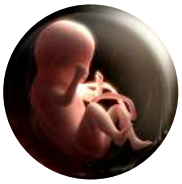
Developmental and Reproductive Toxicology (DART)



Our Mission

The DART Technical Committee provides 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, Division of Translational Toxicology)

Private Chairs
Dr. Kary Thompson (Janssen Pharmaceuticals)
Dr. Christopher Bowman (Pfizer, [incoming 2023])

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/

2022 Committee Highlights

Participating Organizations
10 government/regulatory agencies, 21 industry, 9 academic/research institutes, 5 consulting, 1 other

Publications
1 publication, 5 in progress

Collaborations
1 internal, 2 external
- HESI ITC Committee – Immunomodulators and Pregnancy Risk Working Group
- European Teratology Society – Thyroid Task Force
- Medicines Evaluation Board (MEB, The Netherlands)

Meetings
2 meetings, 1 workshop, 1 symposium

- DART 2022 Annual Spring Meeting (Virual; 75 attendees)
- DART 2022 Annual Fall Meeting (Hybrid; 37 in-person & 100+ virtual attendees)
- DART Fall Adverse Effects Workshop (Hybrid; 100+ attendees)
- DART Fall Career Symposium (Virtual; 57 attendees)

Outreach
2 symposiums

62nd Birth Defects Research and Prevention Annual Meeting
- *Bringing Molecular and Developmental Biology to DART Symposium*. In collaboration with the BDRP science committee.

50th Annual Conference of the European Teratology Society
- *Preclinical Consideration for the Inclusion of Pregnant and Lactating Women*. Dr. Kary Thompson.

Geographic Representation
Belgium, Canada, England, France, Germany, Japan, Netherlands, Spain, Sweden, Switzerland, United States

Working Groups

- **Anogenital Distance (AGD) and Nipple Retention.** The aim of this WG is to promote harmonization of AGD and nipple/areola retention measurement in male rats. This WG is finalizing their paper which includes 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.** This WG aims to review the latest science on the molecular mechanisms of puberty initiation and progression with the goal to identify and publish a manuscript describing reliable markers in the rodent that are predictive correlates for disruption of the HPG and HPA activation event in humans.
- **Juvenile Clinical Pathology Endpoints.** This WG has gathered historical control data for key clinical pathology endpoints in previously conducted juvenile animal toxicity studies. 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.** This WG is finalizing points to consider a manuscript outlining initial approaches to inclusion, the role of nonclinical data, and common practices during global drug development plans.
- **DARTable Genome.** This WG's aim is 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 WG aims to provide additional information and confidence that fetal skeletal examination using micro-CT is acceptable for regulatory use in nonclinical fetal evaluation studies. The study design and participants in a multi-site *in vivo* study comparison microCT and alizarin red staining is being finalized. In-life studies are underway, with cross-laboratory analysis of fetal skeletons and images to commence in 2023.
- **QSAR Model of Rodent Placental Transfer.** Due to challenges in obtaining the requisite number of compounds needed for the model, this project has sunset.
- **Immunomodulators and Pregnancy Risk.** This WG, joint with the 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 WG will sunset after the workshop publication is completed.
- **Preweaning Developmental Endpoints.** This WG aims to define which preweaning developmental landmarks (PDLs) have value, interpretation, and benchmark responses through both a survey and data collection.
- **Adverse DART Effects Training Course.** This WG held a workshop "Interpretation of developmental and reproductive toxicity in Regulatory contexts and frameworks" in October 2022.
- **Dystocia.** This WG aims to to understand how and when dystocia is identified and reported in laboratory rodents and to identify how these calls may differ between organizations. Responses from survey will help to inform a best practices manuscript.
- **DART NAMs/Alternatives.** This working group aims to create a new approach methodology (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 validated for use as a NAM. Three manuscripts are underway: (1) a hypothesis-drive approach to DART testing; (2) Use of NAMs in chemical risk assessment; and (3) Use of NAMS in pharmaceutical risk assessment.

Alternatives to Sexually Mature NHPs for DART Safety Assessments. This WG aims to develop a white paper assessing the current use of sexually mature NHPs for all aspects of developmental and reproductive toxicology (DART; risk of adverse pregnancy outcomes and infertility) including potential alternative approaches.

Extended OneGeneration Reproductive Toxicity Studies: A Retrospective Analysis. The proposed retrospective analysis will evaluate EOGRTS studies to gain insight of the pros and cons of the different study designs, and to determine the overall added value of the EOGRTS. To keep pace with the rapid changes in the regulatory landscape, the WG will compose and publish a critical letter, with multi-sectorial endorsement, to quickly bring attention to animal welfare and ethical issues.

- **DART Trainee Program.** This new initiative aims to leverage HESI DART's network and technical work to facilitate career development (with a focus on training and networking) of the next generation of developmental toxicologists. Program(s) to 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 2023

- The incorporation of computational chemistry/biology and modeling projects to place the committee at the frontier of emerging innovation and tools in the DART field.
- Validation of alternative methods; new concepts or new systems of models for assay validation; creating a validation framework for non-animal methods.
- Broadening participation in DART science by offering experiential learning and mentoring to graduate, postdoc, and early career scientist and heightening 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 evaluating 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 the puberty.

Publications

Published

Campion et al. 2022. The benefits, limitations and opportunities of preclinical models for neonatal drug development. *Disease Models & Mechanisms*. https://doi.org/10.1242/dmm.049065

In Progress

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

Coder et al. Thyroid Hormone Assessments on Developmental and Reproductive Toxicity Studies – Key Technical and Scientific Criteria Influencing Data Collection, Analysis and Interpretation

Thompson et al. Nonclinical consideration for the inclusion of pregnant and lactating women in clinical trials.

Scialli et al. Mechanistic correlates in the rodent for predicting effects on human puberty initiation and progression.

NAMS Series:

1. Daston and Piersma et al. Hypothesis-based reproductive toxicity safety testing.
2. Powles-Glover et al. Current approaches for alternative methods in pharmaceutical testing.
3. Beekhuijzen et al. Current approaches and lessons learned for new approach methodologies in environmental and industrial chemical testing.

Participating Organizations

Government/Regulatory Agencies
Executive Office of the President, Office of Management and Budget
Federal Agency for Medicines and Health Products (Belgium)
Medicine Evaluation Board (The Netherlands)
National Institute for Public Health and the Environment (RIVM, The Netherlands)
National Toxicology Program (NIEHS)
Pharmaceutical and Medical Devices Agency (Japan)
Swedish Chemical Agency
US Environmental Protection Agency (EPA)
US Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER)
US Food and Drug Administration (FDA), National Center for Toxicological Research (NCTR)

Academic/Research Institutes
Creighton University
Erasmus MC Academic Center
Georgetown University
Howard University
McGill University
McMaster University
Medicine Evaluation Board of the Netherlands
University of Antwerp
University of California, Los Angeles

Industry
AbbVie
Amgen
AstraZeneca
Astellas Pharma, Inc.
Bayer
Boerhinger Ingelheim
Bristol-Myers Squibb
Charles River Laboratories
Corteva Agriscience
Eli Lilly and Company
ExxonMobil
Genentech/Roche
GSK
Labcorp Drug Development
L'Oreal Corporation
Janssen Pharmaceuticals
Proctor & Gamble Company
Sanofi
Syngenta
Takeda Pharmaceutical Company, Ltd.
Toxys

Consulting
ApconiX
Exponent, Inc.
Hurley Consulting
Reproductive Toxicology Center
Tacey White Consulting

Other
Medicines for Malaria Ventures