and PFOS (0.2 ug/L) were chosen for initial evaluation with interest in endpoint liver effects.

2. Survey Results on PFAS Levels in Drinking Water: The first survey in drinking water identified 25 drinking water sources with PFAS compounds above reporting limit and 97 below the reporting limit. One well was deemed unsuitable for human consumption based on Health Canada standards (0.6 PFOS, 0.2 PFOA, sum ratios < 1). The presentation highlighted a well with a substantial PFAS contamination level of 1600 mg/L in drinking water, leading to its removal from the water supply.

3. Rationale for Stricter Guideline Values (2023): Due to further reductions in EPA advisory levels and evidence of critical effects at lower concentrations, Health Canada's standards were deemed outdated. Treatment technologies are available to remove over 90% of PFAS contamination, leading to the recommendation to adopt the EU standard of 0.1 ug/L sum of PFAS by January 2026.

4. Grouping Approach for PFAS: The grouping approach was considered appropriate for PFAS due to common chemical, environmental, and toxicological properties.

5. Considerations in Setting Guideline Values: Toxicological thresholds, achievability, and current worldwide standards were considered. Challenges with analytical capacity and evolving recommendations were acknowledged, including the need to expand capacity to meet standards. Broad drinking water guidelines considered whether water can be supplied to the public, monitoring requirements (geographic representation, flexibility), and voluntary steps to reduce PPAS in supplied water (dilution, super flexibility).

6. Comments on Threshold Values and Biomonitoring Data: Berman described a sum value approach (EFSA-4) for PFOA, PFNA, PFHxS, and PFOS. It assumed equipotency for immunotoxic effects, with no correction for potential differences in toxic potencies. Human biomonitoring data and modeling were used to establish protective measures, especially for breastfeeding infants. A health-based guidance value of 6.9 ug/L was used.

7. Impact of PFAS Contamination on Drinking Water Wells: The contamination led to the disruption of water supply from three drinking water wells. An additional ten wells were projected to require treatment by 2026. Quarterly or annual monitoring for tens of wells was deemed necessary based on PFAS concentrations.
8. Ongoing Work on Human Biomonitoring Guideline Values: Work on developing human biomonitoring (HBM) guideline values for PFAS interpretation is underway as part of the Partnership for Chemical Risk Assessment (PARC).

Harvey Clewell, PhD., Ramboll, Alliance for Risk Assessment "Range of the Perfluorooctanoate (PFOA) Safe Dose for Human Health: An International Collaboration"

1. Wide Variability in PFOA Safe Dose Estimates: The author described how various government agencies and expert groups have estimated tolerable daily doses for PFOA to protect human health. He reported that these estimates illustrate significant differences in approaches to identifying a safe dose. He noted that the range of safe doses across nations varies by up to 100,000-fold. This large variation in values calls for scrutiny, explanation, and efforts to reduce uncertainty to better inform the public.
2. Steps in the Assessment: The author described the steps involved in assessing PFOA's safety, including the evaluation of potential modes of action, selection of critical studies, and identification of appropriate extrapolation methods and uncertainty factors for estimating human equivalent doses. He emphasizes that expert judgment plays a crucial role in these assessments.
3. Evidence for PFOA Modes of Action: Clewell described the potential modes of action associated with PFOA, including its mimicry of essential fatty acids and its resistance to endogenous fatty acid metabolism. These mechanisms, including disruption of lipid homeostasis and misincorporation in lipid membranes, were examined for their relevance in assessing PFOA's health effects. For example, the mouse and rat have a secondary fatty acid processing pathway absent in humans that promotes cell proliferation, calling into question the relevance of certain endpoints, like cancer, in animal studies.
4. Impact of Epidemiological Studies: The author described how, historically, critical effects of PFOA were based on animal studies in rodents, but some values are being revised based on epidemiological studies in human populations. He identified key uncertainties related to epidemiological studies, such as the criterion for establishing causality and assessing the clinical relevance of certain observed effects in humans (for example, the importance of a 10% increase in a single liver enzyme when the hour-to-hour variability of that enzyme is 20%). The author emphasized how sensitive effects reported in epidemiological studies, such as increased cholesterol, have not been associated with the expected disease consequence of that health effect (for example, elevated incidence of heart disease). In addition, any associations of PFOA with various developmental outcomes may be attributed to the possibility that the same processes that

drive specific biomarker levels also affect PFOA's presence in the body (referred to as pharmacokinetic bias).

6. Comparing Serum Concentrations and Effects: Harvey Clewell discussed the discrepancy between doses at which toxicity is observed in animal studies, resulting in disruption of lipid metabolism, and the blood concentrations observed in the general population due to PFOA exposure. He questioned how epidemiologists could suggest that PFOA blood concentrations in the general U.S. population could be attributed to various adverse effects simply because some effects were observed in animals at doses 1,000-fold higher than the doses for these humans. For example, some authors suggest that blood lipid changes in humans might be due to PFOA because changes are seen in rodents, but they fail to consider that blood lipid levels vary throughout the day, vary by week, and are not necessarily an adverse effect. A MOA is necessary to soundly link biomarkers to a critical effect.

7. PFAS half-life: Harvey Clewell suggests the long half-life of PFAS within the body at low concentrations may be attributed to its reabsorption in the kidney. A half-life value of 1.3 years for PFAS within the body is likely the "best" value, as contributed by Zhang et al. (2013) and supported by Zu et al. (2020). This value is more accurate than the half-life of 3.8 years used by the USEPA. Joseph Haney commented that the youngest person in the Zhang et al. (2013) human TK study used by ARA for half-life was 20 years old, and asked if children needed special further consideration in regard to TK half-life. Dr. Clewell essentially responded that children would excrete PFOA faster than adults, and therefore there is no need for special accounting for children with an extra TK factor for intrahuman variability.

8. Harvey Clewell emphasized that epidemiologists should not simply be statisticians reporting observations; rather, they have to consider the biological plausibility that the observed effect is related to an agent and that the observed effect (e.g., biomarker) is indicative of an adverse outcome.

