

Rethinking Developmental Toxicity Testing:

Evolution or Revolution

19–20 April 2017
Kimpton Hotel Palomar
Washington, DC

Organized by the
HESI Developmental and Reproductive
Toxicology Technical Committee



The thalidomide tragedy galvanized regulatory agencies into immediate and urgent action to develop a testing scheme to identify the potential teratogenicity of new drugs. The outcome was the three segment testing scheme that covered the reproductive cycle, including the Segment II protocol, which evaluates the effects of an agent on the fetus after maternal administration during organogenesis. While there have been some modifications to the protocol over time, it is largely the same method that was developed in 1965: the same animal models, the same emphasis on fetal morphological evaluation and roughly the same dosing regimens.

What if we were responding to the thalidomide tragedy today instead of 50 years ago, with 21st century science and technology available to us? Would we design the same protocol? If not, would it be radically different, or just an updated version of the 1965 design? This workshop is intended to address that question.

Defenders of the current protocol will point out that it is based on the seemingly solid proposition that embryonic development is so highly conserved across species that evaluation of morphological development in another mammalian species is highly relevant for predicting human teratogenic potential. While this is clearly the case for early stages of development of the embryo, phylogenetic conservation does not seem to be the rule for xenobiotic metabolism, pharmacokinetics, nutrition, placental anatomy and many other factors that have a strong influence on developmental outcome. In fact, scientists who were among the architects of the Segment 2 design pointed out these same limitations (e.g., Wilson, 1973).

We will consider new strategies to identify developmental hazards taking into account the current state of science which may include alternative possibilities or improvements to the current Segment 2 design. These considerations could include the use of new technology to overcome some of the limitations in predicting human response with current animal models or completely new radical approach to developmental toxicity hazard identification. These may range from having a critical paradigm to deciding when non-clinical studies are needed to the use of biotechnology (e.g., transgenic expression of human metabolizing enzymes in a pregnant animal model) and computational models [e.g., use global gene expression screening in a panel of developmentally relevant cell types to determine whether any developmentally relevant pathway (e.g., wnt signaling, retinoid receptor activity, etc.) is affected by the tested chemical] for hazard characterization. Working groups can consider either strategy, or combinations of the two.

The overall outcome of the project will be a paper describing possible approaches identified at the workshop. The intent will be to share the results with the broader scientific and regulatory community so that the ideas can be considered, and if feasible, empirically evaluated.

Literature Cited: Wilson, JG. 1973. Environment and Birth Defects, Academic Press, London.

as of 10/27/2016

DAY ONE – April 19

7:30–8:30	Registration/breakfast	
8:30–8:35	Introduction & Workshop Goals <ul style="list-style-type: none">• Introduce the idea of hypothesis-based testing• Explore ways to improve current whole animal testing	Tony Scialli (Georgetown University)
8:35–9:00	Introduction to hypothesis-based testing <ul style="list-style-type: none">• Explain what does hypothesis-based testing look like• Describe the intoxicatable genome• Explain whether read-across methods can work• Using new tools to formulate and test hypotheses	George Daston (Proctor & Gamble)
9:00–9:30	Hypothesis-based testing in pharmaceutical development <ul style="list-style-type: none">• Explain how pharma might more effectively test using hypothesis-based protocols• Examples of drugs for which hypothesis-based testing might be more efficient	Dinesh Stanislaus (GlaxoSmithKline)
9:30–10:00	Hypothesis-based testing for non-pharmaceutical chemicals <ul style="list-style-type: none">• Explain how companies might more effectively test using hypothesis-based protocols• Examples of chemicals for which hypothesis-based testing might be more efficient	Jennifer Foreman (ExxonMobil)
10:00–10:30	Break	
10:30–11:00	In vitro and in silico approaches for predictive toxicology <ul style="list-style-type: none">• Update on progress towards Tox 21 objectives• Explain the role of currently available methods for predicting reproductive and developmental effects• Informatics• Connecting molecular level events to toxicology• Outline what will be done in the foreseeable future to improve predictability	Tom Knudsen (US EPA)
11:00–11:30	Gene expression to predict mode of action and developmental outcome <ul style="list-style-type: none">• How can we use current gene expression methods to predict reproductive and developmental toxicity• Give an example of where gene expression testing might replace or augment whole animal testing	Aldert Piersma (RIVM)
11:30–12:30	Discussion	
12:30–1:30	Lunch	

1:30–2:00	More Discussion	
2:00–2:15	Flexibility in the EFD protocol: Charge to Work groups	
	1. <u>REVOLUTION</u> : Design a system of developmental toxicity testing from scratch	
	2. <u>EVOLUTION</u>	
	a. <u>Metabolism</u> : Can we improve our approach to dealing with metabolites (human or otherwise)?	
	b. <u>Dose-response</u> : Can we improve our assessment of dose-response? (BMD or other modeling; more doses, fewer animals/dose group; selection of high-dose level on other bases than MTD)	
	c. <u>Humanized models</u> : How can we humanize rabbit-rodent models	
	d. <u>Models of disease</u> : Can we/should we make models of human disease?	
2:15–4:45	Work groups meet to develop presentations for tomorrow. Topics for the presentations:	
	1. What problem are we addressing and why is it a problem?	
	2. What is being done today to address this problem (give examples)	
	3. What can be done in the near future, not requiring much time or money, to address the problem?	
	4. What can/should be done long-term (more time and money)?	
	5. What change in regulations, if any, would be needed to facilitate solutions?	
4:45–5:00	Recap and what happens next	George Daston
5:00–6:00	Reception	

DAY TWO – April 20

8:00–8:30	Breakfast	
8:30–8:45	Welcome back, are we having fun yet?	Tony Scialli
8:45–9:00	Work groups finish their presentations	
9:00–9:30	Metabolite work group presentation and discussion	
9:30–10:00	Dose-response work group and discussion	
10:00–10:30	Break	
10:30–11:00	Humanizing models work group and discussion	
11:00–11:30	Models of human disease work group and discussion	
11:30–12:00	Revolution work group and discussion	
12:00–12:30	Wrap up and next steps	George Daston
12:30-1:30	Lunch (optional)	