International STakeholder NETwork (ISTNET) for Creating a Developmental Neurotoxicity Testing (DNT) Roadmap for Regulatory Purposes

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Advances in neurobiology, coupled with the rise in developmental and adult neurological disorders, have prompted calls for increased testing of chemicals, food additives, and drugs for adverse impacts on the developing brain. New methods (including *in vitro* human stem cell-derived models), hold great promise for more efficient and predictive models for developmental neurotoxicity (DNT) and can be used in an integrated manner to solve regulatory challenges. In order to define a regulatory need for predictive models of DNT and develop a road map for an integrated testing strategy (ITS) for DNT in the context of regulatory requirements, there needs to be truly effective communication and discussion between various stakeholders (regulators, industry, and academia). To establish this, the first meeting of the International STakeholder NETwork (ISTNET) was held in Zurich on January 23-24, 2014 to build consensus on development and use of *in vitro* methods to deliver useful data for regulatory decisions.

The meeting included 28 participants from 10 countries. Participants included experts in the regulation and management of risk (Organisation for Economic Co-operation and Development, OECD; European Food Safety Authority, EFSA; Danish Environmental Protection Agency, Danish EPA; US Environmental Protection Agency, US EPA; Environment Agency Austria, Federal Office of Public Health of Switzerland, Regulatory Science Association of the UK, Bayer, Nestlé) as well as experts in the fields of neurotoxicity and developmental neurotoxicity (Center for Alternatives to Animal Testing Europe and USA, CAAT-Europe and CAAT-USA; European Union Reference Laboratory for Alternative Methods to Animal Testing, EURL-ECVAM; Finnish Centre for Alternative Methods, FICAM; Swiss Centre for Applied Human Toxicology, SCAHT; Centre for Xenobiotic and Environmental Risk Research, XERR; Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany, and GreenTox of Switzerland).

Discussions at the meeting started with a review of animal-based test methods currently used for developmental and adult neurotoxicity evaluation for regulatory purposes and a discussion of government and industry perspectives on the use of such information in risk decisions. There was consensus at the meeting that these methods were not being routinely used due to high costs, use of large numbers of animals, and limited confidence in the use of results for regulatory purposes. This was followed by an intense discussion on whether, and how, regulatory requirements could be met by alternative *in vitro* test methods. It was concluded that a critical aspect in the use of alternative methods is an understanding of regulatory needs, which vary from QSAR and read-across to quantitative models predictive of adverse outcomes. On the second day, review of the adverse outcome pathway (AOP) framework led to a discussion on how it could be useful in both the development of relevant and predictive *in vitro* test methods, as well as identification of knowledge gaps and challenges in extrapolation of both data and models between species.

Regulatory experts recommended that any use of data derived from *in vitro* models relevant to human biology would

be greatly enhanced if it was coupled with models of chemical kinetics and exposure estimates. In addition, it was deemed critical to tackle the difficult question of how to differentiate changes in *in vitro* endpoints, which might be part of adaptive processes normally found in *in vivo* biological systems, from those that are predictive of adverse outcomes. Coupling the adverse or adaptive nature of the measured endpoints with ADME and exposure information would lead to better estimates of the confidence level of the information and what type of regulatory decisions could be made.

Overall, the meeting was successful in generating discussions between scientists and regulators. These discussions are critical for the development of methods and models that provide useful data for regulatory purposes. They also are important in keeping regulators informed and engaged as the science of developmental neurotoxicity evolves. Finally, participants outlined ways to increase use of data from alternative methods in DNT risk management decisions. The next steps include: dissemination of the outcome from the meeting to engage more scientists and regulators; an EFSA-sponsored survey of current alternative test methods for DNT; cross-laboratory testing of currently available methods with known developmentally neurotoxic chemicals to foster creation of a battery of test methods capable of screening the effects of environmental chemicals on major neurodevelopmental processes; and development of efficient tiered testing strategies that are capable of initial screening, hazard characterization, and hazard and risk prediction.

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