Developmental and Reproductive Toxicology Technical Committee

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HESI 2014
Annual Meeting
Washington, DC

The views expressed in this presentation are those of the presenter and do not necessarily reflect the view or policies of the presenter's employer (U.S. FDA)

ILSI Health and
Environmental Sciences
Institute

About the DART Technical Committee

- One of HESI's longest standing committees, ongoing since 1996

- **Committee Mission:**
  - provide a forum where scientists from industry, government and academia can exchange information and initiate activities to advance science related to developmental and reproductive toxicology
  - to develop consensus on the appropriate use of experimental toxicity data for human health risk assessment.

Committee Participants (2014 – 2015)

- AbbVie, Inc.
- Amgen, Inc.
- AstraZeneca
- Bayer HealthCare Pharmaceuticals
- Boehringer-Ingelheim Pharmaceuticals, Inc.
- Bristol-Myers Squibb Company
- Celgene Corporation
- Charles River Laboratories
- Covance Laboratories Inc.
- Creighton University School of Medicine
- DuPont
- Eli Lilly and Company
- E^{x}ponent
- ExxonMobil Biosciences Inc.
- F. Hoffman La Roche Ltd
- Federal Agency for Medicines and Health Products (Belgium)
- Federal Institute for Drugs and Medical Devices (Germany)
- GlaxoSmithKline
- Janssen Pharmaceuticals
- McMaster University
- Medical Products Agency (Sweden)
- Medicines and Healthcare Products Regulatory Agency (UK)
- Medicines Evaluation Board (the Netherlands)
- Merck & Co.
- National Institute for Public Health and the Environment (RIVM, the Netherlands)
- Novartis Pharmaceuticals Corporation
- Pfizer Inc.
- Procter & Gamble Company
- Sanofi
- Swedish Chemical Agency
- Takeda Pharmaceutical Company, Ltd.
- Reproductive Toxicology Center
- US Environmental Protection Agency
- US Food and Drug Administration

Committee Leadership

Co-Chairs

Dr. Wafa Harrouk (US FDA)

Dr. Jane Stewart (AstraZeneca)

HESI Staff

Dr. Connie Chen

Scientific Advisors

Dr. Susan Euling (US EPA)

Dr. Warren Foster (McMaster University)

Dr. Janee Gelineau-van Waes (Creighton University)

Dr. Thomas Knudsen (US EPA)

