EPA's Interagency DNT Study Review Guidance

Charge Questions

Background Information and Goals:

The developing nervous system is known to be especially vulnerable to many environmental contaminants (Grandjean and Landrigan 2006; NRC 1993; Rodier 1995; Spyker 1975), and exposures may result in altered neural development at lower doses or with consequences that may be quite unlike the chemical's effects in an adult nervous system (Grandjean and Landrigan 2006; NRC 1993; Rodier 1995; Spyker 1975). For these reasons, regulatory agencies (OECD 2007; U.S.EPA 1998a) have promulgated testing guidelines for developmental neurotoxicity (DNT). DNT refers to any adverse effect of exposure to a toxic substance on the normal development of nervous system structures and/or functions (U.S.EPA 1998b). The basic purpose of DNT guideline testing is to act as an initial assessment and screen for the potential of chemicals to cause adverse neurodevelopmental outcomes.

The full history of the development, validation, acceptance and use of DNT testing has been reviewed previously (Makris et al. 2009; Raffaele et al. 2010; Tsuji and Crofton 2012). Briefly, the design and test specifics of the US EPA test guidelines were developed at a workshop held in 1989, following which the specific guideline was developed and eventually finalized in 1998 (U.S.EPA 1998a). The OECD updated this guideline (OECD 2007) to include enhancements developed through discussion and international agreement. More recently, OECD included a limited number of DNT endpoints in the Extended One Generation Reproductive Toxicity Study Guideline (OECD 2011). A number of papers have compared these guidelines (Hass 2006; Ladics et al. 2005; Makris et al. 2009; Makris and Vorhees 2015; Piersma et al. 2012; Tsuji and Crofton 2012).

As with all guideline-based testing, data interpretation is first done by the submitting company/organization as part of the final study report submission. In addition to data summaries and interpretation by the study authors, regulatory submissions include detailed procedural information and all study data, including both summary and individual animal data for all measured parameters. Upon receipt of the study report, regulatory agencies conduct their own review of the summary and individual data. *Important to note is that regulatory reviews are conducted independent of any review or interpretation of the data presented by the study authors.* Interpretation of results by Agency reviewers may, or may not, agree with the study submitter's conclusions. Over the past two decades a number of reports have been written to provide assistance in the interpretation of the data resulting from DNT studies (Cory-Slechta et al. 2001; Elsner et al. 1986; Francis et al. 1990; Holson et al. 2008; Li 2005; Makris et al. 2009; Slikker et al. 2005; Tilson and Wright 1985; Tyl et al. 2008; U.S.EPA 1998b; Vorhees and Makris 2015). Recent interactions between international regulatory agencies have highlighted a need for procedures to support consistent interpretation of the results from DNT for use in risk decisions. The interpretation of the behavioral data is the most inconsistent between agencies, and brought into question why different agencies were deriving different interpretations from the same datasets. As a result of these international concerns, Health Canada and the US EPA developed

guidance on the review and interpretation of submitted DNT data. **Thus, the focus of this document is to provide guidance on how to evaluate the quality, the conduct, and resulting data derived from the behavioral methods employed in the OECD and EPA DNT Guidelines.**

This guidance provides information for regulatory agency scientists who perform internal reviews of the behavioral test data that result from the use of the EPA and/or OECD DNT Guidelines studies, especially those who may not be experts in neurotoxicity or developmental neurotoxicity. The guidance was generated by an international collaboration between Health Canada and the US EPA. The overall goal of the guidance is to foster better and more consistent consensus-based reviews of DNT behavioral data between these two countries. This guidance may also be useful for other international regulatory agencies.

Notes:

1) This review is restricted to evaluation of the guidance provided on the interpretation of submitted behavioral data from studies conducted under Good Laboratory Practices (GLP) by sponsoring companies or contract laboratories. *This document is in no way intended to review the test methods recommended in the Guidelines, or to suggest alternative methods*.
2) This document is divided into separate modules for each of the specific behavioral tests included in the test guidelines (motor activity, acoustic startle, learning and memory, and functional observations). In order to be most useful for the regulatory reviewer, the document focuses on and describes only those methods that are most often used by industry in submitted regulatory Guideline studies. This document does not include all the potential experimental approaches to assess these behaviors.

Charge Questions:

In your review of this document, please provide written responses to the following questions. Additional comments and recommendations for improving this document are also welcome.

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?

- 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?

Module Specific Charge Questions

<u>Modules 1-4</u>

- 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?

- 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?

- 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?

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?

References

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