REVIEWER #2

Peer Review:
Standard Evaluation Procedures for Submitted Developmental Neurotoxicity Data - Draft

Overall Charge Questions

- Does the document provide enough information on why and when the guidance should be used? If not, how could it be improved?

The title and Introductory page and table are probably sufficient, but if not an additional two sentences could be added at the bottom of the introduction to specify the purpose of the document.

- What limitations, if any, do you find in the document that would hinder data review and interpretation of DNT studies conducted using the EPA or OECD DNT Guidelines?

Nothing in the draft would specifically hinder data review or interpretation of DNT study reports.

Module A – Observations

- Does the document provide sufficient guidance to assist regulatory scientists in reviewing reports to determine whether critical details regarding procedure, study design, results (including summary and individual data for all relevant parameters), and statistical evaluation are included in the reports for studies conducted under the EPA or OECD DNT Guidelines? If not, why not?

The Observations module provides sufficient guidance to help the regulatory reviewer identify the critical details regarding procedure, study design and results. Few details on statistical evaluation of the observational data are provided; additional information could be helpful.

- Given that regulatory reviews are conducted independent of any review or interpretation presented by the study authors: does the document provide sufficient guidance to assist regulatory scientists in interpreting the data and results from regulatory studies conducted under the EPA or OECD DNT Guidelines? If not, why not?

In general the observations module provides useful guidance for interpretation of the observational data and results from the DNT studies. The Data Checks section is terrific at providing context for evaluation of specific types of data. The Data Interpretation section raises some interesting points, but it isn't clear what the reviewer should do with some of the information. For example, in the next to the last paragraph on page A10, pups are assumed to receive a "highly toxic" dose that elicited convulsions. The text indicates that "…if the pups survive, behavioral changes into adulthood may be expected." It is not clear what the issue is here. Was the dose excessive, such that convulsions would not be expected from an appropriate maximum dose, or do we assume that if the pups live, the dose was appropriate

and the only concern is the effect on behavior later in life? Is there any guidance for the reviewer to decide whether the "highly toxic" dose was appropriate or not?

- Does the document provide the correct summary of the kinds of information to look for in submitted data, provide relevant examples, and assist in interpretation of any treatment-related changes?

There could be a few more specific examples in this section, but it is not bad.

Module B Motor Activity

- Does the document provide sufficient guidance to assist regulatory scientists in reviewing reports to determine whether critical details regarding procedure, study design, results (including summary and individual data for all relevant parameters), and statistical evaluation are included in the reports for studies conducted under the EPA or OECD DNT Guidelines? If not, why not?

Yes. The Motor Activity module provides detailed and specific guidance to help the regulatory reviewer identify the critical details regarding procedure, study design, and results. The section on statistical evaluation of motor activity is particularly good and thorough, as is the discussion of habituation.

- Given that regulatory reviews are conducted independent of any review or interpretation presented by the study authors: does the document provide sufficient guidance to assist regulatory scientists in interpreting the data and results from regulatory studies conducted under the EPA or OECD DNT Guidelines? If not, why not?

Yes, the Motor Activity module does include sufficient guidance that a regulatory scientist could interpret the data and results without reading the interpretation from the study author.

- Does the document provide the correct summary of the kinds of information to look for in submitted data, provide relevant examples, and assist in interpretation of any treatment-related changes?

Yes, the Motor Activity module does describe in detail the types of information the reviewer should look for in submitted data and provides good examples of data to support the interpretation of treatment related changes. The habituation example data in Figure 2 on page B-18 is excellent in showing the different patterns of habituation, but are all of these patterns from one test material? The doses are labeled dose 1 through dose 4, but it isn't clear whether these are all the same test material or not. The fact that they are all on the same graph and have the same label suggests that each line represents a different dose level of one test material, but if so, I would not know whether to believe the data or not, so I don't know if the reviewer would know either. Hopefully these are just examples that support collecting and analyzing ambulatory data in 10 minute bins.