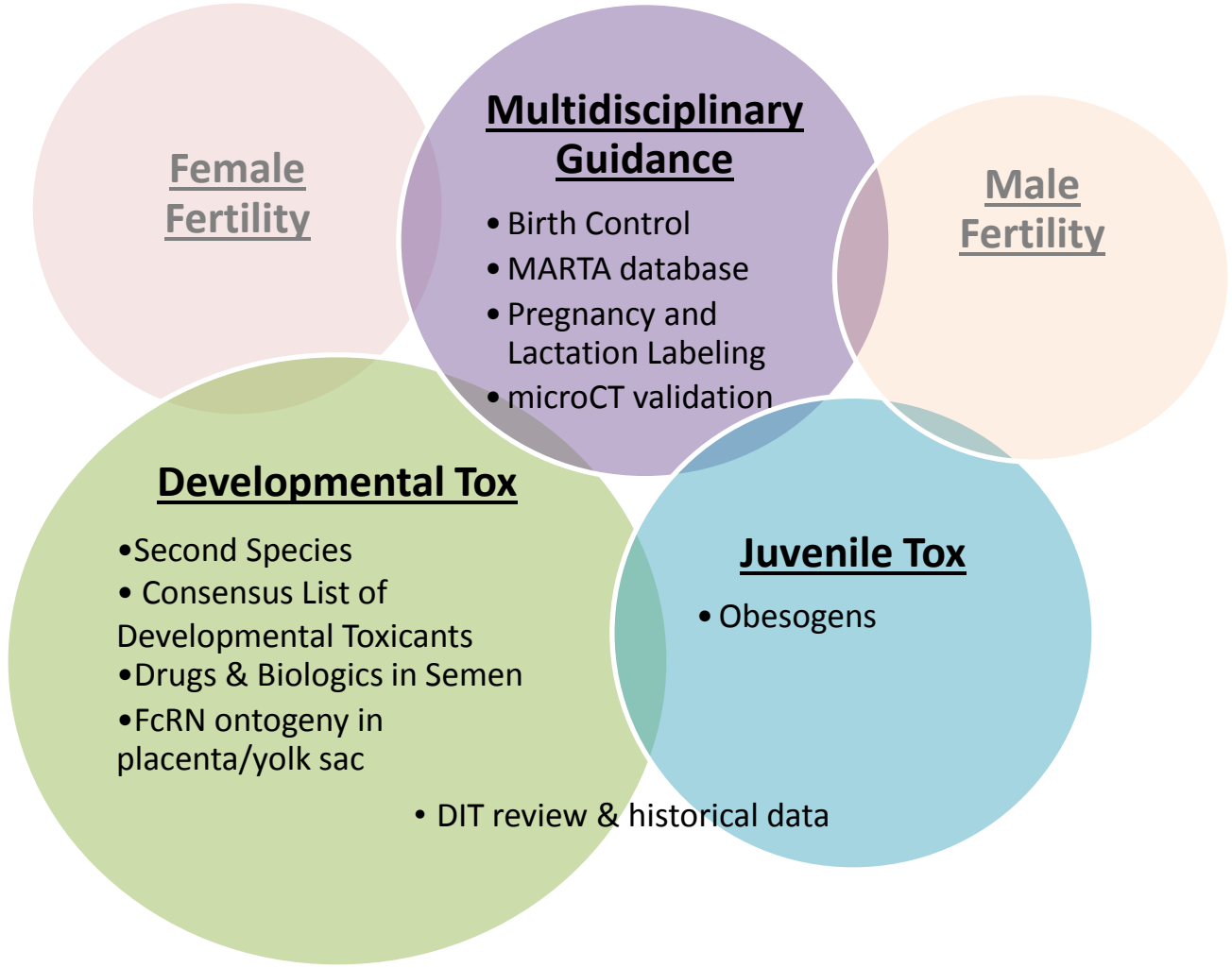
Dr. James Lamb (Exponent)

Dr. Daniel Minck (US FDA)

