

**National Toxicology Program**

**Board of Scientific Counselors**

**February 21, 2020**

**National Institute of Environmental Health Sciences  
Research Triangle Park, NC**

*Summary Minutes*

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## 1. Abbreviations and Acronyms

|       |   |
|-------|---|
| BSC   | Board of Scientific Counselors                        |
| DNTP  | Division of the National Toxicology Program           |
| EPA   | U.S. Environmental Protection Agency                  |
| FDA   | U.S. Food and Drug Administration                     |
| HDP   | hypertensive disorders of pregnancy                   |
| iPSCs | induced pluripotent stem cells                        |
| MPS   | microphysiological systems                            |
| NAMs  | new approach methodologies                            |
| NCTR  | National Center for Toxicological Research            |
| NIEHS | National Institute of Environmental Health Sciences   |
| NIOSH | National Institute for Occupational Safety and Health |
| NRDC  | Natural Resources Defense Council                     |
| NTP   | National Toxicology Program                           |
| OHAT  | Office of Health Assessment and Translation           |
| PFAS  | per- and poly-fluoroalkyl substances                  |
| PFOA  | perfluorooctanoic acid                                |
| PFOS  | perfluorooctanesulfonic acid                          |
| RFR   | radio frequency radiation                             |
| TRAP  | traffic-related air pollution                         |

## 2. Attendees<sup>1</sup>

### **Board of Scientific Counselors (by WebEx)**

*Chair:* David Eaton, PhD, University of Washington  
David Berube, PhD, North Carolina State University  
Paul Brandt-Rauf, DrPH, MD, ScD, Drexel University  
Weihsueh Chiu, PhD, Texas A&M University  
Susan Felter, PhD, Procter & Gamble  
David Michaels, PhD, George Washington University  
Anne Ryan, DVM, PhD, Act 5 Ventures LLC  
Jennifer Sass, PhD, Natural Resources Defense Council  
Donald Stump, PhD, Charles River Laboratories  
Susan Tilton, PhD, Oregon State University

### **National Institute of Environmental Health Sciences/Division of the National Toxicology Program (NIEHS/DNTP) Staff**

|                   |                 |
|-------------------|-----------------|
| Brandiese Beverly | Alex Merrick    |
| Brian Berridge    | Andrew Rooney   |
| Chad Blystone     | Charles Schmitt |
| Michelle Hooth    | Sheena Scruggs  |
| Ruth Lunn         | Robert Sills    |
| Scott Masten      | Mary Wolfe      |
| Elizabeth Maull   | Rick Woychik    |

### **Other Federal Agency Staff**

Miriam Calkins, National Institute for Occupational Safety and Health (NIOSH) (by WebEx)  
Gonçalo Gamboa da Costa, U.S. Food and Drug Administration/National Center for Toxicological Research (FDA/NCTR) (BSC liaison; in-person)  
Anil Patri, FDA/NCTR (by WebEx)  
Elizabeth Whelan, NIOSH (BSC liaison; by WebEx)

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<sup>1</sup>The meeting was webcast. Individuals who viewed the webcast are not listed except as noted.

**Contract Support Staff**

Canden Byrd, ICF

Ernie Hood, Bridport Services

Jeanne Luh, ICF

Blake Riley, ICF

Kelly Shipkowski, ICF (by WebEx)

### **3. Introductions and Welcome**

The National Toxicology Program (NTP) convened a Board of Scientific Counselors (BSC) meeting on February 21, 2020 via webcast. Dr. David Eaton served as chair. Dr. Mary Wolfe served as the Designated Federal Official.

Dr. Eaton called the meeting to order at 12:00 p.m., welcomed everyone to the meeting, and asked all attendees in the room and on WebEx to introduce themselves. Dr. Wolfe read the conflict of interest policy statement and briefed the attendees on meeting logistics.

### **4. Report from the Acting NIEHS/NTP Director**

Dr. Rick Woychik, Acting Director of the National Institute of Environmental Health Sciences (NIEHS) and NTP, welcomed everyone to the meeting. He commented on the honor of being appointed Acting Director of both NIEHS and NTP and noted the different missions of the two groups. Excited about the new vision and proposals for NTP, Dr. Woychik said he would do whatever he could to help implement them.

