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
Ms. Susan Makris (US Environmental Protection Agency)

Private Chair
Dr. Kary Thompson (Bristol-Myers Squibb Company)

HESI STAFF
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2019 COMMITTEE HIGHLIGHTS

Participating Organizations
15 government/regulatory agencies, 9 academic/research institutes, 4 consulting, 22 industry

Publications
5 accepted/published, 1 submitted

Scientific Meetings and Trainings
• 4 committee meetings (2 committee meetings; 2019 Teratology Society Meeting, Thyroid Hormone Assessment Symposium, San Diego, California; and European Teratology Society Annual Meeting, Cologne, Germany)
• 1 workshop (Thyroid Hormone Assessment Workshop, Washington, DC)

Web Tools and Assays
1 web tool

Outreach
• 1 poster (a poster on neonatal kidney physiology was presented at the Benelux Kidney Meeting in Eindhoven, The Netherlands)
• 1 presentation

Collaborations
1 within HESI, 1 external
• The Immunomodulation and Pregnancy Risk Work Group is a collaboration with the HESI Immuno-Safety Technical Committee that seeks to convene key stakeholders to discuss both current and novel methodologies in preclinical and translational safety assessment of pregnancy risk associated with immunomodulatory therapy.
• The HESI-ETS Thyroid Hormone Assessment Workshop was a joint effort with the European Teratology Society to collect information pertaining to analytical methodology and data on thyroid hormone levels in rodents.

Geographic Representation
Belgium, France, Germany, Japan, Netherlands, Sweden, Switzerland, United Kingdom, United States
WORKING GROUPS

- **Developmental Immunotoxicology.** This working group aims to gather disparate information on developmental immunotoxicology as it relates to testing in preclinical species into one authoritative manuscript.
- **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.
- **Neonatal Pediatrics—Survey and Framework.** This working group aims to review and evaluate the available nonclinical literature for six key neonatal therapeutic areas (brain, lung and gastrointestinal injury, neonatal abstinence, infection, and retinopathy of prematurity) to help identify any common elements among the neonatal disease models or specific elements for each disease state.
- **Neonatal Pediatrics—Physiology.** This group aims to elucidate the comparative neonatal physiology/development of the ontogeny of absorption, distribution, metabolism and excretion (ADME)-related processes for multiple organ systems as it relates to preclinical animal models and the human neonate.
- **Neonatal Pediatrics—Starting Dose.** A white paper is being developed using case studies to demonstrate key considerations for nonclinical studies that would better inform starting therapeutic doses for neonatal populations.
- **Thyroid Hormone Assessments.** In collaboration with the European Teratology Society, the joint working group 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 outlining initial approaches to inclusion, the role of nonclinical data, and common practices during global drug development plans is in development.
- **DARTable Genome.** This working group aims to enable better predictive toxicology by curating our knowledge of DART Molecular Initiating Events (MIE) and the quantitative Adverse Outcome pathways they trigger, to build a DART Safety Screening Panel.
- **MicroCT.** This work group aims 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 will be convened to discuss both current and novel methodologies in preclinical and translational safety assessment of pregnancy risk associated with immunomodulatory therapy. The workshop will serve as starting point to address gaps in biology, current tools and other aspects of pregnancy risk that should be considered drug development.
- **QSAR Modeling of Rodent Placental Transfer.** This work group aims to improve developmental toxicological predictions by integrating exposure information into a preliminary QSAR model to predict placental drug transfer in rodents.

AREAS OF FOCUS FOR 2020

- 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, and creating a validation framework for non-animal methods

STRATEGIC IMPACT AREAS

**Enhanced Efficiency and Accuracy in Safety Assessment Practice**

Various projects within the portfolio focus on the harmonization of current regulatory guidance related to developmental and reproductive toxicology, as well as recommending best practices for assessing the risk/safety associated with the exposure of teratogenic agents. This includes but is not limited reviewing test data and current methods for identifying disruptions in developmental/reproductive maturation or function in preclinical species resulting from exposure while evaluating the translational value across species and in humans.

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

Many of the efforts that initiated under the HESI DART pediatrics project seek to further elucidate mechanisms within the critical windows in development and reproduction and to better understand the ontogeny of ADME processes that dictate the disposition of a putative teratogen with an organism.