9. The international collaboration of scientists from 8 different countries developed a range in the PFOA safe dose from 0.01 to 0.07 ug/kg-day based on findings from 5 different studies in experimental animals. This has recently been published as: Burgoon, Lyle D., Harvey J. Clewell, Tony Cox, Wolfgang Dekant, Linda D. Dell, James A. Deyo, Michael L. Dourson, Bernard K. Gadagbui, Philip Goodrum, Laura C. Green, K. Vijayavel, Travis R. Kline, Tamara House-Knight, Michael I. Luster, Therese Manning, Paul Nathanail, Frank Pagone, Katie Richardson, Tiago Severo-Peixe, Anurag Sharma, Jackie Wright. 2023. Range of the perfluorooctanoate (PFOA) safe dose for human health: An international collaboration. Regulatory Toxicology and Pharmacology, Volume 145, December 2023, https://doi.org/10.1016/j.yrtph.2023.105502.

Eric P. Gotting, J.D., Keller and Heckman LLP, Conflicting Scientific Judgments and Judicial Review

1. Judicial Review and Deference: This author discussed what is expected by the law when evaluating the human health hazards of a chemical. He noted that courts give substantial deference to an agency's assessment of the science, rather than "weighing the evidence" itself. This deference is typically given when the court asks more broadly whether the agency's decision-making was "arbitrary and capricious, or an abuse of discretion" under the standard of review rooted in the Administrative Procedures Act (APA). In addition to the APA, the underlying statute governing the dispute (like the Toxic Substances Control Act) might also provide a standard of review for the court to apply, which may be less deferential.

2. Review Limited to the Administrative Record: The court acts as an appellate reviewer of an agency's decision and only considers the scientific evidence that was before the agency when making its decision, which includes public comments, the agency's own data and studies, publicly available research, and evidence submitted in administrative proceedings. Since it is not a civil trial, there are no expert witnesses or expert reports.

3. Limitations on Record Supplements: He noted that litigants are rarely allowed to supplement the record with additional evidence after the agency's decision. This constraint underscores the importance of ensuring that the scientific evidence is well-established before the agency makes its decision, as the court's role is not to reevaluate the science but to review the agency's decision based on the existing record. This places a high premium on stakeholders submitting all relevant data and information to the agency during the underlying proceedings (like during notice and comment rulemaking).

4. "Super" Deference and Justifications: He described the concept of "super" deference and the reasons behind it, including the notion that agency experts, who possess specialized knowledge, should be the ones to resolve complex scientific and technical questions. This deference is rooted in the idea that agency officials are more directly accountable to the public than federal judges and should prevent judges from weighing the evidence and imputing their own views and biases.

5. The "Hard Look" Doctrine: Gotting described the "Hard Look Doctrine", which forces agencies to be more forthright and deliberate in their decision justification. It promotes public participation because agencies must acknowledge different views and explain how they reconciled public comments. It also decreases the risk that the judge will miss any significant errors in agencies' decision-making process.

6. Challenges in Applying Deference: He described the legal challenges of applying such deference, particularly when scientific uncertainty exists, statutory language implicates policy issues, or policy bias might influence the decision-making process. Some red flags that may signal a necessity for less court deference include unexplained or unsupported assumptions, no discussion of significant evidence, a sudden change from past policies, no discussion of a model's analysis and limitations, and significant data gaps. He illustrated these challenges with an example related to the FDA's evaluation of electronic

cigarettes (ECs) under the Tobacco Control Act, which emphasized the need for a comprehensive scientific evaluation in regulatory decision-making.

E. Donald Elliott, J.D., Earth and Water Law LLC, The Quest for Checks and Balances on EPA Science -

1. Use of "Worst Case Analysis": Mr. Elliott described the practice of using "worst case analysis" in regulatory decision-making. This approach involves considering the most conservative or precautionary scenarios rather than central tendencies. It is often employed to ensure that potential risks are not underestimated, especially in cases where public health protection is a primary concern.
2. Ineffectiveness of Judicial Review: He discussed the perceived ineffectiveness of judicial review in challenging the scientific basis of governmental agency decisions. He explained that courts tend to give substantial deference to agencies, particularly when complex scientific or technical issues are involved. Judges are also unfamiliar with the science, contributing to the ineffectiveness of judicial review for science cases at the EPA. The standards for reviewing factual support are often less demanding than those in civil suits, making it challenging for litigants to successfully challenge any agency findings or regulations.
3. Checks and Balances: He described the various checks and balances that exist to oversee the quality of science in governmental agencies. These mechanisms include:
    - Judicial review of factual support in the administrative record.
    - Science advisory committees that provide expert input to agencies.
    - Pre-promulgation review by the Office of Information and Regulatory Affairs (OIRA).
    - Reviews conducted by the National Academy of Sciences (NAS) and the Board on Environmental Studies and Toxicology (BEST).
    - Congressional oversight.
    - The Information/Data Quality Act.
    - Appropriations riders that can impact agency actions.
4. Default vs. Specific Statutory Requirements: Mr. Elliott described the default standards for judicial review under the Administrative Procedure Act (APA), which are not very demanding. Terms like "substantial evidence" and "capricious and arbitrary" are used, which are less stringent than the "preponderance of evidence" standard in civil suits. The presentation notes that courts are generally supposed to provide "super" deference to scientific issues "on the frontiers of science." The Supreme Court has agreed to consider

overruling *Chevron v NRDC (1984),* which would grant more court "authority to decide how precautionary EPA's scientific risk assessments should be."

5. EPA's Precautionary Approach: EPA often interprets statutes protecting public health in a highly precautionary manner. This involves balancing the risk of false negatives against false positives, which leads to conservative, safe reference levels and monetary assessments of very low or nonexistent risks. He noted that some statutes impose more demanding requirements for scientific evidence, which can serve as the basis for challenging EPA's discretion and specific rulemaking. The speaker concludes with a discussion of the lack of checks on EPA science in court, enabling cases to be won without sufficient questioning of scientific conclusions.

