U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA)
FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)
SCIENTIFIC ADVISORY PANEL (SAP)
PUBLIC VIRTUAL PEER REVIEW MEETING
SEPTEMBER 15-18, 2020

FIFRA SAP WEB SITE: https://www.epa.gov/sap
DOCKET ID NUMBER: EPA–HQ–OPP–2020–0263

MEETING LOCATION: Phone and Webcast
For Video Link and Audio Registration (to Receive call-in number) go to:
https://www.epa.gov/sap

[Please note that all times are approximate as noted at the end of the Agenda. Agency speakers may change based on availability.]

Title: U.S. Environmental Protection Agency Peer Review for:
The Use of New Approach Methodologies (NAMs) to Derive Extrapolation Factors and Evaluate Developmental Neurotoxicity for Human Health Risk Assessment

Day 1
Tuesday, September 15, 2020

10:00 A.M.	**Opening of Meeting –** Tamue L. Gibson, MS, Designated Federal Official, EPA, Office of Chemical Safety and Pollution Prevention (OCSPP), Office of Science Coordination and Policy (OSCP)
10:10 A.M.	**Introduction and Identification of Panel Members –** Robert E. Chapin, PhD, FIFRA SAP Chair
10:20 A.M.	**Greetings and Introduction from the Office Director and Division Director**– Edward Messina, Acting Office Director, EPA, Office of Pesticide Programs (OPP); Dana Vogel, Division Director, EPA, OPP, Health Effects Division (HED)
10:30 A.M.	**OPP Technical Presentation –Introduction and Overview of the Regulatory Use of the New Approach Methodologies (NAMs)** – Monique Perron, ScD, EPA, OPP, HED
TBD: 10:40 A.M.	**Welcome** – Alexandra Dapolito Dunn, Esq, Assistant Administrator, EPA/OCSPP
10:45 A.M.	**OPP Technical Presentation (Continued) –Introduction and Overview of the Regulatory Use of the New Approach Methodologies (NAMs); Developmental Neurotoxicity (DNT) Guideline and Regulatory Context for Organophosphate (OP) Case Study** – Monique Perron, ScD, EPA, OPP, HED

11:30 A.M.	**BREAK**
11:45 A.M.	**FIFRA SAP Discussion on OPP Technical Presentation**
12:15 P.M.	**LUNCH BREAK**
1:15 P.M.	**Introduction to DNT NAM Assay Development and the USEPA Network Formation Assay** – Tim Shafer, PhD, EPA, Office of Research and Development (ORD), Center for Computational Toxicology and Exposure (CCTE)
2:00 P.M.	**USEPA High Content Imaging (HCL) Cellular Event Assays for Assessing Chemical Effects on Neurodevelopment Processes** – Joshua Harrill, PhD, EPA, ORD, CCTE
2:40 P.M.	**Overview of International DNT NAMs Efforts** – Tim Shafer, PhD, EPA, ORD, CCTE
3:00 P.M.	**BREAK**
3:15 P.M.	**DNT-NAMs: Fit-For-Purpose, Results with Organophosphates, and Administered Equivalent Dose Comparison to *In Vivo* Benchmark Doses for Acetylcholinesterase Inhibition** – Katie Paul Friedman, EPA, ORD, CCTE
4:15 P.M.	**FIFRA SAP Discussion on ORD Technical Presentation**
4:45 P.M.	**Use of *In Vitro* Acetylcholinesterase Inhibition Data to Develop Data-Derived Extrapolation Factors** – Monique Perron, ScD, EPA, OPP, HED
5:15 P.M.	**FIFRA SAP Discussion on OPP Technical Presentation**
5:30 P.M.	**Adjourn**

Day 2
Wednesday, September 16, 2020

10:00 A.M. **Opening of Meeting –** Tamue L. Gibson, MS, Designated Federal Official, EPA, OCSPP, OSCP

10:05 A.M. **Panel Members: Follow-up from the Previous Day –** Robert E. Chapin, PhD, FIFRA SAP Chair

10:15 A.M. **OP *In vitro* Inhibition Program: Introduction to Testing Program –** Richard Reiss, ScD, GVP, Principal Scientist, Exponent

10:30 A.M. **Experimental Procedures and Results –** Janice Chambers, PhD, Professor, Mississippi State University

10:50 A.M. **Statistical Analysis of Data –** Kelly Higgins, PhD, Senior Scientist, Exponent

11:05 A.M. **Results of Supplemental Variability Study –** Richard Reiss, ScD, GVP, Principal Scientist, Exponent and Kristin Lennox, PhD, Managing Scientist, Exponent

