Developmental and Reproductive Toxicology (DART)

Our Mission

The committee's mission is to provide a forum where scientists from industry, government, academia, and other key stakeholders can exchange information and initiate activities to advance science related to developmental and reproductive toxicology, and to develop consensus in the scientific community on the appropriate use of experimental toxicity data for human health risk assessment.

Chairs

Public Chair

Ms. Susan Makris (US Environmental Protection Agency)

Private Chair

Dr. Kary Thomspon (Janssen Pharmaceuticals)

HESI Staff

Dr. Connie Chen (cchen@hesiglobal.org)
Dr. Shermaine Mitchell-Ryan (smitchell-ryan@hesiglobal.org)

2020 Committee Highlights

Participating Organizations

12 government/regulatory agencies, **8** academic/research institutes, **21** industry, **1** other, and **4** consulting

Publications

2 published and **7** in progress

Scientific Meetings and Trainings

1 workshop and **2** meetings

- FDA/CDER-HESI Immunomodulators and Pregnancy Risk Workshop (February 2020 in Silver Spring, Maryland; 85 attendees)
- Spring and Fall Committee Meetings (virtual)

Outreach

1 symposium: committee-sponsored symposium at the 2020 Society for Birth Defects Research and Prevention 60th Annual Meeting (June 2020, virtual; 111 attendees)

Collaborations

1 internal and **1** external

- HESI ITC: immunomodulators and pregnancy risk
- European Teratology Society: Thyroid Task Force

Geographic Representation

Belgium, Canada, France, Germany, Italy, Japan, Netherlands, Spain, Sweden, Switzerland, United Kingdom, and United States

Working Groups

- **Anogenital Distance and Nipple Retention.** To promote harmonization of anogenital distance (AGD) and nipple/areola retention measurement in male rats, this project aims to publish a review of existing methods and recommend best practices and considerations for these two methods.
- **Thyroid Hormone Assessments.** In collaboration with the European Teratology Society, the joint workgroup has collected historical data on thyroid hormone measurement in rodent studies to determine best practices for these measurements.
- **Pubertal Assessment.** This working group aims to identify reliable *in vivo* rodent markers and *in vitro* assays that are predictive of agents (chemical or pharmaceutical) that affect human puberty timing (and by puberty timing, this includes initiation, progression, and completion).
- **Juvenile Clinical Pathology Endpoints.** Clinical pathology data from control animals in previously conducted juvenile animal toxicity studies will be gathered. The goal is to author a manuscript that could be used as a reference across the industry.
- **Preclinical Considerations for Pregnant and Lactating Women in Clinical Trials.** A points-to-consider manuscript is in development, outlining initial approaches to inclusion, the role of nonclinical data, and common practices during global drug development plans.
- **DARTable Genome.** This working group aims to enable better predictive toxicology for DART effects by sharing relevant knowledge of chemical-protein target interactions, pharmacokinetics, and major developmental toxicity study outcomes.

- **microCT.** This group strives to provide additional information and confidence that fetal skeletal examination using microCT is acceptable for regulatory use in nonclinical fetal evaluation studies.
- **Immunomodulators and Pregnancy Risk.** Key stakeholders were convened at a 2019 workshop and a 2020 symposium to discuss both current and novel methodologies in preclinical and translational safety assessment of pregnancy risk associated with immunomodulatory therapy.

NEW **Preweaning Developmental Endpoints.** This project aims to define which preweaning developmental landmarks (PDLs) have value, interpretation, and benchmark responses through both a survey and data collection.