Susan Bodine, J.D., Earth & Water Law LLC, Legal/Policy Aspects of Differing Science Judgments "Best Available Science" and EPA Decision-Making

1. Dispute in Environmental Cleanup: To provide an example of the use of "best available science" data by regulatory agencies, Susan discussed a dispute related to an environmental cleanup project at an Air Force facility, governed by a Tri-Party Agreement involving the Department of Defense, the Environmental Protection Agency (EPA), and the state of California. The disagreement primarily concerned the cleanup standards for perchloroethylene (PCE) contamination, specifically the levels of PCE vapor entering the buildings.
2. Differing Interpretations: The Air Force wanted to change the cleanup standards established for the site to be less stringent because EPA had revised its Integrated Risk Information System (IRIS) value to reflect EPA's determination that PCE posed less risk than previously thought. California objected and advocated for even more stringent PCE standards. Both EPA and California reviewed the same scientific studies to reach their different conclusions. This case illustrates how different entities can have varying interpretations of acceptable risk levels based on the same scientific data. Thus, following the "best available science" from a regulatory decision standpoint is ultimately a judgment call.
3. Weight of the Evidence: She discussed the concept of "weight of the evidence." In the Air Force facility example, even though the EPA's Office of Research and Development (ORD) and the EPA reviewed the same studies, they reached different conclusions due to differing judgments about the significance of certain studies. Telling an agency to use the "weight of the evidence" when making regulatory decisions does not limit agency discretion. The term is simply too loose to be useful without clear definition.
4. Selective Use of Changing Risk Standards: She discussed the evolution of risk-based standards, such as blood lead levels. Susan discussed how the Centers for Disease Control and Prevention (CDC) has over time lowered its blood lead level of concern from 10 to 5 to 3.5 µg/dL. However, EPA has not changed it cleanup standard for lead in

soils, even though its current standard is based on achieving blood lead levels of 10 µg/dL.

5. Use of Risk in Statutory Standards and Judicial Review: While, as Don Elliott discussed, courts generally defer to the judgment of expert regulatory agencies on scientific matters, Susan noted that Congress can limit agency discretion. Citing the recent D.C. Circuit opinion in Maine Lobstermen's Ass'n v. National Marine Fisheries Service, Susan noted that Congressional use of terms such as "likely" to describe outcomes can limit an agency's discretion to adopt a precautionary approach when making a regulatory decision. Further, when directed by a statute to use "best available science," courts expect agencies to rely on sound and objective scientific practices.

Charlie Mullin, PhD, Bates White Economic Consulting, Potential Impact of Science and Policy Decisions on the Scope of Tort Claims

1. DuPont Settlement and PFOA Contamination: Mr. Mullin presented several case studies of important policy and legal decisions of the past 20 years surrounding PFOA/PFOS. He mentioned that the DuPont settlement in 2004 revolved around the use of perfluorooctanoic acid (PFOA) at the DuPont Washington Works plastics facility in Parkersburg, WV. This facility released approximately 1.7 million pounds of C8 (a type of PFAS) between 1951 and 2003. Remediation efforts significantly reduced PFOA levels in drinking water. DuPont settled a class-action lawsuit for around $340 million.
2. C8 Science Panel: As part of the settlement, DuPont established a C8 science panel to investigate the potential link between PFOA exposure and medical conditions. The panel identified a probable link and estimated the relative risk for six medical conditions. Subsequently, DuPont settled thousands of plaintiff claims for over $670 million.
3. Diverse Health Claims: The DuPont litigation involved a range of health claims attributed to PFAS exposure, including high cholesterol, ulcerative colitis, thyroid disease, kidney cancer, testicular cancer, and pregnancy-induced hypertension. It continues. These claims may be brought before different courts, and plaintiffs often choose the most favorable jurisdiction for their cases.
4. Public Water System Settlements: Recent settlements related to public water systems contaminated with PFAS have reached billions of dollars. For instance, there was multidistrict litigation involving aqueous film-forming foams. Companies like 3M, DuPont, Chemours, and Corteva agreed to substantial settlements, ranging from $1 billion to $12.5 billion. These cases involved groundwater contamination by PFAS contamination.
5. Future Litigation Trends: Several expected trends in future PFAS litigation. Remediation efforts are likely to become a central focus. Regulatory developments, such as the Unregulated Contaminant Monitoring Rules, have identified PFAS contamination in

various public water systems. However, PFAS-related personal injury claims face challenges due to the absence of a single "signature disease," the need for blood tests, and potential confounding factors, making it more complex to recruit claimants and establish causation, particularly as blood levels of PFAS decline.

Highlights from Day 3: Thursday, October 19th, 2023

Usha Vedagiri, PhD, VP, WSP Engineering and Design Consulting, PFAS Risk Implications in the General Food Supply: Is Commercial Food "Safe"?

1. Regulatory Agencies: Dr. Vedagiri discussed the roles of different regulatory agencies in ensuring the safety of the commercial food supply. The US Environmental Protection Agency (EPA) regulates pesticides and some pathogens in food but is not involved with PFAS in commercial food. The US Department of Agriculture (USDA) oversees various aspects of food production, including raw produce, meat, poultry, and processed egg products. The Food and Drug Administration (FDA) regulates food, dietary supplements, and food contact materials (for example, packaging and handling).

2. PFAS Regulation: The USDA does not have specific standards for per- and polyfluoroalkyl substances (PFAS) in food and defers to the EPA for drinking water and the FDA for PFAS in food. The FDA employs a risk-based approach for seven PFAS (PFOA, PFOS, PFNA, PFHxS, HFPO-DA [GenX], PFBS, PFBA), assessing their presence in the total diet of different populations, including children and the general population. All these PFAS substances have non-cancerous toxicity values. Other PFAS substances are not assessed, if detected at all.

3. FDA's Approach to PFAS: The FDA has been actively addressing PFAS in food by developing analytical methods (2021), executing a sampling program for both fresh and processed foods (2019-2023), performing human health assessments (2020-2023), and providing recommendations (2020-2023). The agency also authorizes PFAS in specific food contact applications (initiated in 2016).

4. Exposure Assessment: The FDA's Total Diet Study (TDS) (2019-2022) of over 700 food samples detected PFAS in 2-3% of the samples; there was no indication that the PFAS found presented a human health concern. Fish and seafood samples were prone to higher detection frequencies. Targeted seafood studies (2022,2023) identified canned clams from China as having the highest PFOA levels. Additional bioaccumulation studies in filter-feeder organisms (clams, mussels, oysters, scallops) are underway. Studies of dairy farms and produce grown in PFAS- contaminated environments suggest that there may be no detectable PFAS within the food, given current detection limits. The Vedagiri et al. (2020) study of commercial fish and seafood revealed that the total detected PFAS was

typically less than ten ppb, with PFOS being the dominant PFAS detected. There were higher levels of PFAS in some purchased finfish from the Great Lakes. International seafood samples generally had undetectable levels of PFAS. Hazard Quotients (HQs) were estimated based on the maximum detected PFAS concentration in a single food item (e.g., one fish sample) and calculated with the 95th percentile consumption rate per age group for that entire food group (all fish consumption), resulting in very conservative and unrealistic HQs that may lead to overestimated perceptions of risk.