Following his initial meetings with NTP committees in September 2019, he perceived a great deal of interest in strategic planning and working with NTP partners. There will be an analysis of NTP's strengths, weaknesses, opportunities, threats to identify opportunities to work together to transform toxicology research. A meeting was proposed for May 2020 to establish specific goals to address the results of the analysis.

### **5. Introduction to Meeting Agenda**

Dr. Brian Berridge, Associate Director of NTP and Scientific Director of the Division of the NTP (DNTP), opened the meeting by introducing the day's agenda. He thanked everyone for attending and agreeing to use remote technology.

Prior to going over the agenda, he described the productive conversations between NTP and the BSC, which have guided much of what NTP has done since Dr. Berridge's arrival. Based on BSC feedback, NTP has refined its strategic intent, defined a translational toxicology pipeline, and started Health Effects Innovation initiatives. NTP has maintained and grown a focus on contemporary challenges, and has engaged in developing novel capabilities.

Dr. Berridge noted the growth of the NTP research portfolio and described the staff teams leading progress and strategy development in the different spaces.

He outlined the aims for this BSC meeting:

- Continue NTP's collaboration with the BSC to evolve the NTP model.
- Share outcomes of recent key efforts.
- Use those efforts as a focus of strategic conversation.
- Gain the BSC's input on how to continue to innovate NTP's approaches and remain aligned with the BSC's sense of NTP's unique value.

He went over the agenda for the rest of the day, starting with his own presentation.

Dr. Eaton asked Dr. Berridge to elaborate on his reference to “RFR 2.0.” Dr. Berridge explained that some radio frequency radiation (RFR) exposure chambers had been built that would allow for some short-term studies. The chambers are now being validated to ensure that they meet the specifications for investigative mechanistic studies planned as a follow up to NTP’s earlier RFR study.

## **6. Evolving the Paradigm: In Vivo to In Vitro Extrapolation, Microphysiological Systems-Enabled “Virtual Human” Hazard Assessment: A Concept**

Dr. Berridge prefaced his presentation by describing his thoughts on how NTP might re-invent traditional toxicology or hazard assessments. The goal is to try to leverage traditional experience while also having confidence in newer models and approaches. Microphysiological systems (MPSs), in particular, offer an opportunity to get closer to the complexity of *in vivo* systems to potentially re-invent how toxicology is done. His aims for the presentation were to:

- Reflect on the primary stakeholder in NTP’s hazard assessment efforts.
- Acknowledge the value of current approaches.
- Challenge whether a novel approach can be developed.
- Identify key existing enablers.
- Get the board’s perspective.

Dr. Berridge identified three primary stakeholder interests: (1) environmental public health, (2) personal (individual health), and (3) pharmaceutical companies. He pointed out that while natural human experiments occur every day, animals have traditionally been used as surrogates for humans in testing, and the regulatory community has varying levels of expectations about the use of animal testing in protecting human health. Confidence in the animal testing platform has evolved over time and, while there have been gaps, overall the platform has been good at protecting human health. There is, however, potential that the platform overestimates hazards.

Dr. Berridge outlined the questions typically posed in relation to animal studies:

- Under the conditions of this study, does this agent have a biological effect?
- Where does that effect occur?
- What is the morphologic character of that effect?
- Is the effect adverse?
- At what dose/exposure does the effect occur?

Dr. Berridge described several challenges in answering those questions, including (1) the use of human questions in a non-human system, (2) the fact that they are restricted to “conditions” that don’t generally mimic the human condition, (3) they are not personalized, (4) the pathogenesis is speculative, and (5) the mechanism of action is typically unknown. By leveraging advances in modeling technology, different questions can be asked that still protect human health:

- Does this agent have human bioactivity?

- What human cell or tissue types are most susceptible to that bioactivity?
- Under what human conditions does that susceptibility occur (genetically variable vs. perturbed biology)?
- Is that human bioactivity adaptive, maladaptive, or reversible?
- At what human exposures does that activity occur?
- What is the temporal and cellular pathogenesis of the activity?
- Can this information be more broadly extrapolated to the complex *in vivo* human condition?

These questions represent fundamental shifts from “animal” to “human,” from “effect” to “activity,” and from “population” to “precision.” Dr. Berridge, reviewing the field’s experience with toxicity and progress in mechanistic screening strategies, including some of the mechanisms of failure, proceeded to describe the current knowledge and capabilities that might enable such fundamental shifts.