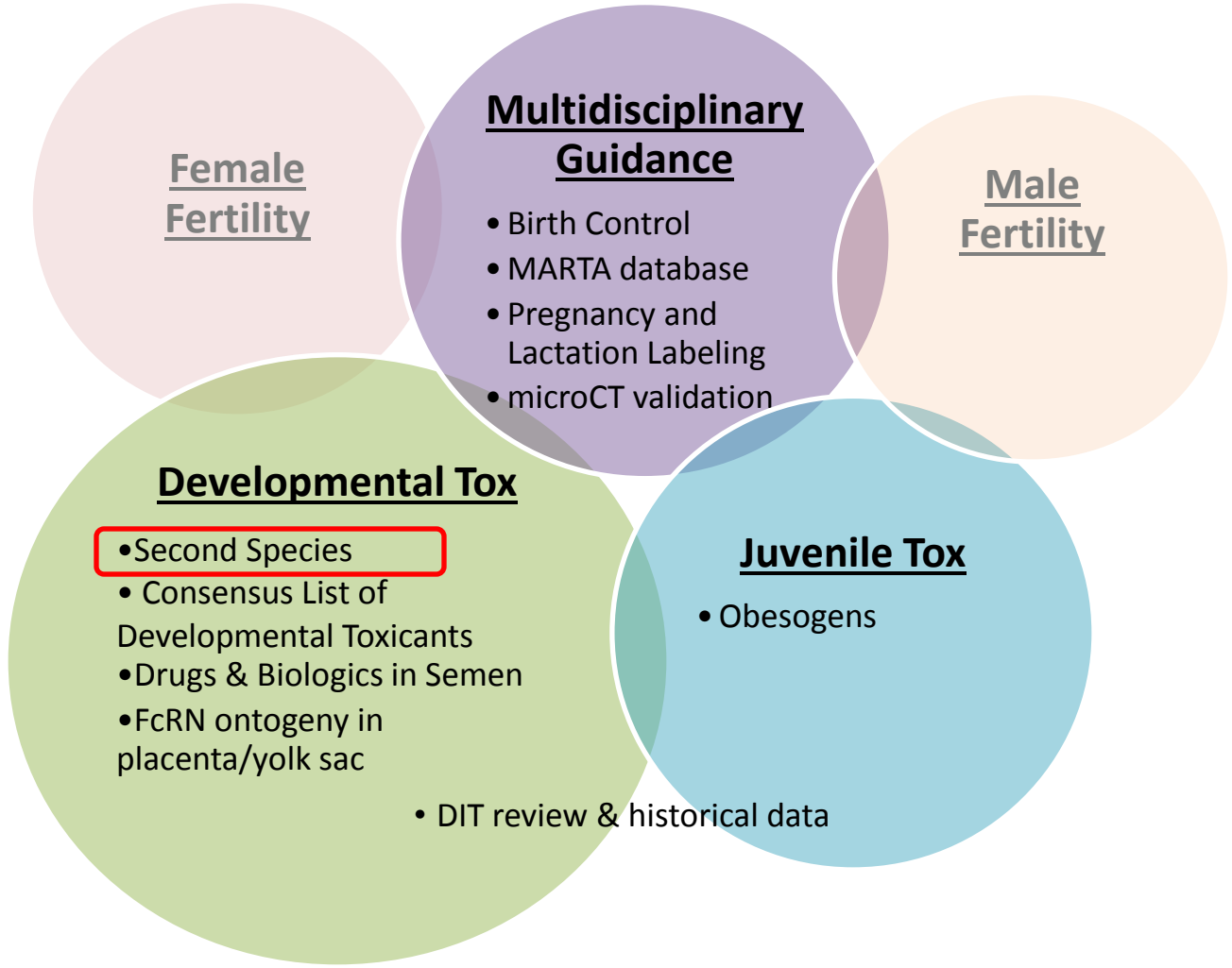
Dr. Aldert Piersma (RIVM)

Dr. Anthony Scialli (Reproductive Toxicology Center)