5. PFAS in Food Packaging: The speaker notes the continued presence of PFAS in food packaging materials, including nonstick cookware, gaskets, o-rings, and processing aids, as authorized by FDA. Several states have enacted regulations related to PFAS in food packaging materials due to the potential for PFAS "sidechain" to migrate under certain conditions. California, Washington, Hawaii, New York, and Vermont are among the states with such regulations.

6. Current status and future of PFAS: The presentation reiterates that PFAS has a low detection frequency in the general food supply: it is generally not detected in produce, food, and grains and is most detected in fish and shellfish over other meat products. PFOS is the most frequently detected PFAS in food, and it is found at less than a 25 ppb average in fish and seafood. Local sources and non-commercial food supplies may present a concern. There are still uncertainties regarding PFAS without toxicological reference values (TRVs) in risk assessments and trends between PFAS in food and blood serum levels. It is known that PFAS blood levels have been decreasing over time. Expected future steps in PFAS include continued phasing out of the substances in food packaging and reducing its presence in the commercial food supply. In general, regulatory and voluntary efforts to regulate and monitor PFAS in commercial food supplies coupled with efforts to phase out PFAS in products appear to be effective in identifying the few food components that may warrant further attention while acknowledging the uncertainties in this rapidly evolving field.

Steve Via, American Water Works Association, Impact of Draft PFAS MCLs on US Water Purveyors

1. PFAS Rulemaking Challenges and Regulatory Levels: Mr. Via discussed the challenges and circumstances present in cleaning up PFAS in drinking water at the proposed maximum contaminant level (MCL) of 4.0 ng/L for PFOA and PFOS, including the lack of permanent disposal/destruction technology, significant advocacy, and concerns in communities with gross contamination. The maximum contaminant level goal (MCLG) is the level at which "no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety" and is 0.0 ng/L for both PFOA and PFOS. The PFAS Lifetime Health Advisory Levels for PFOA, PFOS, HFPO-DA, and PFBS were 0.004 ng/L, 0.02 ng/L, ten ng/L, and 2000 ng/L, respectively. Their minimum

reporting levels (all between 3-5 ng/L) were also included. These values highlight the extremely low concentrations at which PFAS are restricted in drinking water.

2. Impact on Public Water Systems: Mr. Via stated that approximately 66,560 public water systems (PWS) could be subject to the proposed PFAS drinking water standard. Many of these systems are small, serving less than 10,000 people, and may face significant costs in implementing treatment measures. The EPA estimates that 6.5% of PWSs will have PFAS levels exceeding the MCL and require treatment or an alternative water supply. Other calculations believe the EPA's analysis is underestimated, with almost 7,300 PWSs predicted to have PFOA and PFOS levels above the MCL.

3. EPA's Benefit-Cost Analysis: Mr. Via stated that the EPA had performed a benefit-cost analysis, showing that the costs associated with implementing the PFAS standard are substantial. An analysis performed by Black and Veatch for the American Water Works Association (AWWA) estimated annualized costs of the EPA PFAS water treatment plan to be at least three times as great as the EPA's predictions, with varying estimates of the total cost ranging from $2.9 billion to $3.8 billion at 3% and 7% discount rates, respectively. The analysis also assumes that the capacity for laboratories and manufacturing required for treatment and installation is adequate. Perhaps most importantly, the study emphasizes that the smaller the size of the PWS service, the higher the cost of upholding the PFAS MCLs per household, with equipment installation at the smallest water systems predicted to potentially add thousands of dollars annually to household water bills.

4. Meaningful Opportunity for Public Health Risk Reduction: Mr. Via questioned whether regulating PFAS in drinking water represents a meaningful opportunity for public health risk reduction when weighing competing infrastructure demands and other pressing societal needs. He mentioned that to many toxicologists and epidemiologists, it is unclear whether there are any genuine health benefits of a drinking water MCL of less than 100 ppb. He highlighted the challenges in crafting meaningful policy due to the diverse health contexts and the need for comprehensive and understandable information. Regulations are only effective if they are implementable. In response to other panel members asking about PFOA and PFOS serum concentrations in the general public and how they compare to those relevant to EPA's new interim health advisory levels (e.g., serum concentrations at the RfDs and/or their points of departure(POD)), Joseph Haney pointed out that based on NHANES data: (1) the geometric mean (GM) for every group is above the PFOA POD, including the young children most relevant; the hazard quotient (HQ) based on the GM for ages 3-5 is 11.8; and (2) The GM for every group is above the PFOS POD, including the young children most relevant; the HQ based on the GM for ages 3-5 is 4.7. Mr. Haney further pointed out that despite serum concentrations for every age group exceeding the RfD PODs, incidences of tetanus and diphtheria as the endpoints associated with the purported RfD critical effects (supposed lower tetanus and diphtheria immunity) appear rare in the U.S. population. The average annual number of tetanus cases in the U.S. from 2009-2018 was 29, with the CDC attributing most cases to

individuals who either have not been vaccinated or who are not current on their boosters. The incidence of U.S. diphtheria cases is even more rare, with the CDC reported only 14 cases from 1996 through 2018. So, U.S. surveillance disease incidence data are not supportive of adversity or severity of effect; that is, U.S. surveillance disease incidence data do not support that serum PFOA (or any other serum PFAS) is suppressing tetanus and diphtheria vaccine responses and leaving people vulnerable to infection from these diseases.

Chad Seidel, Ph.D., PE, Amlan Ghosh, Ph.D., P.E, Carleigh Samson, Ph.D., PE, Corona Environmental Consulting; Katherine Alfredo, Ph.D., PE, University of South Florida; Does regulating PFAS represent a meaningful opportunity for health risk reduction in drinking water?

