OECD/EFSA Workshop on Developmental Neurotoxicity (DNT): the use of non-animal test methods for regulatory purposes

Brussels, 18-19 October 2016

Workshop Objectives

- Develop consensus on which testing battery of alternative DNT methods could be applied right now and used in a fit for purpose manner for each of the following:
  - Chemical screening for prioritisation, or;
  - Hazard identification for specific chemical risk assessment.
- Depending on the level of readiness of the alternative test methods, identify what next steps are needed to encourage the regulatory use of the alternative methods (e.g. more precise test method description; better definition of limitations and applicability domain; frameworks for defining "fit for purpose"; Test Guideline Development) either individually or in combination.
- Outline what could become an integrated approach to testing and assessment (IATA) for the purposes for screening and prioritisation or for hazard assessment.

Programme

Overall Chairperson | Ellen Fritsche, *IUF - Leibniz Research Institute for Environmental Medicine (DEU)*
Overall Rapporteur | Kevin Crofton, *U.S. Environmental Protection Agency (USA)*

DAY 1 | TUESDAY, 18 OCTOBER 2016

07.45-08.30	**Registration**	
SESSION 1 | OPENING ADDRESS		
08.30-08.50	**Welcome and introduction to the event**	**Anne Gourmelon**, *Organisation for Economic Co-operation and Development (OECD)* **Thorhallur Halldorsson**, *University of Iceland on behalf of European Food Safety Authority (EFSA)*
08.50-09.20	**Alternative Test Methods for Developmental Neurotoxicity: A History and Path Forward** *Questions*	**Kevin Crofton**, *U.S. Environmental Protection Agency (USA)*
SESSION 2 | What can be learned from regulatory authorities regarding DNT data requirements and testing strategies based on alternative DNT assays?		
09.20-09.40	**EU regulatory perspective with special focus on pesticides** *Questions*	**Roland Solecki**, *German Federal Institute for Risk Assessment (DEU)* & **Susanne Hougaard Bennekou**, *The Danish EPA (DNK)*
09.40-10.00	**Developmental neurotoxicity under the REACH** *Questions*	**Hannele Huuskonen**, *European Chemicals Agency (ECHA)*
10.00-10.30	**COFFEE / TEA BREAK**	
10.30-10.50	**US regulatory perspective with special focus on pesticides** *Questions*	**Elissa Reaves**, *U.S. Environmental Protection Agency (USA)*
10.50-11.10	**US Regulatory Perspective on Developmental Neurotoxicity Testing with Special Focus on Endocrine Disrupting and Industrial Chemicals** *Questions*	**Stanley Barone Jr.**, *U.S. Environmental Protection Agency (USA)*

SESSION 3 | What can be learned from industry's experience with DNT testing strategies based on alternative assays?		
11.10-11.30	**EU industry perspective: Emphasis on Pesticides** *Questions*	**Gaby Schmuck** *representing European Crop Protection Association (BEL)*
11.30-11.50	**U.S. Industry Perspective: DNT Testing Strategies Based on Alternative Assays** *Questions*	**Sue Marty** *DOW (USA)*
SESSION 4 | Why should we encourage the use of DNT testing strategies based on non-animal test methods?		
11.50-12.10	**Perspectives on how the Adverse Outcome Pathway (AOP) concept informs the use of *in vitro* DNT data for regulatory purposes** *Questions*	**Anna Price**, *European Commission Joint Research Centre (JRC)*
12.10-12.30	**How to link test systems to the prediction of developmental neurotoxicity (DNT)** *Questions*	**Marcel Leist**, *University of Kostanz (DEU)*
12.30-13.30	**LUNCH BREAK**	
SESSION 5 | Discussion Group (DG) sessions: OECD case studies for potential testing strategies based on non-animal test methods and a draft framework for building a DNT testing battery		
13:30—14:00	**Introduction to OECD case studies for potential testing strategies and a draft framework for building a DNT testing battery** *Questions*	**Ellen Fritsche**, *IUF - Leibniz Research Institute for Environmental Medicine (DEU)*
14:00-16:00	**DG session 1 | The regulatory need** DG Chairperson | **Roland Solecki**, *German Federal Institute for Risk Assessment (DEU)* DG Rapporteur | **Martin Wilks**, *University of Basel (CHE)* *1. Define a general DNT-based problem formulation for risk assessment of chemicals under the different regulations.* *2. What is needed to achieve regulatory acceptance of alternative methods for DNT to be applied for screening and prioritisation?* *3. What types of data from alternative DNT methodologies can be used to inform regulatory needs for hazards identification of different chemical classes?* *4. How we can justify the need for a mandatory tiered approach (e.g. for specific classes of pesticides) for conducting in vitro and (targeted) in vivo DNT studies?* *5. What input do scientists need from the risk assessors and risk managers to help guide development of in vitro methods?* **DG session 2 | Proposing a draft DNT testing battery** DG Chairperson | **Antonio Hernandez-Jerez**, *University of Granada School of Medicine (ESP)* DG Rapporteur | **Anna Price**, *European Commission Joint Research Centre (JRC)* *Based on the background document provided, and different regulatory needs, recommend a testing battery based on alternative DNT methods considering the following items:* *1. What are the criteria for combining assays to create ITS/IATA for different regulatory purposes to identify compounds with DNT potential?* *2. How to improve readiness and standardisation of available in vitro assays?* *3. How AOP concept can assist assay selection for DNT testing?* *4. How to overcome major limitations of alternative approaches?*	

