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

Dr. Vicki Sutherland (National Institute of Environmental Health Sciences, National Toxicology Program)

Private Chair

Dr. Kary Thomspon (Janssen Pharmaceuticals)

HESI Staff

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

Webpage

https://hesiglobal.org/developmental-and-reproductive-toxicology-dart/

2021 Committee Highlights

Participating Organizations

12 government/regulatory agencies, **9** academic/research institutes, **23** industry, **1** other, and **5** consulting

Publications

1 published, **1** submitted, and **8** in progress

Scientific Meetings and Trainings

2 meetings

- DART Spring Business Meeting (virtual; 80 attendees)
- DART Fall Business Meeting (virtual; 68 attendees)

Outreach

1 poster presentation, **2** oral presentations, and **1** symposium

- **1** poster presentation at the 2021 Society of Toxicology (SOT) Annual Meeting on "Quantifying the DARTable Genome for Prediction of Teratogengic Doses: A Case Study Using Retinoic Acid Pathway-Induced Developmental Toxicity" (March 2021, virtual)
- **1** oral presentation at the 11th World Congress on Alternatives and Animal Use in the Life Sciences on "Quantitative Prediction of Developmental Toxicity by Modeling the DARTable Genome" (August 2021, virtual)
- **1** oral presentation at the US FDA's Toxicology Seminar Series (TSS) on "Public-Private Initiatives: HESI DART Technical Committee and the Botanical Safety Consortium" (October 2021; virtual)
- **1** committee-sponsored symposium at the 2021 Society for Birth Defects Research and Prevention Annual Meeting (June 2021, virtual)

Collaborations

1 internal and **1** external

- HESI Immuno-Safety Technical Committee (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.** The aim of this working group is to promote harmonization of anogenital distance (AGD) and nipple/areola retention measurement in male rats by publishing 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. The workshop proceedings will be submitted for publication by the close of the year. Next steps for a new round of data collection and database development are under discussion.
- **Pubertal Assessment.** The goal of this exercise is to determine the degree of reliability and human relevance of *in vitro* rodent markers/assays for puberty timing endpoints by critically evaluating the epidemiological and toxicological literature on both normal development and altered development after exposures. A series of review articles are underway and anticipated to be completed in 2022.
- **Juvenile Clinical Pathology Endpoints.** Clinical pathology data from control animals in previously conducted juvenile animal toxicity studies has been gathered. Data analysis is underway, and a manuscript that could be used as a reference across the industry is in development.
- **Preclinical Considerations for Pregnant and Lactating Women in Clinical Trials.** A points-to-consider manuscript is being finalized, 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. To this end, the team has initiated two case studies on the well-characterized teratogens, Retinoic Acid and Thalidomide.
- **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. The study design and participants in a multi-site *in vivo* study comparing microCT and alizarin red staining is being finalized. Experimental work is anticipated to begin in 2022.
- **QSAR Model of Rodent Placental Transfer.** This working group will collect data on a diverse set of compounds to increase the predictive power of a QSAR model for the prediction of placental transfer in rats; outputs from this model can be used as a tool to enhance the exposure based predictions of *in vitro* assays.
- **Immunomodulators and Pregnancy Risk.** This working group, in collaboration with the HESI Immuno-Safety Technical Committee (ITC), convened key stakeholders to discuss both current and novel methodologies in preclinical and translational safety assessment of pregnancy risk associated with immunomodulatory therapy. This group will sunset after the workshop publication is completed.
- **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.

NEW **Adverse DART Effects Training Course.** This working group is organizing a series of webinar modules to train federal and international regulators, clinicians, academic investigators, contract research organization scientists, and private sector scientists on the best practices and principles of interpreting DART data in the context of regulatory frameworks and processes. Modules aim to be held in 2Q 2022.

NEW **Dysotcia.** The goal of the project is to survey labs using HanWister and Sprague Dawley rats in DART studies to understand if reproductive performance in the strain is waning/evolving. Team will publish findings on this analysis.

- **DART NAMs/Alternatives.** This scoping group aims to create a new approach methodologies (NAMs) toolbox that will provide for and clarify the context of use for alternative assays that will comply with various regulatory guidelines so that they can ultimately validate for us as a NAM.

NEW **DART Trainee Program.** This new initiative aims to leverage the HESI DART Committee's membership and technical work to facilitate career development (with a focus on training and networking) of the next generation of developmental toxicologists. The program(s) will be advertised outside of the traditional and well-established networks to expand our reach to individuals who belong to historically under-represented groups, thereby broadening the pool of trainees.

Areas of Focus for 2022

- Incorporate compututational chemistry/biology and modeling projects to place the committee at the frontier of emerging innovation and tools in the DART field.
- Validate alternative methods, new concepts, or new systems of models for assay validation, and create a validation framework for non-animal methods.
- Broaden participation in DART science by offering experimental learning and mentoring to graduate, postdoc, and early career scientists and heighten the awareness of DART career opportunities.

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.

2021 Awards, Grants, and Recognition

The HESI DART Committee DARTable Genome Working Group recently received the first external government-supported grant of $14,000 from the Belgian Federal Public Service (FPS) Health, Food Chain Safety and Environment to develop a provisional AOP wiki on retinol dehydrogenase/retinaldehyde dehydrogenase (RDH/RALDH) and cardiovascular developmental defects.

Publications

Published

van Groen BD, Nicolaï J, Kuik AC, Van Cruchten S, van Peer E, Smits A, Schmidt S, de Wildt SN, Allegaert K, De Schaepdrijver L, Annaert P, Badée J. Ontogeny of hepatic transporters and drug metabolizing enzymes in humans and in non-clinical species. *Pharmacological Reviews*. doi: 10.1124/pharmrev.120.000071.

Submitted

Campion et al. (2021) Establishing a research framework for nonclinical models for neonatal drug development. *Disease Models and Mechanisms*. Submitted

In Progress

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

Coder et al. Thyroid hormone assessments on developmental and reproductive toxicity studies: key technical and scientific criteria influencing data collection, analysis, and interpretation. In preparation.

Thompson et al. Title TBD. In preparation.

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. In preparation.
- Beyer et al. Pubertal development: relevance of animal models including recent advances in neurobiological mechanisms. In preparation.
- Euling et al. Mechanistic correlates of human puberty timing endpoints: systematic review of the toxicology literature. In preparation.
- Scialli and Foster. Epidemiology of human puberty. In preparation.
- Hoberman et al. Regulatory perspectives on puberty timing endpoints used in chemical and pharmaceutical evaluation. In preparation.

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
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
Pharmaceuticals 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
Georgetown University
Howard University
McGill University
McMaster University
University of Antwerp
University of Barcelona
University of California, Los Angeles

Industry

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

Other

Medicines for Malaria Venture

Consulting

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