Module C Acoustic / Auditory Startle Response

- Does the document provide sufficient guidance to assist regulatory scientists in reviewing reports to determine whether critical details regarding procedure, study design, results (including summary and individual data for all relevant parameters), and statistical evaluation are included in the reports for studies conducted under the EPA or OECD DNT Guidelines? If not, why not?

Yes. The Acoustic / Auditory Startle Response module provides detailed and specific guidance to help the regulatory reviewer identify the critical details regarding procedure, study design, and results. The detailed technical discussions of the testing equipment and the testing procedures are particularly good and thorough. The statistical models section was very clear, specific and straightforward.

- Given that regulatory reviews are conducted independent of any review or interpretation presented by the study authors: does the document provide sufficient guidance to assist regulatory scientists in interpreting the data and results from regulatory studies conducted under the EPA or OECD DNT Guidelines? If not, why not?

Yes, the Acoustic Startle Response module does include sufficient guidance that a regulatory scientist could interpret the data and results without reading the interpretation from the study author. The section on the use of positive control data in study data interpretation was important.

- Does the document provide the correct summary of the kinds of information to look for in submitted data, provide relevant examples, and assist in interpretation of any treatment-related changes?

Yes, the Acoustic Startle Response module does describe in detail the types of information the reviewer should look for in submitted data and provides excellent examples of data to support the interpretation of treatment related changes. The auditory startle response data in Table 4 on page C-20 and the accompanying explanation of instrument calibration and sensitivity is very nice. Figure 5 on page C-24 and the accompanying explanation is a terrific example of the importance of analyzing the data from males and females together using a model that has gender nested in the litter. Table 6, Potential interpretation of some common problems for startle results found in DNT study reports, is a handy guide for troubleshooting the data that can help a reviewer do a quick reality check when it seems that something has gone wrong.

Module D Learning and Memory

- Does the document provide sufficient guidance to assist regulatory scientists in reviewing reports to determine whether critical details regarding procedure, study

design, results (including summary and individual data for all relevant parameters), and statistical evaluation are included in the reports for studies conducted under the EPA or OECD DNT Guidelines? If not, why not?

Yes. The Learning and Memory module provides detailed and specific guidance to help the regulatory reviewer identify the critical details regarding procedure, study design, and results. The descriptions of each test are detailed, well-organized, and easy to follow. The statistical evaluation procedures described are sufficient for the reviewer to follow, but there might be a suggestion in this section for the reviewer to seek the help of a statistician if the analyses provided in the report are not clear, or may not be adequate.

- Given that regulatory reviews are conducted independent of any review or interpretation presented by the study authors: does the document provide sufficient guidance to assist regulatory scientists in interpreting the data and results from regulatory studies conducted under the EPA or OECD DNT Guidelines? If not, why not?

Yes, the Learning and Memory module does include sufficient guidance that a regulatory scientist could interpret the data and results without reading the interpretation from the study author. Each test method summary includes sufficient information to allow the reviewer to understand what the testing apparatus looks like, how the test is done, what data to expect, and how to interpret the data.

- Does the document provide the correct summary of the kinds of information to look for in submitted data, provide relevant examples, and assist in interpretation of any treatment-related changes?

Yes, the Learning and Memory module does describe in detail the types of information the reviewer should look for in submitted data and provides very good examples of testing methods and study data to support the interpretation of treatment related changes. The lists of data to be reported for each test method are especially useful.

Module E Data Considerations and Integration (WOE Module)

- Is this weight-of-evidence chapter consistent with the presentations from the rest of the document? Does it present a logical approach to integrating data from different behavioral endpoints to make scientifically justified conclusions?

1. The Weight of Evidence chapter is far less specific than the rest of the document in describing how to integrate DNT data.
2. Section 3.1.3, Determining Biological Significance seems inconsistent with the sections on biological significance in Modules B and C.
3. Section 5, on Human relevance seems of little use in evaluation of the DNT data.

4. The conclusion section is fine, but the last bullet may require the reviewer to rely on some of the “interpretation” text from the study author unless other study reports are readily available to the reviewer, and sufficient time is available to get information from other study reports.