Areas of Focus for 2021

- DART aims to incorporate computational chemistry/biology and modeling projects to place the committee at the frontier of emerging innovations and tools in the DART field.
- The committee will explore validation of alternative methods, including developing new concepts or new systems of models for assay validation and creating a validation framework for non-animal methods. The committee is also exploring projects in the following areas:
  - Dystocia (understanding if reproductive performance in rodents is waning or evolving)
  - Male reproductive endpoints (determining the value of functional reproductive toxicity endpoints relative to the profile generated by routine microscopic evaluations of the male reproductive tract in repeat-dose toxicity studies)
  - What is an adverse DART effect (developing a training workshop that can help differentiate hazard identification and risk assessment)

Strategic Impact Areas

Enhanced Efficiency and Accuracy in Safety Assessment Practice

The committee continues to carry on and initiate new programs that address key concerns in evaluation of pharmaceutical and environmental chemicals.

Enhancement of the Societal Knowledge Base on Human Biological Processes of Relevance for Protecting Human Health

Several programs are contributing to increased knowledge regarding potential endocrine-related effects on puberty.

Publications

Published

Bueters R, Bael A, Gasthuys E, Chen C, Schreuder MF, Frazier KS (2020) Ontogeny and cross-species comparison of pathways involved in drug absorption, distribution, metabolism, and excretion in neonates (review): kidney. *Drug Metabolism and Disposition*. 48:353–367. doi: 10.1124/dmd.119.089755.

Van den Anker JN, McCune S, Annaert P, Baer GR, Mulugeta Y, Abdelrahman R, Wu K, Krudys KM, Fisher J, Slikker W, Chen C, Burckart GJ, Allegaert K (2020) Approaches to dose finding in neonates, illustrating the variability between neonatal drug development programs. *Pharmaceutics*. 12:685. doi: 10.3390/pharmaceutics12070685.

In Progress

Campion et al. Establishing a research framework for nonclinical models for neonatal drug development.

Villano et al. Assessing the impact and risk of immunomodulatory compounds on pregnancy.

The puberty assessment series includes the following manuscripts:

- Euling et al. Impacts of chemical exposures on pubertal timing in humans: relevance of pharmaceutical and chemical testing approaches.
- Scialli et al. Pubertal development: relevance of animal models including recent advances in neurobiological mechanisms.
- Euling et al. Mechanistic correlates of human puberty timing endpoints: systematic review of the toxicology literature.
- Scialli and Foster. Epidemiology of human puberty.
- Gamse et al. Regulatory perspectives on puberty timing endpoints used in chemical and pharmaceutical evaluation.

Participating Organizations

Government/Regulatory Agencies

Executive Office of the President, Office of Management and Budget
Federal Agency for Medicines and Health Products (Belgium)
Istituto Superiore di Sanità (Italy)
Medicines Evaluation Board (The Netherlands)
National Institute for Public Health and the Environment (RIVM, The Netherlands)
National Institute of Environmental Health Sciences, National Toxicology Program
Pharmaceutical and Medical Devices Agency (Japan)
Swedish Chemicals Agency
US Environmental Protection Agency
US Food and Drug Administration, Center for Drug Evaluation and Research
US Food and Drug Administration, Center for Food Safety and Applied Nutrition
US Food and Drug Administration, National Center for Toxicological Research

Academic/Research Institutes

Creighton University
Erasmus MC Academic Center for Thyroid Diseases
Howard University
McGill University
McMaster University
University of Antwerp
University of Barcelona
University of California, Los Angeles

Industry

AbbVie
Amgen, Inc.
AstraZeneca
Bayer
Boehringer Ingelheim
Bristol-Myers Squibb Company
Charles River Laboratories
Corteva Agriscience
Covance
Eli Lilly and Company
ExxonMobil Biomedical Sciences, Inc.
Genentech
GlaxoSmithKline
Janssen Pharmaceuticals
Merck & Co.
Pfizer, Inc.
Procter & Gamble Company
Roche
Sanofi
Syngenta
Takeda Pharmaceutical Company, Ltd.

Other

Medicines for Malaria Ventures

Consulting

Aclairo Pharmaceutical Development Group, Inc.
Penman Consulting
Quality Scientific Solutions
Scialli Consulting, LLC