Dr. Berridge noted the significant investment in human- and physiologically-relevant modeling platforms such as MPSs and tissue-on-a-chip initiatives. He stated that, while the human condition cannot entirely be replicated, enough is known to target the location of toxic bioactivity. There is tension between the challenges of a “one size fits all” approach and the need for a platform that can define a different paradigm. He described several of the recently developed tools that will enable the new approaches.

The overarching need is to define a novel paradigm that deliberately couples all of the tools to allow movement through the process in a more evidence-based and human-relevant way; a paradigm that is different from the traditional animal-based testing. He acknowledged that it is “a bit of a brash change in the way we traditionally do business.”

Board members were asked to discuss the following questions:

- Are we asking the right questions? What’s missing?
- Animal studies do not assess every possible biological effect. How do we know which biological scope is most important to assess?
- How far down the temporal progression of pathogenesis do we need to model to predict an acute outcome? A chronic outcome?
- What is the tractability of a “Virtual Human” hazard assessment platform?
- What technical capabilities would we need to develop to be successful?

Dr. Eaton opened the floor for clarifying questions from the board members.

Dr. Felter asked about the tractability of a virtual human risk assessment platform, as opposed to limiting it to hazard assessment. Dr. Berridge replied that he had written the original question while trying to stay within the scope of NTP, a hazard assessment organization, but the intent would be to enable risk assessment as well.

Dr. Eaton noted that there were no written or oral public comments on this topic.



## 6.1. BSC Discussion

Dr. Chiu, the first discussant, had three questions for NTP to consider. First, what should be the dose, and second, what toxicities should we monitor for? When it comes to environmental chemicals, we are looking more for an assurance of safety, as we will never really have experimental human data. This goes back to the question of what is adverse and is it applicable to humans. Dr. Chiu's third question asked who the customer is for the new platform, as he was not sure it would be possible to design a single generic virtual human platform to address multiple decision contexts. He cited the varying needs of a drug company as an example. He described a Venn diagram in which there are three circles encompassing toxicity in the human population, animal toxicity studies, and new approach methodologies (NAMs), and wondered what was being missed in animal studies that would benefit from a NAMs approach. He addressed the progression of pathogenesis, and said rather than mechanisms of failure, the more important question might be about biomarkers of increased probability of failure.

Dr. Tilton, the second discussant, supported the approach Dr. Berridge described as exciting with a lot of potential, though it is still in its early stages. She could see several research opportunities, the first being the ability to compare the predictions that might be made using these approaches with data from historical animal studies, leveraging the existing data within NTP to validate confidence in these new approaches. She proposed the idea of using animal-derived cell systems to make comparisons with the animal studies. The flexibility of the model would allow for the evaluation of different routes of exposure, for example, as well as the variability of response. Similar to Dr. Chiu, she wondered who the studies would actually be for, as the applications could range from developing models to prioritize chemicals or animal studies within NTP, or to supplement studies with human-relevant data. Determining which biological systems are important to assess depends on the purpose of the study. When developing successful capabilities, she said, it is important to create systems that rely on adverse outcome pathways and are linked to an outcome of interest. She also recommended collecting pharmacokinetic data that may be relevant.

In response, Dr. Berridge noted that both discussants mentioned identifying specific context of use and acknowledged Dr. Tilton's comment about using NTP's existing animal experience to build confidence in the newer systems by looking at animal-to-animal extrapolations. He expressed interest in the idea of focusing on specific customers and how they would use the systems, and was intrigued by Dr. Chiu's mention of biomarkers of impending failure. He said he had observed two overriding phenomena in his career that made him interested in pushing this envelope. First, in pharma, there was little room for innovative approaches, as there always needed to be a take-away in order to get to the next stage. NAMs provide incremental opportunities to adopt novel approaches. Second, he added that he has "a burning desire to see a monumental leap in the way that we do this that really pushes the envelope." He believes that the pieces are there, but the real challenge is to establish human confidence.

Dr. Woychik said that increasing confidence in hazard evaluations is a great goal, and that he hoped the board would discuss the major challenge of inter-human variability when assessing toxicity.