DART Technical Committee Scientific Portfolio 2014-2015

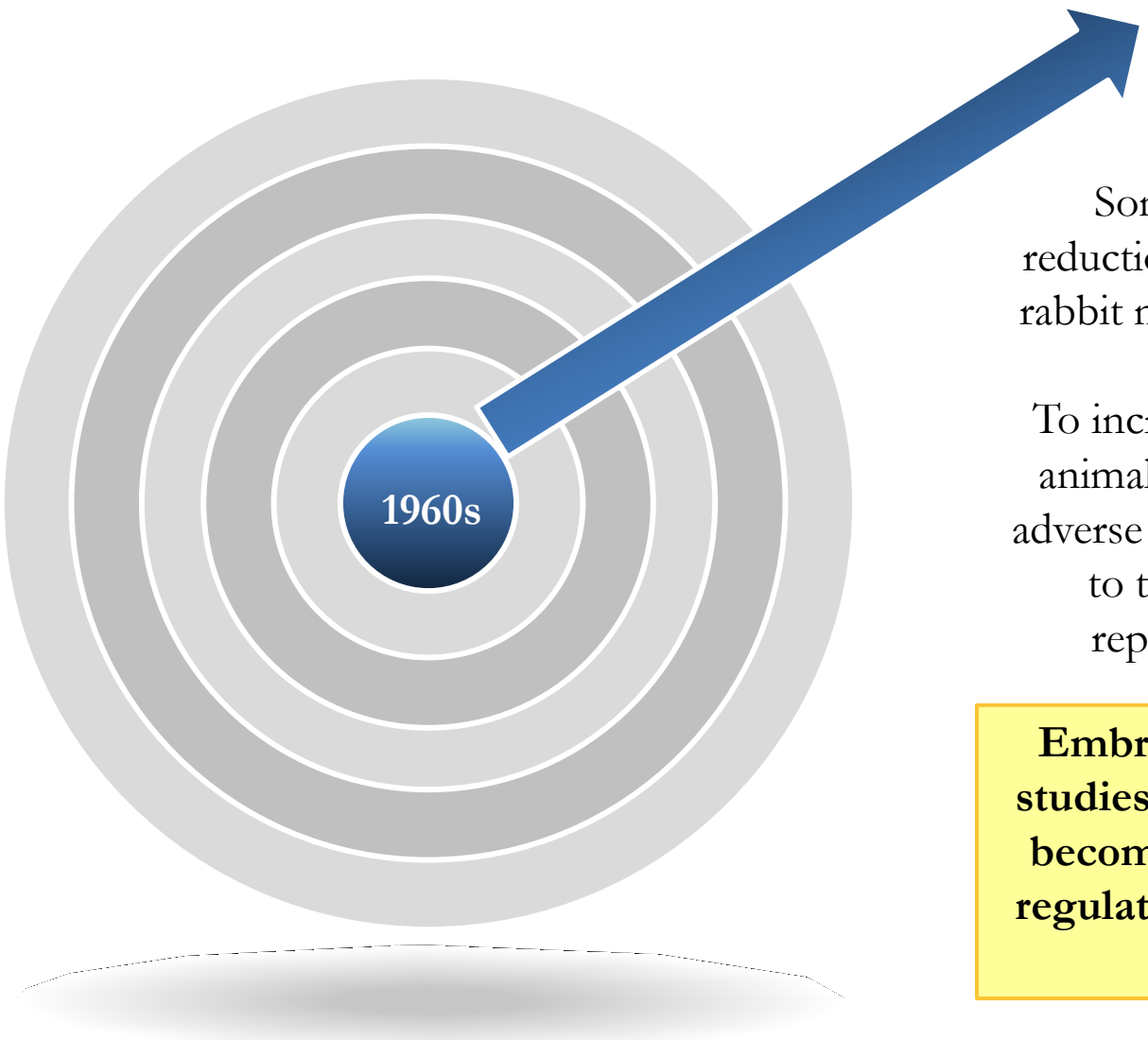


DART Technical Committee Scientific Portfolio 2014-2015



Evaluating the Value of the Rabbit as a Second Species

Historical Perspectives

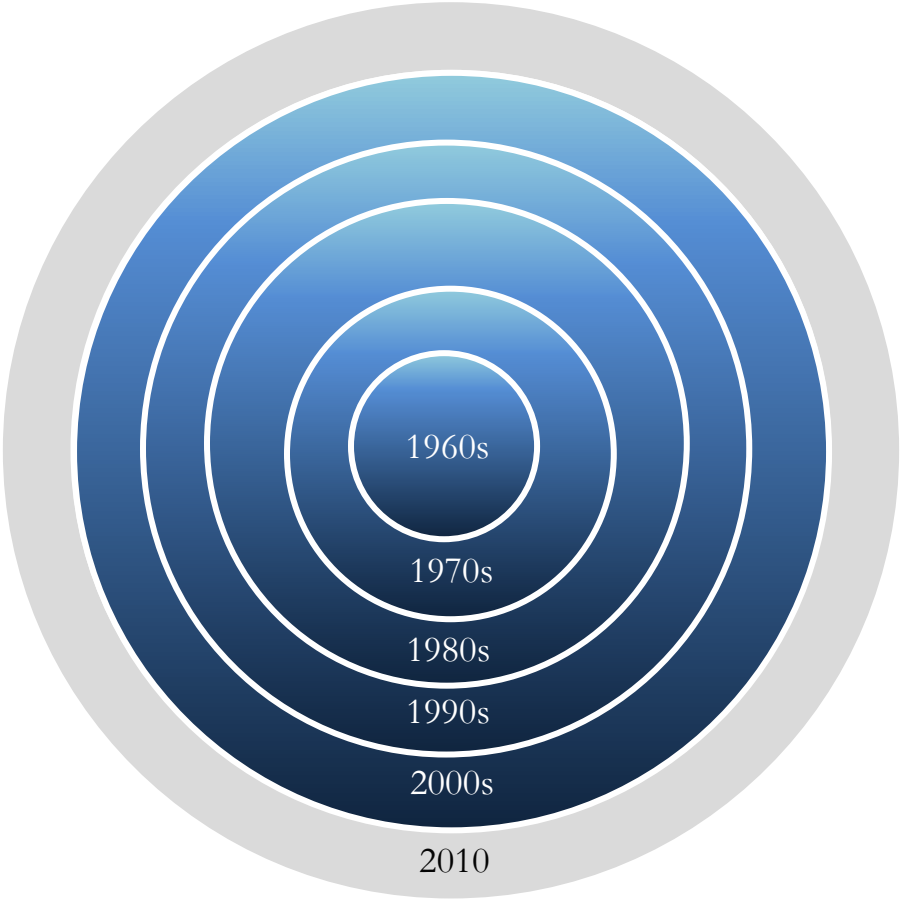


Thalidomide

Some malformations (limb reductions) were reproduced in the rabbit model but not the rat model.

To increase the predictivity of the animal model to potential human adverse events, the rabbit was added to the testing battery of the reproductive toxicity assays