11:20 A.M. **Biological Understanding of Interspecies and Intraspecies Variability –** Rudy Richardson, ScD, Professor, University of Michigan

11:40 A.M. **Wrap-Up –** Richard Reiss, ScD, GVP, Principal Scientist, Exponent

11:45 A.M. **FIFRA SAP Discussion on OP *In vitro* Inhibition Presentation**

12:15 P.M. **LUNCH BREAK**

1:00 P.M. **Public Comments**

- **Richard Reiss, ScD,** On behalf of the OP Coalition of Registrants **[10 minute comment]**
- **Kristie Sullivan, MS,** Physicians Committee for Responsible Medicine **[5 minute comment]**
- **Anna van der Zalm, MS,** People for the Ethical Treatment of Animals **[5 minute comment]**

1:20 P.M. **Charge to the Panel**

New Approach Methodologies for Development Neurotoxicity

Question 1. *For charge questions 1-3, the overall focus is on the ability of the developmental neurotoxicity (DNT)-new approach methodologies (NAMs) to evaluate important biological*

processes related to neurodevelopment. EPA is soliciting feedback on whether the NAMs adequately reflect the biology such that data may be incorporated into the assessment of a chemical's effects on neurodevelopment.

Using primary rat cortical neurons grown on microelectrode arrays (or MEAs), the EPA's Office of Research and Development has developed a network formation assay (NFA) to assess the potential impact of chemical exposure on neural network formation and function as described in Sections 2.3.1 - 2.3.4 of the Agency's Issue Paper. *Please comment on the strengths and limitations of using this assay to evaluate the biology underlying network formation as a component of neurodevelopment that may be susceptible to modulation by chemical exposure.*

2:30 P.M. BREAK

2:45 P.M. Charge Question 2

Question 2. The EPA's Office of Research and Development has used high content imaging (or HCI) with a variety of rat- and human-derived *in vitro* models to investigate the potential impact of chemical exposure on cell proliferation, apoptosis, neurite outgrowth, and synaptogenesis as described in Sections 2.3.1 - 2.3.4 of the Agency's Issue Paper. *Please comment on the strength and limitations of using the HCI assays to evaluate the biological processes underlying proliferation, apoptosis, neurite outgrowth and synaptogenesis as components of neurodevelopment that may be susceptible to modulation by chemical exposure.*

4:00 P.M. Charge Question 3

Question 3. As discussed in Section 2.1 of the Agency's Issue Paper, EPA has shifted its testing focus from the developmental neurotoxicity guideline study to more targeted testing due to several challenges associated with the study and its limited impact on human health risk assessments for pesticides. New approach methodologies (or NAMs) provide an opportunity to overcome some of these challenges by evaluating underlying critical processes of neurodevelopment and incorporating human relevant information. NAMs covering critical processes in neurodevelopment developed by EPA's Office of Research and Development and researchers funded by the European Food Safety Authority are presented in Table 3 and Figure 2 of the Agency's Issue Paper (Section 2.3.2). Based on this information and considering the goal of developing a NAM testing strategy or an integrated approach to testing and assessment (or IATA) within the next year for evaluating developmental neurotoxicity to inform chemical risk assessments, *please comment on whether this NAM battery reasonably evaluates the biology underlying the critical processes related to neurodevelopment that may be susceptible to modulation by chemical exposure.*

5:30 P.M. ADJOURN

Day 3
Thursday, September 17, 2020

10:00 A.M. **Opening of Meeting –** Tamue L. Gibson, MS, Designated Federal Official, EPA, OCSPP, OSCP

10:05 A.M. **Panel Members: Follow-up from the Previous Day –** Robert E. Chapin, PhD, FIFRA SAP Chair

10:20 A.M. **Charge to the Panel: Charge Question 4**

Question 4. Organophosphate pesticides share the ability to inhibit the acetylcholinesterase enzyme, which prevents the breakdown of acetylcholine leading to neurotoxicity. Inhibition of acetylcholinesterase is the basis of current OP human health risk assessments. In order to compare the relative sensitivity of the MEA NFA and HCI assay results to doses that inhibit acetylcholinesterase in laboratory animals, *in vitro* to *in vivo* extrapolation (or IVIVE) approaches were used to approximate NAM administered equivalent doses for a subset of organophosphate pesticides as described in Section 2.3.6. *Please comment on the strengths and limitations of this comparison and whether there are alternative approaches for this evaluation using the available data.*