1. Limited Health Risk Reduction: Dr. Seidel discussed the paper *"Does regulating per- and polyfluoroalkyl substances represent a meaningful opportunity for health risk reduction*" by Katherine Alfredo et al. (2021). He discussed the paper's conclusion "that the regulatory levels for PFOA and PFOS alone will not achieve a national meaningful health risk reduction as compared with previously regulated contaminants." That paper indicated that regulating PFAS may not be as effective in reducing health risks as expected.
2. Challenges in Crafting Meaningful Policy: Dr. Seidel discussed the challenges in updating the analysis related to PFAS regulation due to the diversity of health contexts. Crafting meaningful policy in this context is a complex task. PFAS can be regulated at the source, treatment, distribution system, and building plumbing system, yet each comes with a cost to install and maintain.
3. Lack of Comprehensive Reporting on Health Outcomes: In the United States, the only cause of death due to drinking water that is consistently counted on an annual basis is death from legionnaires disease. This underlines the need for comprehensive reporting on health outcomes associated with different contaminants.
4. Relative Health Indicator (RHI): The RHI is a part of cumulative risk assessment methodology and looks at cancer, non-cancer, and microbial risk in drinking water. These values are difficult for practitioners to put into context. PFAS drinking water exposure is not associated with any meaningful risk, according to Alfredo et al. (2021)
5. Changes in Toxicity Estimates: Dr. Seidel reviewed the changes in toxicity estimates for PFOA and PFOS over the years, including lifetime health advisories, reference doses, the basis for reference doses, drinking water intake per body weight, and relative source contributions from water. For PFOA, the toxicity estimates are as follows: Lifetime Health Advisory (ng/L): 70 in 2016, 0.004 in 2022 (interim); Reference Dose (RfD) (mg/kg/day): 0.0002 in 2016, 0.0000000015 in 2022; DWI/bw (L/kg-day): 0.054 in 2016, 0.0701 in 2022. For PFOS, the toxicity estimates are as follows: Lifetime Health Advisory (ng/L): 70 in 2016, 0.02 in 2022 (interim); Reference Dose (RfD) (mg/kg/day):

0.0002 in 2016, 0.0000000079 in 2022; DWI/bw (L/kg-day): 0.054 in 2016, 0.0701 in 2022. The basis of the drastic decrease in RfD for PFOA and PFOS was the suppression of tetanus and diphtheria vaccine response, respectively, in 7-year-old children.

6. Impact on US Population: Dr. Seidel discussed the impact of PFAS on the US population based on data from UCMR5. He noted the percentage of the population with PFOA/PFOS contamination in their water system greater than 4.0 ppt (14.4 and 14.8% of the population, respectively), and he emphasized that smaller water systems may bear a higher cost for addressing the issue. 219 PWSs (or 10.9%) were shown to have max PFAS values exceeding the EPA proposed regulation. When broken down by substance, 152 PWSs (7.6% of PWSs) have PFOA values more significant than the EPA's proposed MCL, and 164 PWSs (8.2% of PWSs) have PFOS values greater than the EPA's proposed MCL.
7. EPA estimate compared to UCMR5 data: Dr. Seidel discussed the likelihood that the EPA overestimated the number of large PWSs and underestimated the number of small PWSs that the ruling would impact. Additionally, this likely reality will increase the cost burden and decrease any potential health benefits. The speaker emphasized that limited funding needs to be prioritized for needs that will achieve the most significant health benefits.

Chuck Chaitovitz, US Chamber of Commerce, PFAS Policy Landscape: Costs & Impacts

1. Diversity of the PFAS chemical family: Various PFAS chemicals (Per- and Polyfluoroalkyl Substances) are not similar in many ways. Different types of PFAS have other characteristics and potential risks that need to be considered in the cleanup approach.
2. Costs and Impacts: Mr. Chaitovitz discussed the importance of considering costs and impacts when addressing PFAS contamination. He mentioned the economic implications of cleanup, including the costs associated with different regulations and the potential financial burden on households. The EPA's final PFAS reporting rule will cost an estimated 845 million dollars, with the total net benefits not quantified. The proposed CERCLA rule will have an estimated cost of $370,000 ($17.4 billion by the chamber of commerce), again with net benefits not quantified. The proposed drinking water rule will cost $771,770,000, with net benefits quantified at $461,210,000. The Monte Carlo estimates private cleaning costs could fall anywhere from $9-11 billion to $22 billion. The speaker emphasizes that cleanup costs are just a part of the entire economic impact; waste treatment, disposal, real estate, transaction costs, and land values must also be considered. Annual household water bills could increase by hundreds of dollars.
3. Valuable Applications: Mr. Chaitovitz discussed how PFAS has many valuable societal applications and how this class of chemicals plays a critical role in national security and

public safety. He said this highlights the need to balance regulation with the importance of these substances in various applications.

4. Inadequacy of CERCLA: He discussed how The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) is not the right policy tool for addressing PFAS contamination because endless litigation will come of it. The cost of technology and other associated costs for assessing and remediating contaminated sites still need to be fully realized. CERCLA possesses insufficient information to assess economic costs and impacts on communities properly. He suggested that alternative authorities and regulations should be considered for addressing the PFAS matter.
5. Alternative Authorities: Mr. Chaitovitz mentioned that, among others, alternative authorities to CERCLA, such as existing Superfund sites, Brownfields grants, Resource Conservation and Recovery Act (RCRA), Safe Drinking Water Act (SDWA), Clean Water Act (CWA), and other relevant regulations can be used to address PFAS contamination.

Mark S. Johnson, PhD, DABT US Defense Centers for Public Health - Aberdeen, Use of Evidence Integration Techniques to Derive Toxicity Reference Values

1. Data Interpretation: Dr. Johnson discussed the importance of interpreting toxicological data, highlighting the differences between animal studies and human data. Animal studies are controlled and include factors like absorption, disposition, metabolism, and excretion (ADME), whereas human epidemiology data often involves correlational evidence with potential confounders and exposure issues. Techniques such as *in vitro* to *in vivo* extrapolation (IVIVE) are needed to bridge the gap between these types of data. Non-animal-based approaches (computational modeling, biochemical/molecular endpoints, physiological endpoints, and functional endpoints) can expand toxicity testing.
2. Mechanistic Insights: The significance of mechanistic and mode of action studies, which address the biological plausibility of toxicity, are needed for the PFAS chemicals. Understanding the underlying mechanisms of toxicity is very important if one wants to effectively extrapolate dose response information (often from rodents) to humans in order to conduct an accurate risk assessment.
3. Evidence Integration Procedure: Dr. Johnson discussed the significance of the structured evidence integration procedure that begins with problem formulation, followed by a comprehensive literature review guided by population, exposure, comparator, and outcome (PECO) criteria. The method includes hazard identification, dose-response evaluation, and risk assessment, which involves deriving health effect concentrations (HECs), implementing Bayesian uncertainty factors, and selecting occupational exposure limits (OELs). This is virtually the same as the NAS risk assessment paradigm.

4. Rigor of Literature Review: Dr. Johnson discussed the importance of rigor in the literature review process. He indicated that criteria for evaluating studies should be established, and the procedure aims to be objective, comprehensive and must be clearly described.