Dr. Chiu stated that MPSs will not be ready to replace anything on a broad scale in the next ten years. He considered that induced pluripotent stem cells (iPSCs) have more potential to replace test species in the medium term. Regarding biomarkers of impending failure, he suggested

identifying key characteristics of chemicals that are “bad,” as opposed to using a full mechanistic approach. iPSCs derived from multiple individuals would be an ideal approach to address human variability. In addition, iPSCs may have the potential to support a movement towards replacing a second species in animal studies. Dr. Chiu considered it important to continue work in the area, whether with mouse models or human *in vitro* models, and reiterated the importance of developing systems to identify intermediate biomarkers.

Dr. Felter asked if it would be appropriate to consider human-relevant exposures at the start of the process, as systems are being built with specific concentrations of a test chemical. Dr. Berridge agreed and noted that Dr. Felter’s comment related back to human relevance and predictivity of the model system.

As they pertain to the *in vivo/in vitro* process and human relevance, Dr. Eaton commented that there is value in animal studies as they can identify key events that lead to pathology. In turn, this allows for human-based *in vivo/in vitro* approaches, such as MPSs, to more carefully evaluate the human relevance of key events identified in animal models. The challenge is to identify the false negatives that may occur when human biology relies on a different pathway than found in the animal models. Dr. Eaton thought that the new approaches have the capability of addressing human variability, particularly when it comes to key events in human cells. He said it is important to integrate *in vitro* approaches among different organ systems and acknowledge that it is usually tissue-specific metabolism and metabolites, rather than the primary chemical, that are responsible for toxicity.

## **7. Understanding Human Exposure to Nanoparticles/Microplastics: Novel Agents Bring Novel Challenges**

Dr. Anil Patri, Chair of the Nanotechnology Task Force and Director of Nanocore at the National Center for Toxicological Research (NCTR), U.S. Food and Drug Administration (FDA), briefed the board on recent developments in research on human exposure to nanoplastics and microplastics, including the global challenge represented by plastic waste, and provided an update on activities by national and international regulatory agencies addressing the problem.

Dr. Patri commented that there are no standard definitions for microplastics and nanoplastics; the compositions, shapes, and sizes of the particles are diverse. Adding to the challenge are (1) the proprietary additives found in many of the particles, and (2) the other chemicals often found bound to them. He described the degradation process that forms microplastics and nanoplastics from bulk plastic waste.

There has been considerable and growing interest in the issue from U.S. governmental entities in recent years, including the Nanoplastics Interest Group, which is comprised of several agencies and centers. There is also a great deal of research and review activity by international groups such as the World Health Organization and the European Food Safety Authority. Dr. Patri highlighted two recent events addressing the problem: the 2019 Global Summit on Regulatory Science and January 2020 National Academies of Sciences Emerging Technologies to Advance Research and Decisions on the Environmental Health Effects of Microplastics. Dr. Patri noted that the general conclusion that may be drawn from these and other workshop reports is the need for robust, reproducible, and quantitative methods and standards to characterize complex mixtures of micro- and nanoplastics to evaluate the human exposure to these mixtures. On the

positive side, he noted that there is no significant concern currently about human health effects, albeit effects from unknown longer-term exposures are unknown.

Dr. Patri delineated the many studies relevant to human exposure, but noted that overall very few studies exist on nanoplastics, and there is a lack of appropriate methods for detecting them in the natural environment, leading to many unanswered questions and knowledge gaps for both micro- and nanoplastics, including:

- Lack of robust, rigorous, reproducible science and standardized methods for the collection, isolation, separation, identification, and quantitation of micro- and nanoplastics, additives, and bound chemicals from complex mixtures for real-world sample analysis.
- Lack of methods for evaluating micro- and nanoplastic mixtures quantitatively in complex matrices such as food and seafood.
- Lack of performance standards, reference material standards, test methods, and quality controls.
- Challenges in methodological gaps for nanoplastics.
- Lack of systematic studies on hazard, exposure, and risk assessment of micro- and nanoplastic mixtures.

He described several of the methods currently in use for analysis and listed several potential collaborative studies between NTP and FDA to add to understanding of exposure and hazard.

The questions for BSC discussion were:

- Are we asking the right questions? What might be missing?
- Based on the questions, what other routes of exposure or materials of exposure should be considered?
- Are there technical capabilities that we need to develop to be successful?

## **7.1. BSC Discussion**

Dr. Sass, the first discussant, noted that her organization, the Natural Resources Defense Council (NRDC), has been getting a lot of questions on the topic from concerned members of the public. NRDC is very concerned about chemical contaminants and toxicity from exposure, and she was struck by the idea that other chemicals attach to the particles. She was also concerned about the issue of mixtures and the difficult questions they raise. Dr. Sass noted that it is important that NTP take the lead in not only doing important work but also in helping the public, regulatory agencies, and scientists think about how to interpret the data.