	DG session 3 | *How can knowledge from new DNT tests contribute to epidemiology and vice versa?* DG Chairperson | **Stanley Barone Jr.**, *U.S. Environmental Protection Agency (USA)* DG Rapporteur | **Marcel Leist**, *University of Kostanz (DEU)* *How can in vitro methods contribute to the following issues:* *1. Building confidence in a scientific argument based on mode of action leading to adverse effects, supporting epidemiological observations (AOP and other tools)* *2. Identification of DNT hazards from chemicals present in environmental samples (e.g. diesel exhaust)* *3. Characterisation of the hazard level of suspected toxicants* *4. Hazard ranking of related compounds – relation to exposure* *5. Identification of potential toxic mechanisms* *6. Identification of biomarkers for toxicants - relation to exposure (biomonitoring)* *7. Comparison of species susceptibility* **DG session 4 | Implementing a draft DNT testing battery** DG Chairperson | **Susanne Hougaard Bennekou**, *The Danish EPA (DNK)* DG Rapporteur | **Elissa Reaves**, *U.S. Environmental Protection Agency (USA)* *If the proposed draft testing battery is deemed adequate for considered use, then:* *1. What is necessary to apply the testing paradigm as a screening tool as a first step for DNT?* *2. Depending on the intended use, which are the critical methodological gaps that can be identified?* *3. What additional work is needed for the regulatory implementation of the methodologies in the evaluation of DNT-related hazards for single chemical entities or (relevant) chemical classes?* *a) More in-vitro screening testing (i.e. define specificity and sensitivity)?* *b) Mechanistic validation (i.e. transcriptome analysis, pathways)?* *c) What are the appropriate steps of a road map?* *d) Can regulators agree on this road map and how to implement it?*
16:00-16:30	**COFFEE / TEA BREAK**
16:00-18:00	**DG sessions: case studies continued**
18.00-19.30	**NETWORKING COCKTAIL**

DAY 2 | WEDNESDAY, 19 OCTOBER 2016

SESSION 6 | Reports from Discussion Group (DG) sessions		
08.30-08:50	**Report from DG session 1**	**Martin Wilks**, *University of Basel (CHE)*
08.50-09.20	**Report from DG session 2**	**Anna Price**, *European Commission Joint Research Centre (JRC)*
09.20-09.40	**Report from DG session 3**	**Marcel Leist**, *University of Kostanz (DEU)*
09.40-10.00	**Report from DG session 4**	**Elissa Reaves**, *U.S. Environmental Protection Agency (USA)*
10.00-10.30	**COFFEE / TEA BREAK**	
10.30-12.00	**Discussion on DG reports/outcomes**	**Kevin Crofton**, *U.S. Environmental Protection Agency (USA)*
12.00-12.30	**Conclusions and recommendations**	**Ellen Fritsche**, *IUF - Leibniz Research Institute for Environmental Medicine (DEU)* & **Kevin Crofton**, *U.S. Environmental Protection Agency (USA)*
12.30-13.00	**Closing remarks**	