5. Adjusting for Confounding and Misclassification: Dr. Johnson discussed the importance of addressing confounding or misclassifying exposure and acknowledged that this was a challenge (particularly when interpreting epidemiological data). The talk highlighted the need for careful reflection when small increases in relative risk are observed. Mechanistic data can be valuable in extrapolating experimental controlled laboratory animal data to humans. The importance of incorporating all relevant evidence and using a systematic, structured approach rather than relying on a single critical study is now greater than ever. In his conclusion, the speaker emphasized the necessity of including all the evidence in a risk assessment. PODs should be considered only for toxicity endpoints with sufficient evidence across all data streams (human, animal, in vitro/mode of action).

David Belluck, Ph.D., *Lost Science* and Sally Benjamin, MS, JD, Tumbleweed Books LLC, Revisiting the Basis for Nitrate Drinking Water Standards: Interim Findings for an Upcoming CRC Book by David Belluck and Sally Benjamin

1. Reliability of Historical Data: The authors presented the nitrate drinking water case study as an example of how one could assess the situation with PFAS. In this case, the USEPA recognized the unreliability of concentration data from Walton's 1951 article. By 1984, both the CDC and the EPA indicated that the data from this study may not be considered trustworthy or its limitations affected its use in assessing the safety of nitrate and nitrite in drinking water. The EPA derived nitrate and nitrite RfDs, MCLGs, and MCLs from a flawed conceptual model, inadequate literature reviews, unreliable IAM datasets, and calculation errors. The EPA assumed that the concentration data it utilizes for the development of nitrate and nitrite drinking water guidelines "are without flaw, have no uncertainty, are of high confidence, and are, therefore, completely reliable" despite the lack of knowledge of the source nitrate water concentration and reliable linkages of cases to nitrate concentrations. For many years, this has raised concerns about the foundation of the regulations and standards based on such data. Instead, it is far more likely that the reported IAM cases were due to ingestion of a mixture of substances that include "nitrate, nitrite, ammonia/ammonium, and/or bacteria" and further mediated by inherent infant health, age, sex, ascorbic acid intake, etc.

2. Intraspecies Variability: The speaker described how many scientists questioned the assumption that all infants have the same susceptibility to methemoglobinemia (IAM) caused by nitrate exposure. There is likely variability among infants, such as differences in physiological health, age, sex, prematurity, and dietary patterns, which can impact their sensitivity to nitrate exposure. This lack of consideration for variability raises questions about the accuracy of risk assessments. This is exemplified by the fact that all

infants ingesting high nitrate water do not develop IAM, suggesting the presence of unknown factor(s) regarding exposure and disease occurrence.

3. Use of Proprietary RfDs: The USEPA calculated its proprietary reference dose (RfD) values for nitrate and nitrite, which may not align with the official US EPA Integrated Risk Information System (IRIS) RfDs. This introduces a lack of transparency in the assessment process and raises concerns about consistency and reliability in regulatory decision-making. The presentation notes that "if the current IAM paradigm and RfD/MCL approach is to be kept," there should be much lower values based on the current weight of evidence, with the lowest valid LOAEL found to be 0.4 ppm nitrate-N (the current low-end LOAEL of 11 ppm).
4. Lack of Precedents and Guidelines: Instead of following recommended practices, the EPA's approach appears to differ significantly, potentially resulting in vastly different RfD values. Several RfD, MCLG, and MCL assumptions are made by the EPA that call into question how scientifically defensible their risk assessment is. Crucially, the belief that the "USEPA systematically and objectively followed standard practices and procedures to calculate final RfDs for Nitrate and Nitrite" is untrue.
5. Blurred Lines Between Risk Assessment and Risk Management: It was noted that there is a blurred distinction between risk assessment and risk management in the process of setting RfDs for nitrate and nitrite. This blurring may be due to the uncertainty in the available data and a focus on managing risks rather than purely assessing them. The risk assessment and risk management processes may have become intertwined, potentially leading to regulatory decisions based on factors other than scientific assessment alone.

Rick Becker, PhD, American Chemistry Council, Beyond Key Characteristics of Carcinogens (KCCs): An Improved Approach for Integrating Mechanistic Data in Cancer Risk Monographs

1. Key Carcinogen Characteristics (KCC): Dr. Becker discussed ten key characteristics of carcinogens identified by the International Agency for Research and Cancer (IARC), which are being used by IARC for identifying and evaluating potential cancer-causing agents using mechanistic data. These characteristics encompass factors such as genotoxicity, epigenetics, electrophilic activity, oxidative stress, immune suppression, and alterations in cell proliferation, among others. His talk is based on evaluating the KCCs for identifying cancer-causing agents, building from the paper he and colleagues previously published titled *How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data* in 2017.
2. IARC's Use of Key Characteristics of Carcinogens (KCCs): He discussed the International Agency for Research on Cancer's (IARC) use of key characteristics in organizing and evaluating mechanistic evidence for human carcinogenic hazards. The

strength of mechanistic evidence is expressed by IARC as "strong," "limited," or "inadequate."

3. Evaluation of Evidence: He discussed some challenges in evaluating mechanistic evidence, particularly regarding criteria for identifying "strong" evidence. He noted that the new IARC Preamble does not specify how many or which of the ten characteristics of carcinogens constitute "strong evidence," but noted that IARC infers strong evidence for carcinogenicity from evidence in exposed humans, in experimental systems using human cells. Dr. Becker tested the question of how well carcinogenicity can be predicted by high throughput "characteristics of carcinogens" mechanistic data in his 2017 paper. This research systematically retrieved ToxCast/Tox21 HTS data, performed analysis using EPA cancer classifications to denote chemicals having positive and negative cancer hazard potential, and used machine learning algorithms to evaluate the predictiveness of the KCCs. By performing this analysis with his team, the results clearly indicated that "the ability to predict cancer hazard for each key characteristic, alone or in combination, was found to be no better than chance." Therefore, there is little confidence or significance in the IARC's inference models or KCCs to predict cancer.