Embryo-fetal developmental studies in the rat & rabbit have become the gold standard for regulatory reproductive hazard assessment tools



Where are we 50 years later?

Brainstorming

Where rat main EFD data exist prior to Phase III AND

i) rat has been shown to be a pharmacologically relevant species, AND
ii) exposures in the rat are considered adequate AND
iii) phase III clinical trial can maintain effective contraception

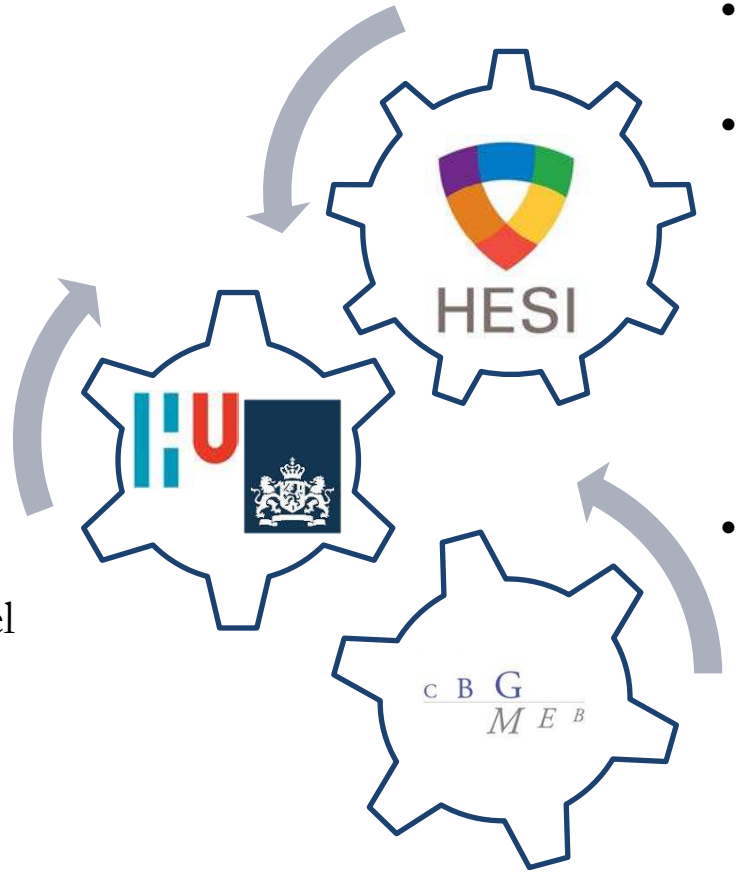
What impact would delaying main EFD study of the (rabbit) second species have on risk assessment and informed consent for the Phase III trials?