Data-derived Extrapolation Factor's Using In Vitro AChE Inhibition Data

11:30 A.M. **Charge Question 5**

Question 5. *In vitro* acetylcholinesterase inhibition data have been generated for rats and humans to develop interspecies and intraspecies data-derived extrapolation factors (or DDEFs) for pharmacodynamics for 16 organophosphate compounds in accordance with EPA's 2014 *Guidance for Applying Quantitative Data to Develop DDEFs for Interspecies and Intraspecies Extrapolation*. The studies are briefly described in Section 3.2 of the Agency's Issue Paper and more details can be found in MRIDs 50773501 to 50773503. Please comment on the strengths and limitations of these data. *Please include in your comments a consideration of the study design and methods, appropriateness of the selected measures, sufficiency of reporting, and robustness of the in vitro acetylcholinesterase inhibition data, including sample size.*

12:30 P.M. **LUNCH BREAK**

1:15 P.M. **Charge Question 6**

Question 6. Given the structure of correlated data, nonlinear mixed-effects models were used to analyze the *in vitro* inhibition data in order to calculate the interspecies and intraspecies pharmacodynamic DDEFs as described in Section 3.2 of the Agency's Issue Paper and MRID 51182301. The ratios of the biomolecular rate constants between species or subpopulation were estimated from the nonlinear mixed-effects models, which are reported in Section 3.3 of the Agency's Issue Paper and MRID 51182301. For a number of chemical-specific datasets analyzed by Exponent, the fitted non-linear mixed model generated warning statements due to a full rank final Hessian matrix. Additionally, for several of the chemical-specific datasets

analyzed, visual evaluation of diagnostic plots revealed severe outliers or a severe imbalance in the distribution of residuals leading to questionable model fit. In an attempt to resolve the warning statements and outlier issues, EPA consulted with its statistical contractor at ICF, which submitted a supplemental analysis (see EPA Coversheet and ICF Statistical Analysis).

a. Please comment on the methods or techniques employed by Exponent using the nonlinear mixed-effects models.

b. Please comment on any concerns associated with the warning statements and model-fit issues. Taking into consideration the supplemental ICF analysis to address these issues, suggest, if necessary, other methods or techniques that could be suggested for addressing such warning statements and model-fit issues.

3:00 P.M. **BREAK**

3:15 P.M. **Charge Question 7**

Question 7. For the intra-species analyses, Exponent conducted stratified analyses, where the 18 human samples were subset into smaller groups to estimate the bimolecular rate constant ratios for these subgroups as described briefly in Sections 3.2 and 3.3 of the Agency's Issue Paper, with more details provided in MRID 51182301. EPA has concerns with the reliability of these stratified analyses due to the small sample sizes of the subgroups, as well as concerns with warning statements and outliers. EPA's statistical contractor, ICF, provided a supplemental analysis to address the warning statement and outlier issues (see EPA Coversheet and ICF Statistical Analysis). *Please comment on these intraspecies analyses performed by Exponent and their utility to evaluate intraspecies human variability in response to organophosphate exposure taking into consideration the sample sizes and the supplemental ICF analysis.*

5:30 P.M. **Adjourn**

Day 4
Friday, September 18, 2020

10:00 A.M.	**Opening of Meeting –** Tamue L. Gibson, MS, Designated Federal Official, EPA, OCSPP, OSCP
10:05 A.M.	**Panel Members: Follow-up from the Previous Day –** Robert E. Chapin, PhD, FIFRA SAP Chair
10:20 A.M.	**Charge Question 8**

Question 8. For intraspecies analyses, a limited subset of chemicals had three replicate analytical results on each of the four sources of human samples. The results from these analyses were used by Exponent to characterize the total variability of the estimates in terms of experimental variability and subject variability as described briefly in Sections 3.2 and 3.3 of the Agency Issue Paper with more details provided in MRID 51182301. The results were not consistent across the chemicals, ranging from 3% to 84% of the total variability due to differences in the replicate analyses.

a. Please comment on the utility of these analyses to characterize human variability in response to organophosphate exposure.

b. If there is utility in generating these data for additional OPs, please provide any suggestions for improving the design and conduct of the study.

11:45 A.M.	**Closing Remarks –** Robert E. Chapin, PhD, FIFRA SAP Chair & Other Panel Members
12:00 P.M.	**Adjourn**

Please be advised that agenda times are approximate; when the discussion for one topic is completed, discussions for the next topic will begin. For further information, please contact the Designated Federal Official for this meeting, Tamue Gibson, MS, via email: gibson.tamue@epa.gov.