UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
National Health and Environmental Effects Research Laboratory
Toxicity Assessment Division (MD-B105-04)
Research Triangle Park, NC 27711

OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

DATE: November 3, 2016

SUBJECT: Reconciliation Memorandum on Review of *Standard Evaluation Procedures for Submitted Developmental Neurotoxicity Data*

FROM: Virginia C Moser
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TO: Virginia Houk
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The developing nervous system is known to be especially vulnerable to environmental agents, which may produce long-lasting neurodevelopmental alterations in early to adult life. For these reasons, the US EPA and OECD have promulgated testing guidelines for developmental neurotoxicity (DNT), the basic purpose of which is to act as an initial assessment and screen for the potential of chemicals to cause adverse outcomes on nervous system function and structure. These test guidelines have been/will be included in the testing of a number of environmental agents.

As with all guideline-based testing, data interpretation is first done by the submitting company/ organization as part of the final study report, followed by independent reviews by the regulatory agencies. DNT studies present some challenges in interpretation, especially for people not trained in the area. Recent interactions between international regulatory agencies have highlighted a need for procedures to support consistent interpretation of the results from DNT studies, especially since differences across countries in regulatory decisions involving DNT data have led to trade barriers for imports/exports of some chemicals. As a NAFTA-inspired multi-governmental initiative, experts from US EPA (ORD, OLEM, OCSPP) and PMRA (Pest Management Regulatory Agency) of Health Canada in 2012 formed a working group to create this document that would serve as an internal guidance document for regulatory evaluators. These standard evaluation procedures (SEPs) address each of the neurobehavioral endpoints in DNT studies conducted according to US EPA and OECD test guidelines. For each, there is a description of the behavior itself followed by pragmatic explanations of what to look

for in the data and what it can mean. The focus of this document is how to evaluate the quality, conduct, and resulting data derived from these behavioral methods: the document is not intended to critique the specific test methods in the guidelines or to suggest alternative methods.

While this was initially termed an internal guidance document for regulatory evaluators, it has since become apparent that it may be made publicly available by Health Canada, NAFTA, and/or OPP/OCSPP. In March 2016 NHEERL management determined that this document would be classified as Influential Scientific Information. As such, external peer review was solicited from four expert neurotoxicologists: one from another federal agency, one from a consulting company, and two from academia. The resulting reviews totaled 40 single-space pages, and all comments and corrections have been addressed and the SEP document revised accordingly.

None of the reviewers had comments that these evaluation guidelines were "wrong"; instead, the many comments addressed improvements and minor corrections. Some of the comments suggest that the reviewers were not fully cognizant that much of the submitted data is very problematic and almost none are published – that is the exact reason these SEPs were written. Several reviewers spent considerable time recommending specific equipment and experimental procedures that are not part of the DNT guidelines. In addition, one reviewer wrote many pages about how to conduct these studies and the methods he uses in his laboratory. While these are reasonable comments, they are not germane to the purpose of this document, which is to help the regulatory reviewer understand and interpret data that are submitted. The reviewer cannot dictate experimental practices, testing equipment, or alter the existing guideline requirements. Comments along these lines were considered but in some cases no changes were made. A number of comments dealt with clarifying information and corrections for which revisions were straightforward. Finally, statements that were complimentary but did not provide specific comments/questions were only briefly summarized in the response to reviewers.

We thank the four reviewers for the time and effort put into their thoughtful and thorough reviews. Their substantial contributions have improved the clarity and usefulness of the document. The following are all the reviewers' comments and our responses. The reviewers' comments have been edited/modified to decrease the 40 pages to a somewhat reasonable length; however, the essence and intent of all comments have not changed. Our responses follow each individual comment.

Accompanying this response to reviewers is the original document with major changes indicated using tracked changes, as well as the document with all changes accepted. Please note that final formatting corrections are being made at the same time as this clearance package to avoid yet more delays. Finally, we feel that this extensive review has greatly improved the document and trust that it will be cleared and released in a timely manner. Please contact me or any of the authors if there are any questions or comments.