4. Concerns with the logic of IARC's use of KCCs: The IARC maintains that using KCCs allow the focus to move away from evaluating "specific pathways and hypotheses" and instead, emphasize "a broad, holistic consideration of mechanistic evidence." IARC states that this approach using KCCs avoids identifying and restricting attention to specific pathways and hypotheses, which they purport will "provide a more agnostic and unbiased" survey of mechanistic literature. Dr. Becker made the point that generation of hypotheses and use of the scientific method to test hypotheses should not be considered a biased approach. Instead, hypothesis formulation, testing and analysis is essential to assessing mechanistic data and integrating this with epidemiological and animal toxicity testing data. He discussed the limitation of using KCCs to represent "heterogeneous data/endpoints across one or more levels of biological organization," making it impossible to produce a meaningful causality assessment.

5. Improved Approach for Integrating Mechanistic Data: He mentioned that this proposed approach includes the use of Adverse Outcome Pathways (AOPs)/ Modes of Action (MOAs) and Key Events to articulate the sequences of events leading to specific adverse outcomes. In this approach, hypotheses are formulated for how a chemical acts to cause cancer (e.g., mutagenic MOA, cytotoxic MOA, receptor-mediated proliferation MOA, or immunomodulation MOA). Then assays associated with each KCC are mapped to the key events in each relevant hypothesized MOA. He provided examples of hypothesized cancer MOAs to be evaluated and suggesting the use of a quantitative confidence scoring approach for evaluating different hypothesized cancer MOAs. Dr. Becker expressed the viewpoint that this improved approach allows for scientifically supportable use of KCC data for evaluating postulated causal linkages and determining the risks of cancer developing from exposure to specific chemicals.

Tracie Phillips, PhD, Texas Commission on Environmental Quality, Derivation of Comparison Values and Action Levels for In-Motion (Mobile) Air Monitoring: An Update

1. In-Motion Monitoring Vans: Dr. Phillips' presentation discussed six mobile monitoring vans, one stationed in Austin, Texas, at TCEQ headquarters and the rest deployed in surrounding TCEQ regions. These vans are equipped with various instruments, including Selective Ion Flow Tube-Mass Spectrometers (SIFT) or Differential Ultra-Violet Absorption Spectrometers (DUVAS), that have the capability of collecting instantaneous (measured in seconds) real-time measurements of chemical concentrations while in-motion on the road or parked, thus allowing for immediate data evaluation.

2. Averaging Times: The speaker emphasized the importance of averaging time when assessing the instantaneous data from a human health standpoint. Unlike traditional ambient air monitoring, which typically reports concentrations over one hour or 24 hours, these mobile monitoring instruments enable measurements in seconds, providing immediate insights into concentrations of chemicals in the ambient air. Evaluating instantaneous chemical concentration data from these mobile units is important because it can help identify abnormal levels of chemicals in the ambient air and potential sources, and help staff determine if they should consider exposure mitigation while in the field. It is important to have comparison values that are reflective of the instantaneous averaging time of the data. The Texas Commission on Environmental Quality identifies two types of mobile monitoring comparison values (MMCVs): one to identify abnormal levels of chemicals in the ambient air and one to help determine if staff should consider exposure mitigation while taking samples in the field. Levels to identify abnormal levels of chemical in the ambient air are based on instrument- and chemical-specific baseline levels and are not based on health effects. Instantaneous MMCVs are designed to be conservatively compared directly with instantaneous concentration data.

3. Instantaneous Baseline and Investigation Levels: The speaker mentioned that instantaneous baseline-derived investigation levels (iBDILs) are calculated using baseline measurements, and concentrations exceeding ten times the baseline are flagged for further investigation. This approach helps identify abnormal levels of chemicals in the ambient air and helps with potential source characterization.

4. Action Levels: Different action levels used in response to specific concentration thresholds were discussed. Acute Health-Based Comparison Values (AHBCVs) were used to derive all toxicity-based mobile monitoring comparison values (MMCVs); they are designed to be health-protective without being overly conservative. Instantaneous Health Protective Investigation Levels (iHPILs) were introduced, which are set equal to the AHBCVs. In cases where the iHPIL is exceeded, stationary monitoring should be considered to more comprehensively assess the situation. Instantaneous Health-Based Action Levels (iHBALs) are set at three times higher than the 1-hour AHBCVs and indicate stationary monitoring should be initiated when detected and that evaluation of the data for ^{EM}HBAL levels should begin. These are all health-protective screening levels.

5. Exposure Mitigation Health-Based Action Levels (^{EM}HBALs): The speaker discussed the ^{EM}HBAL levels, which help protect field staff from potential chemical exposures during sampling. These levels consider both health-based comparison values and occupational short-term exposure limits. When the ^{EM}HBAL is exceeded, it triggers the consideration of exposure mitigation measures for field staff.
6. Decision Support Tools: The presentation highlighted the development of decision support tools for field staff, including fact sheets and quick reference tables. These tools provide a visual aid for interpreting concentration data and determining appropriate actions. For example, they help field personnel quickly assess whether a measured concentration falls below or exceeds health-protective levels.

Mel Andersen, Ph.D., A. Rasim Barutcu, Ph.D., and Michael Black, Ph.D., ScitoVation LLC Examining modes of action for PFAS using Transcriptomics

1. PPARα Activation in PFAS Toxicity: Dr. Andersen's talk focused on a likely mechanism of action for PFAS. He noted that the class of substances is known to activate PPARα, a nuclear receptor, and that this activation may lead to gene expression changes associated with toxic responses.
2. Inconsistencies with PPARα-KO Animals: He noted that studies involving PPARα-knockout (KO) animals are inconsistent with activation of this receptor as the sole reason for responses to PFAS. Some reproductive and liver responses were observed in wild-type (WT) and KO animals, indicating that other MOAs might be at play.
3. Wasting Syndrome and TCDD Comparison: He described that the wasting syndrome was observed in rodents exposed to perfluorodecanoic acid (PFDA) in the early 1980s, and he compared the responses to those seen with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). These responses include rodents losing significant body weight and experiencing high mortality.
4. Differential Gene Expression Analysis in Rats: He discussed experiments examining differential gene expression (DEG) after exposure to TCDD and PFAS. For TCDD, downregulation of fatty acid and steroid metabolism pathways was observed at doses causing wasting.
5. Pathway Enrichment Differences Among PFAS: He described differences in gene expression changes caused by various PFAS compounds at treatment concentrations ranging from 10 um to 100 um. Studies using human primary hepatocyte spheroids revealed qualitative differences between perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), indicating distinct MOAs and dose dependence. The genes affected appear to primarily be involved in fatty acid and steroid metabolism, although the up and down-regulation of these genes depends on the PFAS molecule and dose. The differences in pathway enrichment suggest that various PFAS compounds may

have different MOAs, and it may be helpful to group PFAS into short- and long-chain species when studying MOAs.