Dr. Brandt-Rauf, the second discussant, wondered whether there were any studies on the occupational exposure of workers producing engineered nanoparticles, who would have more uniform and higher exposures. Dr. Patri replied that the National Institute for Occupational Safety and Health (NIOSH) has been doing a significant amount of work in that space and that NIOSH and the Consumer Product Safety Commission are interested in the particles produced by 3D printers. NIOSH is also interested in micro- and nanoparticle mixtures. Dr. Brandt-Rauf was glad to hear about the interest in 3D printers and asked if there had been any thoughts on

using biodegradable plastics as a solution. Dr. Patri said that had been extensively discussed at the recent National Academy of Sciences meeting and noted that degradable plastics may be limited to certain products where longer-term stability is not required. He added that efforts in that area were just beginning to form degradable plastic in such a way that the final products are gases, rather than smaller plastics. Dr. Whelan, the NIOSH liaison to the BSC, said that NIOSH is part of the interest group, and shared information about a science blog NIOSH had recently published on nanoplastics.

Dr. Stump, the third discussant, said that, currently, the general public considers nanoplastics and microplastics as one substance; therefore, efforts to determine the composition of the various nanoplastics and microplastics are very important. He is concerned about the variability of different plastics and the challenge this poses for testing; having reproducible materials to test could prove difficult. Dr. Stump was glad to hear there is an attempt to produce a reference standard. As plastics are ubiquitous in the environment, he wondered if there would be low confidence in the control groups of studies analyzing these compounds. He noted additional hurdles in determining how long the materials persist and the potential for bioaccumulation; he wondered whether the materials would preferentially accumulate in certain organs in humans. Dr. Patri commented that, based on available literature, microplastics tend to stay in the gut in fish, which could mean potentially less human exposure from consumption. Nanoplastics, however, can translocate barriers and accumulate in other organs and tissues. It is also important to consider the chemicals that can bind to the materials and result in exposures.

Dr. Eaton, noting that one of the common biological responses to engineered nanoparticles is the induction of oxidative stress and activation of macrophages, asked Dr. Patri if this was also true for micro- and nanoplastics. He added that most nanoplastics are polymers, made of monomers with known toxicities, and asked if the release of monomers was a concern. Dr. Patri replied that potential immunological effects, such as macrophage uptake, are known, but dependent on the nanoparticle surface and charge. Dr. Patri said there is a large existing literature base on polymers; however, many of the reported studies have been done with commercially available nanoparticles and may not be applicable to real-world exposures of mixtures.

Dr. Wolfe indicated that no written or oral public comments were submitted for this topic.

In response to a question posed by Dr. Ryan on NTP capabilities and opportunities in this area, Dr. Berridge replied that this is an active area of collaboration with FDA/NCTR that needs to grow. In terms of capabilities, Dr. Berridge commented on the importance of taking responsibility for defining the problem. He added that it was not the kind of problem that would lend itself to animal studies. Rather, it would be a perfect opportunity to use some of the alternative modeling capabilities previously discussed, and some of that work is already being done.

Dr. Gamboa da Costa agreed that it would be important to define the problem and said that the area is a prime example of the type of work NTP should be taking on in cooperation with FDA/NCTR.

## **8. Hypertensive Disorders of Pregnancy and Environmental Exposures: Disease as a Toxicology Focus**

Dr. Brandiese Beverly from the DNTP Office of Health Assessment and Translation (OHAT) briefed the board on recent work related to hypertensive disorders of pregnancy (HDP) and environmental exposures. She described the HDP: gestational hypertension, preeclampsia/eclampsia, chronic hypertension, and chronic hypertension with superimposed preeclampsia. HDP affect up to 10% of pregnancies worldwide and are a leading cause of maternal and fetal mortality and morbidity. Preeclampsia is the most common form of hypertension during pregnancy and causes 60,000+ maternal deaths and 500,000 fetal deaths each year.

Dr. Beverly delineated the short- and long-term effects of HDP on maternal and offspring health. She noted that known risk factors only explain a fraction of cases, leading to the question of whether environmental exposures are contributing to HDP. Based on the NTP nomination to evaluate emerging health issues associated with ambient air pollution, HDP were identified as an emerging air pollution-related health issue affecting mother and child.