2nd Species Workgoup Technical Objective:

Compare Rat and Rabbit Embryo Fetal Developmental (EFD) toxicity data for pharmaceuticals:

- Strength of developmental toxicity signal in each species
- Putative safety margin against human therapeutic dose/exposure in each species
- Pharmacologic relevance of each species

- Customization of US EPA's ToxRefDB
- Data entry
  - Microsoft Access-based
  - Exportable to Excel for analyses
- Data analyses



- Sponsoring of RIVM post-doc
- Data (non-registered/non-approved compounds) submitted by sponsors
  - Written & tabulated summaries (eCTD)
  - Both rat and rabbit EFD studies
- Data blinded by HESI staff

- Provided access to EMA registered compounds

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

RIVM
Aldert Piersma
Peter Theunissen

CBG MEB

CBG-MEB
Jan-Willem van der Laan
Kris Siezen
Members of FTBB department

University of Applied Sciences Utrecht

ILSI-HESI-DART 2nd species workgroup

Public:
Belgium FAGG
CBG-MEB
EMA
RIVM
US-FDA
US-EPA

Private:
AbbVie
AstraZeneca
BMS
Celgene
Charles River
Covance
Dow Chemical
Eli Lilly
Exxon Mobil
GSK
J&J
Merck
Pfizer
Roche
Sanofi
Takeda

Workgroup Chairs:
Gregg Cappon (Pfizer)
Alan Hoberman (CRL)
Aldert Piersma (RIVM)

HESI

ILSI-HESI Staff
Connie Chen
Megan Harries
James Kim

This research is funded by:
HESI ILSI-HESI DART Technical Committee
SLIM (Synergy in Life Science, Innovation and Marketing) SLiM

Data Analyses

- 381 (out of 450 compounds) entered into the database
  - ~80% with TK data

- Analysis scenarios:
  1) Difference in maternal systemic **exposure** at LOAEL
  2) Difference in **severity** among effect types at LOAEL
  3) Developmental toxicity in relation to **maternal toxicity** at LOAEL
  4) Differences in **mode of action/indication**
  5) Cases with fetal **LOAEL in only one species**.

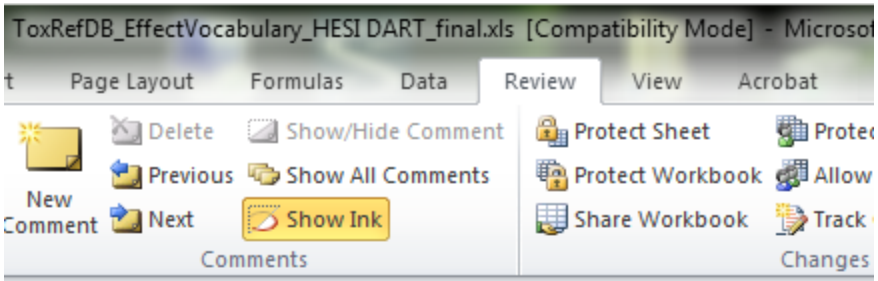
Difference by severity type

- Consensus on 4 major categories of endpoints
  - Malformation
  - Variation
  - Fetal growth
  - Death

Endpoints that varied across companies.