6. General summary: The speaker discusses how gene expression changes with hepatocyte spheroids indicate considerable differences in pathway enrichment within PFAS. Wasting syndrome with dioxins and longer-chain PFAS are associated with downregulation of lipogenesis. The speaker discusses the likelihood that the PPARα pathway is more important for biological response with shorter chain PFAS, while other MOAs would be responsible for downregulation seen at higher doses. He and his team hypothesized that longer-chain PFAS are recognized in a manner yet to be determined as a signal that the cell has too many long-chain fatty acids, thus initiating the production of signals to downregulate steroid and fatty acid synthesis.

Edward Calabrese, PhD, University of Massachusetts, The Historical Foundations of the Linear Non-Threshold (LNT) Dose Response Model for Cancer Risk Assessment

1. Mistakes in Muller's Claims: Dr. Calabrese focused on the early history of the Linearized Multistage Model (LMS) or Linear No-Threshold (LNT) model (a topic about which he has written 15 papers). He discussed mistakes made by Hermann Muller in his claims about radiation-induced gene mutations and evolution. Muller's assertion that background radiation was a cause of evolution was based on several critical mistakes, including the assumption that the genome is highly stable and that gene mutation due to radiation operates linearly with no repair mechanism. The proportionality rule (LNT) was created using these findings to explain evolution. Dr. Calabrese noted that Muller failed to account for internal repair mechanisms that prevent a mutation from becoming a part of the genome, and the 'mutations' that Muller claimed he had created with radiation were only large DNA deletions.

2. Research on Dose Rate Effects: He discussed research conducted by Russell and others on the effects of dose rate on mutation induction in 1958. Studies with female oocytes revealed a threshold effect with significantly reduced mutations at low dose rates, while male spermatogonia showed a 70% decrease in mutation but did not achieve a threshold. This research challenged the linear no-threshold (LNT) model and supported the existence of DNA repair. Decades later, recalculation of the spermatogonia control group's mutation rates resulted in the radiation-exposed group being comparable to the control, thus removing the remaining support for the LNT model from the Russell data.

3. Russell Cover-Up Study: Dr. Calabrese discussed a study conducted by William Russell and Arthur Upton in 1959-1960. They found that the results did not support a connection between reduced lifespan and radiation cancer study with mice, and these findings were suppressed with the justification "that publication of a negative finding could mislead the public into a false feeling of safety." The study was not shared with various organizations and was only published in 1993 to win a UK litigation.

4. Challenges to LNT: Dr. Calabrese challenged the LNT model by emphasizing that endogenous metabolism produces 200 million times more mutagenic oxy-radicals than background radiation in the same amount of time. DNA repair mechanisms evolved to correct damage from endogenous metabolism, not background radiation, which challenges the fundamental assumptions of LNT. Furthermore, these findings assert that mutations due to endogenous metabolism, not background radiation, drive evolution.

5. Historical Flaws and Deceptions: He closed his presentation by focusing on the flawed historical foundations of LNT, including deceptive practices, scientific misconduct, and self-interest within the scientific community. The regulatory and scientific toxicology communities were criticized for failing to provide oversight and correct these errors. Dr. Calabrese identified renowned journals he described as played a role in promoting the acceptance of LNT by publishing influential papers that were fundamentally flawed and deceptive. He discusses how the EPA plays a significant role in perpetuating flawed scientific notions and errors in cancer risk assessment, and Dr. Calabreses encourages the EPA to understand and correct the mistakes and consequences resulting from this flawed history.

Expert Panel Final Thoughts

- James Bus: If multiple scientifically sophisticated international regulatory agencies reach substantively differing positions on a societally-important health value, such as is the case with PFOA, then it as the *responsibility* of a properly functioning global public health scientific community to *understand* the scientific bases underpinning the differing positions with the objective of possibly achieving the most scientifically reliable health value. Perhaps the differing values are due to intrinsic and immutable *policy and/or legislative* mandate differences amongst international regulatory agencies. However, and importantly, over the course of workshop no such policy/legislative specific reasons accounting for the differing values were expressed, but rather only differences in overall scientific approaches to the *interpretation* of the data.
- Chris Chaisson: Contemporary approaches to setting "safe dose" metrics may need a comprehensive re-evaluation given circumstances where:
    - Experimental data present "changes at magnified cellular biochemical levels" being presumed to be adverse health effects, or
    - Where multiple "safety margins, uncertainty factors or such" are utilized in the calculation, or
    - Where there are radically different conclusions from other recognized international Agencies and/or expert commissions, or
    - Where robust epidemiological evidence counters the conclusions based on experimental evidence, or
    - Where "safe dose" conclusions initiate expensive public health postures which have questionable health avoidance advantages and also initiate public health expenses that compete with other health protection budgets.

This topic deserves examination and debate by the highest levels of international scientific bodies, supported by all US Agencies and their counterparts internationally.

- Linda Dell: Epidemiological studies are an important line of evidence in hazard identification. As regulatory agencies increasingly turn to observational epidemiological studies for dose-response assessment, more consideration should be given to uncertainties in low-dose risks when epidemiological data are used and whether mechanistic data support or argue against the use of epidemiological data. In the case of PFOA, perhaps develop an epidemiology study at high-dose using available information in Australia.
- Michael Dourson: Government groups need to work together to harmonize risk assessment values. Not doing so make it difficult to explain disparities to different constituencies and complicates trade among nations.
- Tarah Hagen: Governments need to sit down to work out differences in a large diversion of toxicity reference values. Otherwise, this disparity is not readily explainable to various stakeholders and interested parties.
- Joseph Haney: Sometimes it takes a village, a global one if need be, to work together and arrive at least to some consensus about the most scientifically defensible data and approaches.
- Wallace Hayes: Great meeting; some really important thoughts and suggestions for moving forward.
- Mark S. Johnson: Complete a hazard identification linking lines of evidence and leading with mode of action and then dose response. PFOA might evoke effects via a fatty acid mode of action?
- Greg Paoli: Be more careful in the use of adjectives describing risk assessment, otherwise we may be using the same language to mean very different concepts. At least we need to define these adjectives in our conversation with others in order to avoid confusion.
- Pamela Williams: A new approach to risk assessment by an expert committee might be helpful by looking at multiple stressor and coming to a consensus on what is the best way forward.