Initial scoping efforts found that traffic-related air pollution (TRAP) is potentially associated with HDP, and OHAT conducted a systematic review that confirmed the association. However, there may be other environmental exposures of concern, leading to continuing research in the area that is aligned with new NTP programmatic directions and pipeline, including the Cardiovascular Health Effects Innovation effort. The program will employ scoping reviews and evidence mapping to further understand human-relevant biomarkers and mechanisms of HDP that can be evaluated using animal models. Tools and resources will include 21<sup>st</sup> century toxicology methods, systems biology approaches, and engagement of stakeholders and institutes/agencies.

Dr. Beverly outlined the many challenges facing the study of HDP. The project is characterized by broader goals and is considered a case example of engaging the NTP pipeline to address a contemporary issue. The outcomes of the project will also aid in the understanding of how the environment affects HDP, and the contribution of HDP to overall cardiovascular disease risk in women, especially minority women. Also, it will develop communication strategies to better incorporate environmental health considerations in public health and patient care.

Dr. Beverly listed the shared interests across the National Institutes of Health to address research gaps to better understand the impact of environmental exposures on HDP.

The board was asked to consider the following questions:

- One of the aims of our Health Effects Innovation efforts is to shift our focus from “agents of concern” to “environmental effects on diseases of concern.” How does this change in focus influence the questions we ask in our hazard characterization studies?
- If you consider environmental effects on HDP as an exemplar, how does that change our approach to hazard characterization?
- Are there unique technical capabilities or approaches that we’ll need to develop to be successful?
- What challenges are we likely to encounter in making this fundamental shift in focus?

## 8.1. BSC Discussion

Dr. Eaton noted that no written or oral public comments were received for this topic.

Dr. Felter, the first discussant, thought the project was a great example of the change in approach NTP is taking to focus on human diseases of concern, instead of focusing on the agent first. She asked if there was any information on the change in incidence of HDP over time that could inform the understanding of the role of TRAP in HDP. She indicated that there were still many questions related to human exposure that might be important for future epidemiological studies and gave examples of (1) accounting for elevation when relating exposure to distance from major roadways, and (2) considering how much time a person spends in their residence relative to commuting or at a workplace. If NTP is changing its focus to understanding what causes human disease, she said the questions should include consideration of how different risk factors compare with others; this will inform how NTP prioritizes research. She wondered if there was a way to determine which environmental agents were most important in contributing to HDP, and asked if there was any dose/response information available to inform the need for intervention.

Dr. Beverly, responding to Dr. Felter's comments, acknowledged that there were more questions than answers at this point. She indicated that the incidence of HDP is rising over time, along with increases in air pollution and the number of older mothers, both of which are confounding factors that lead to the increased incidence. She said it will be important to determine what information is needed to characterize exposure and identify appropriate molecular biomarkers. She noted that there are personal monitoring studies coming out which may yield data important for answering HDP questions. Dr. Beverly thought that the proposed scoping document would help with efforts to compare risk factors and prioritize which chemicals are more concerning. She agreed that it would be important to look at genetic and epigenetic factors that may lead to HDP and said there is still a need for information about the effects of specific chemicals. She noted that dose/response data are lacking at this point, but information emerging from personal monitoring studies may help fill that gap.

Dr. Stump, the second discussant, considered that one of the biggest challenges with NTP's change of focus will be establishing the right environmental factor to concentrate on in any given condition. For example, if TRAP only has a minor impact on preeclampsia, it would be useful to focus elsewhere. Overall, the challenge will be to determine the environmental effects leading to the diseases of concern.

Dr. Beverly indicated that the scoping effort would reveal which environmental chemicals are the most important to focus on.

Dr. Michaels, the third discussant, said it was a great initiative to move toward environmental effects on diseases of concern; the limitations of animal models have led to greater reliance on observational studies in humans. He thought it was important to think about real-world situations with multiple exposures, as it is hard to find human populations that have only been exposed to a single agent. TRAP is a great example, as it represents a case where researchers are looking for populations exposed to a mixture and have a known endpoint, cardiovascular disease. He likened the HDP studies to current studies of maternal and child exposures in autism spectrum disorders. He noted that the challenge of measuring air pollutant exposures in humans is quite complicated, as much of the exposure estimates are based on the distance from exposure monitoring stations and there are challenges with evaluating multiple exposures. The exposures interact with known

risk factors and are confounded by socioeconomic and status-related factors, and it is necessary to employ natural experiments to gather human evidence. He thought the HDP initiative was a great effort and was happy to see it take shape.