- 3 companies scored 900+ endpoints (ToxRefDB) as:
  - Malformation
  - Variation

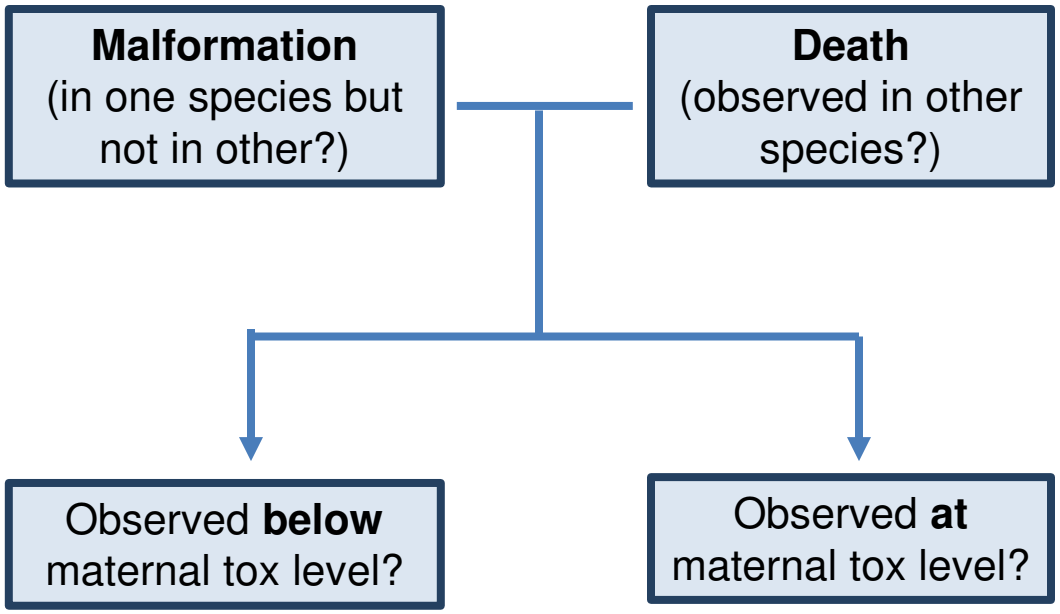
- Majority decision entered into database for analysis



B	C	I
EFFECT TARGET	EFFECT DESCRIPTION	Final Call
Adrenal Gland	Absent	**Malformation**
Adrenal Gland	Enlarged	**Variation**
Adrenal Gland	Extracapsular Tissue	**Variation**
Adrenal Gland	Fused	**Malformation**
Adrenal Gland	Hemorrhagic	**Variation**
Adrenal Gland	Malpositioned	**Malformation**
Adrenal Gland	Misshapen	**Variation**
Adrenal Gland	Small	**Variation**
Adrenal Gland	Supernumerary	**Malformation**
Aorta	Aortic atresia	**Malformation**
Aorta	Dilated	**Variation**
Aorta	Double	**Malformation**
Aorta	Malpositioned	**Malformation**
Aorta	Narrowed	**Malformation**
Aorta	Overriding	**Malformation**
Aortic arch	Atresia	**Malformation**
Aortic arch	Dilated	**Variation**
Aortic arch	Interrupted	**Malformation**
Aortic arch	Narrowed	**Variation**

