

European Stakeholder Workshop on New Approach Methodologies for Developmental Neurotoxicity (DNT) *Health Canada (PMRA) Perspective*

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Disclaimer

The views expressed in this presentation are those of the presenters and do not necessarily reflect the views or policies of Health Canada or the Pest Management Regulatory Agency.

Regulation of Chemicals in Canada

- In Canada, regulation of chemical substances at the federal level falls under the responsibility of Health Canada and Environment and Climate Change Canada and is governed under several legislations to protect human health and the environment.
- Health Canada uses a variety of approaches to conduct science-based assessments, including screening, prioritization, hazard identification and both qualitative and quantitative risk assessments.
- Health Canada's Pest Management Regulatory Agency (PMRA) is responsible for pesticide regulation in Canada.
 - The PMRA conducts risk-based health assessments to protect human health and the environment (PMRA, 2021)
 - Most pesticide risk assessments are quantitative and rely on reference values that are established by selecting the most appropriate points of departure from animal toxicity studies and application of relevant uncertainty factors to protect all populations including vulnerable groups. Pest control products are considered acceptable for registration if exposure levels are below these reference values.

Health Canada's Current Approach to DNT Assessment

- Health Canada has a broad regulatory landscape with different branches involved in regulating a wide variety of chemicals.
- Each branch of Health Canada has their own specific regulatory requirements.
- Not all branches require the routine assessment of developmental neurotoxicity (DNT) potential.
- However, some legislation, including the *Pest Control Products Act* (PCPA), allows Health Canada to request data to assess the developmental neurotoxic potential of chemicals when sufficient concern for neurotoxicity is identified.

Health Canada's PMRA - Current Approach to DNT Assessment

The PMRA requires an extensive battery of toxicity studies to support pesticide registration. DNT data are required if neurological effects are noted in other animal toxicity studies, and may be requested if the active ingredient:

- Demonstrates neuropathology or neurotoxicity in adult animals;
- Is hormonally active in vivo; or
- Induces other types of nervous system involvement at a developmental stage.

When required, the potential of pesticides to induce developmental neurotoxicity is assessed based on the results from:

- In vivo guideline DNT study (OECD TG 426 or US EPA OPPTS 870.6300 (1998)) [when available];
- Neurotoxicity cohort from the in vivo extended one-generation reproductive toxicity study (OECD TG 443) [when available];
- Guideline in vivo neurotoxicity studies; and/or
- USEPAs developmental thyroid toxicity study [when available].

How Does the In Vivo DNT Study Meet the PMRA's Regulatory Needs?

- To date > 50 in vivo DNT studies have been submitted to the PMRA.
- The endpoints from these studies have been used as the point of departure for establishing reference values when they have been determined to represent a critical endpoint for risk assessment.
- The PMRA recognizes the limitations of the current in vivo testing paradigm for DNT, which can include high variability in the data, low sample sizes/statistical power, inconsistencies in methods used, and use of less sensitive assays.
- Despite the limitations, in vivo DNT studies have played an important role in PMRA's quantitative risk-based health assessments.

Health Canada's Regulatory Perspective on NAMs

- Health Canada is involved in several initiatives related to IATA (Integrated Approaches to Testing and Assessment), NAMs (New Approach Methodologies) and ongoing development of test guidelines.
- A Canadian regulatory perspective on next generation risk assessments for pest control products and industrial chemicals was recently published (Bhuller *et al.*, 2021).
- Health Canada researchers are contributing to NAM development
 - e.g., involvement in the OECD DNT zebrafish sub-group, which is exploring development of a zebrafish behavioural model.
- The PMRA has an ongoing project to explore how the DNT NAMs and/or IATA might be useful for integration into the Canadian pesticide regulatory process.
- The PMRA also participates in the OECD DNT Working Group, which is exploring the development of a DNT in vitro battery (IVB) and draft guidance on application and interpretation of the battery.

Health Canada's Potential Use of DNT NAMs

- International regulatory requirements for pesticides have resulted in a data-rich environment
 - PMRA relies primarily on a full complement of guideline in vivo toxicity studies to set reference values that feed into human health pesticide risk assessments.
- To date, the PMRA has used alternative approaches such as in silico (e.g. QSAR) and in vitro assays, primarily as part of a weight of evidence (WoE)/IATA approach and/or to better understand a chemical's mode of action.

Health Canada's Potential Use of DNT NAMs

- Health Canada acknowledges the utility of additional tools that are being developed to characterize the developmental neurotoxicity potential of regulated chemicals, including pesticides.
 - In the near future, Health Canada envisions being able to use these additional tools for hazard identification, prioritization and screening assessments, as part of a WoE approach, and to inform targeted in vivo testing.

Current Challenges with DNT NAMs from a Canadian Regulatory Perspective

- A limited number of laboratories have the expertise to conduct the assays that have been developed to date, which can lead to challenges with
 - Transferability between laboratories
 - Validation process to ensure intra- and inter-laboratory consistency
- Many of the current DNT NAMs appear to have been designed to minimize false positives; from a regulatory perspective, there is a need for balance between false negatives and positives.
- Currently available DNT NAMs do not provide complete coverage of neurodevelopmental processes, which may lead to challenges with the degree of confidence in negative findings in the context of hazard-based assessments.
- Current lack of internationally accepted guidance on IVIVE procedures and models for extrapolating results from in vitro DNT assays to an in vivo equivalent dose that can be used in a quantitative risk assessment.

Considerations Moving Forward with Use of DNT NAMs

- On-going efforts for the development of a common database for results from DNT NAMs, including the OECD DNT IVB, will increase regulatory confidence.
- There is value in comparing the results of DNT NAMs with the findings from available guideline in vivo DNT studies.
 - Although divergent results are not unexpected, this exercise may assist in understanding the scientific basis for these differences, and lead to increased regulatory confidence in the outcome of the in vitro NAMs.
 - This knowledge could also lead to more targeted in vivo DNT testing strategies.
- Further guidance on integration and interpretation of data from DNT NAMs and potential for a tiered testing strategy would increase regulatory uptake.

Health Canada's Future Use of DNT NAMs

- Health Canada will continue to explore how DNT NAMs can be incorporated into current Canadian risk assessment paradigms, while ensuring regulatory needs are still met.
- Near future: Potential for use in hazard identification, prioritization and screening assessments, as part of WoE considerations, and to inform targeted in vivo testing.
- Longer-term: Support development of internationally accepted guidance and models for extrapolating in vitro results to equivalent effect levels in vivo to allow use in quantitative risk assessments.
- The acceptance and reliance of DNT NAMs by the international regulatory community will impact the amount of data generated and progress made for consideration of these data in the context of quantitative health risk assessments.

Conclusions

- Health Canada acknowledges the different needs that exist for various regulatory programs and regulated chemical sectors.
- Going forward, the development of DNT NAMs and testing strategies that will meet these diverse regulatory needs is critical.
- Health Canada's PMRA is encouraged by the progress made on the development of DNT NAMs, including the OECD DNT IVB, and the draft OECD guidance document on application and interpretation of the DNT IVB.
- Health Canada will continue to explore how the DNT NAMs and/or IATA may be useful for integration into the Canadian pesticide regulatory process.

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