Dr. Beverly agreed that whatever is done needs to be anchored in the human data and incorporate human observational studies; NTP can't look solely at animal or *in vitro* studies. Thinking about real-world exposures is a challenge in systematic reviews, she noted, and the TRAP efforts were a good example of a first step in how to deal with complex exposures.

Dr. Eaton commented that he liked the idea of starting from a specific disease or exposure, and commended Dr. Beverly on a great presentation. He noted that the talk had illustrated a number of the challenges associated with starting a project using a disease focus.

## **9. NTP Studies of Per- and Poly-fluoroalkyl Substances: Understanding Human Translation**

Dr. Chad Blystone, from the DNTP Toxicology Branch, briefed the board on NTP studies of per- and poly-fluoroalkyl substances (PFAS). He defined PFAS and noted that manufacturers agreed to discontinue the use of perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) due to widespread exposure and health concerns. While exposure has declined for some PFAS, newer PFAS have been identified. He described the PFOA cancer assessments undertaken in 2016 by the International Agency for Research on Cancer and the U.S. Environmental Protection Agency (EPA). NTP PFAS studies include:

- *In vitro* evaluations.
- Toxicokinetic, immunotoxicity, and 28-day toxicity studies of multiple PFAS in rodents.
- Carcinogenicity studies of PFOA in rats.
- An NTP monograph (2016) evaluating the human immunotoxicity hazard of PFOA and PFOS.
  - The monograph concluded that PFOA and PFOS are *presumed immune hazards to humans*.
- Newer PFAS evaluated under NTP's Responsive Evaluation and Assessment of Chemical Toxicity program.

Following up on previously published PFOA carcinogenicity studies, NTP tested the hypothesis that including perinatal exposure (gestation and lactation) would quantitatively or qualitatively alter the PFOA response. Two types of comparisons were made during the analysis and interpretation of the data:

- Exposed groups were compared to the control group to determine if exposure increased effects in various endpoints.
- Exposed groups were also compared to determine if animals with perinatal exposure had different effects compared to animals without perinatal exposure.

Dr. Blystone described the study design and summarized the results. There was *clear evidence* of carcinogenic activity of PFOA in male rats based on the increased incidences of hepatocellular neoplasms and acinar cell neoplasms of the pancreas. There was *some evidence* of carcinogenic

activity of PFOA in female rats based on the increased incidences of pancreatic acinar cell neoplasms. The draft technical report was peer-reviewed by an external panel in December 2019. While uncertain regarding the effect of perinatal exposure on hepatocellular carcinomas, the panel generally agreed with the report's conclusions. These NTP studies provide the most robust animal data on the carcinogenic activity of PFOA to date.

Typically, in characterizing the potential for human health impacts:

- NTP technical reports provide a general exposure comparison between animals and humans if exposure data are available.
- Previous assessments of carcinogenicity are included, whether animal studies or hazard assessments by federal or international institutions.
- Generally NTP *does not* state that the findings from a study are *directly related or not related* to human health outcomes, but may identify consistencies in results or purported mechanisms with those in the literature.

The questions for the BSC to consider were:

- What should be NTP's responsibility for relating specific NTP study outcomes, using PFAS as an example, to potential human health impacts?
- What can the NTP do to add value to the next phases of interpretation and application of data from NTP studies in the public health decision making processes?

### **9.1. Oral Public Comment**

Mr. Joseph Manuppello, a Senior Research Analyst with the Physicians Committee for Responsible Medicine, provided comments on the NTP studies. He said that the PFOA studies in rats used "an extraordinary number of animals," with a large number of litters generated. Citing a 2006 Organisation for Economic Co-operation and Development study that concluded clear carcinogenic activity of PFOA, and stating that it was conclusively known that PPAR $\alpha$  is species-specific and not applicable to human carcinogenicity, he questioned why NTP had chosen rats as its species for the studies.

Dr. Blystone agreed that the studies used many litters per dose group to populate the study, necessitated by the types of questions being addressed. He indicated that the usual 90-day dose selection studies were skipped to reduce the number of animals used.

### **9.2. BSC Discussion**

Dr. Ryan, the first discussant, mentioned that she had participated in the recent peer review of the draft technical report. She was impressed with the detailed review from both a scientific and technical perspective, as well as the messaging and interpretation provided by the peer reviewers. Dr. Ryan was struck by the challenges in (1) contextualizing the results, (2) extrapolating the study data to humans, and (3) communicating the results and interpretation to the public. She described several of the differences between the rodent results and humans, including differences in gender, differences in developing metabolism of animals during pre-weaning and post-weaning periods, difference in half-life between humans and rodents, and species differences in the relevance of PPAR $\alpha$  activation, and said that in communicating the findings, it is important to articulate what is known to be certain and what is uncertain.



Dr. Sass, the second discussant, indicated that her comments would center on communication and interpretation to help the public understand how the data can be used to inform public health decisions. She discussed the issue of tumor site concordance (i.e., across organs, across species) in terms of human relevance and noted that this may be intuitive for scientists but not for the public. She said that PPAR $\alpha$  is one mechanism, but probably not the only mechanism, and there are likely other target organs besides liver. She noted that “where NTP really shines” is data interpretation, particularly for helping the public and public health agencies use the data to understand when mechanisms are known or not known.

Dr. Berube, the third discussant, stated that if there is interest in helping in the public dialogue about PFAS and PFOA, there are several challenges that need to be addressed first. He had five recommendations, based his experience in communication with the public about toxicology.

- First, it should be determined if, when, and how much to communicate to the public.
- Second, it needs to be asked, “When should you take the lead in communicating material like this?”
- Third, there is the issue of linking animal studies to human impacts.
- Fourth, is the question of how much information is needed in the public dialogue.
- Fifth, technical findings can be misinterpreted, leading the public to wrong decisions. He noted that this is a big opportunity to initiate a strong public dialogue.

Dr. Blystone agreed that uncertainties and site concordance are challenges in communicating this material to the public. In terms of the report, he said there would be more effort to address potential discrepancies and inconsistencies with human health.

Dr. Felter said she appreciated NTP asking the questions about what the data mean for human health, and how the exposures relate to the actual human exposures, which are likely 6-7 orders of magnitude lower. She noted that EPA had recently published a paper stating that the PPAR $\alpha$  mode of action is not relevant to human health and thought it would be helpful to explore the human relevance of PPAR $\alpha$  further.

Dr. Sass responded to the comments about what the animals exposures were exposed to as opposed to real-world exposures. She said the reasons would be difficult to communicate without also providing the statistical justifications for that approach. She said it was a complicated issue.

Dr. Gamboa da Costa said he felt that the discussion was bordering on risk assessment, but the dialogue was important.

## **10. Adjournment**

Dr. Eaton said the discussion had been quite interesting, and pointed to the challenges of communicating science, including issues such as the relevance of modes of action such as PPAR $\alpha$ . He noted that the design of the animal studies necessitates the use of a large numbers of animals, and that there is a communication challenge involved. There are many classical issues in toxicology involved, and NTP is to be commended for its work on communicating the results of the studies.

Dr. Berridge thanked the board members for their help in thinking through “these meaty, complicated issues.” He noted the board’s consistency in recognizing the types of issues NTP should address, and said he appreciated the board’s comments, questions, and queries. He felt there was considerable support for the relevance of the issues and how to incorporate new ways of thinking along with the traditional approaches in NTP’s work.

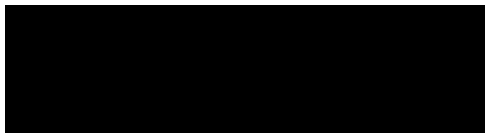
Dr. Woychik thanked all staff involved in coordinating the meeting. He said the meeting had covered a lot of ground, in regard to both the science and the communication considerations, such as communicating the science to the public in ways they could understand. He thanked the board members and Dr. Eaton for their contributions to the meeting.

Dr. Eaton thanked the board members and everyone involved. Dr. Wolfe thanked the board members for their participation.

Dr. Eaton adjourned the meeting at 4:15p.m.

### **11. Approval of the Summary Minutes by the NTP BSC Chair**

These summary minutes have been read and approved by the chair of the February 21, 2020 NTP Board of Scientific Councilors.



David Eaton, PhD, University of Washington

NTP BSC Chair

Date: June 23, 2020