Difference by severity type

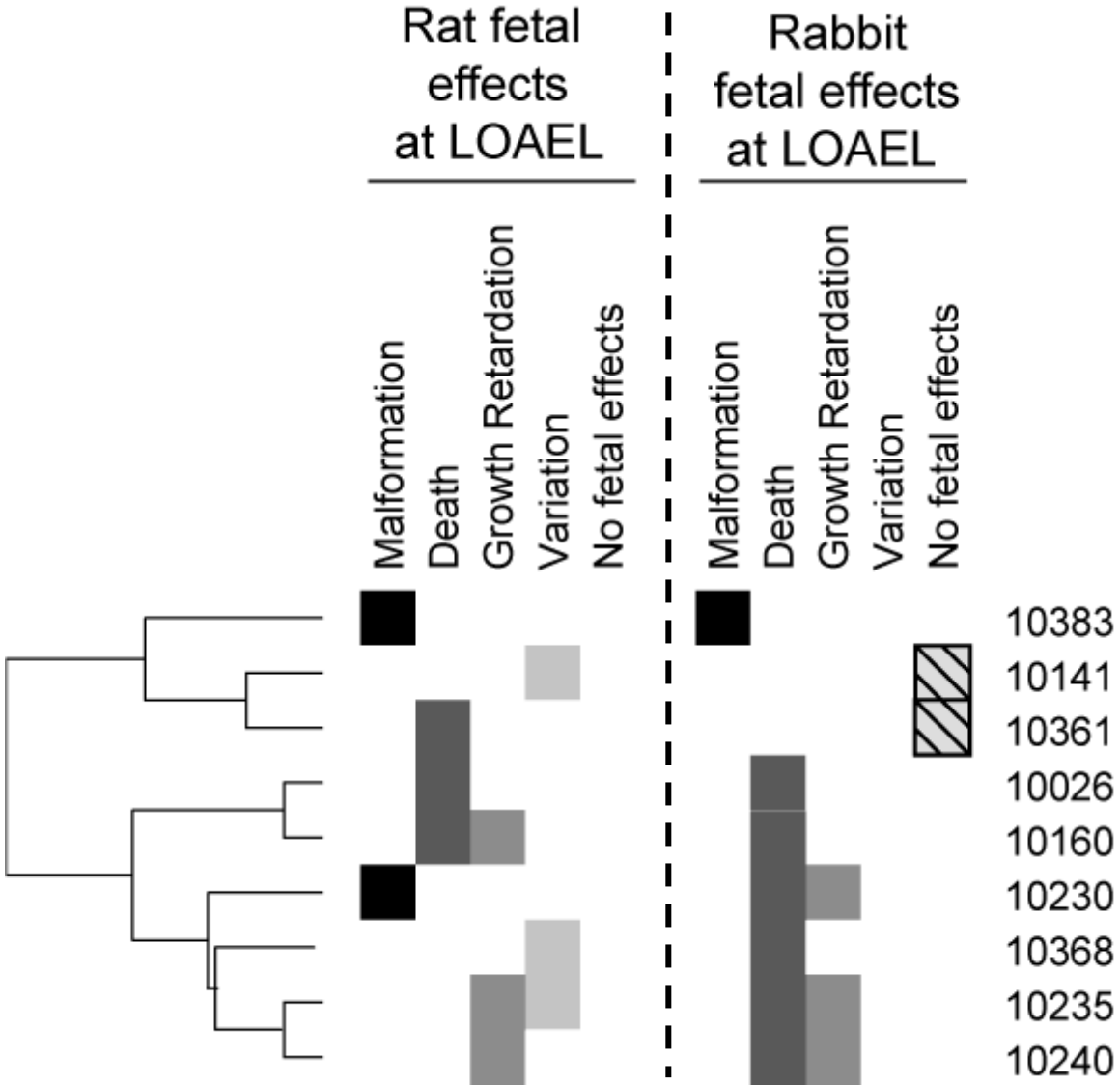
- Does one species show more severe developmental tox than the other?



Considerations:

- Grading of Severity:
  Variation/growth retardation <<
  Death = EFD loss <<
  Malformation
- Look at LOAEL for all compounds
  - Differences in severity of effect type?
  - Difference in magnitude?

Example: Examination of the effects for compounds where at fetal LOAEL, the **rat** exposure is significantly lower than rabbit exposure.



What have we learned so far?

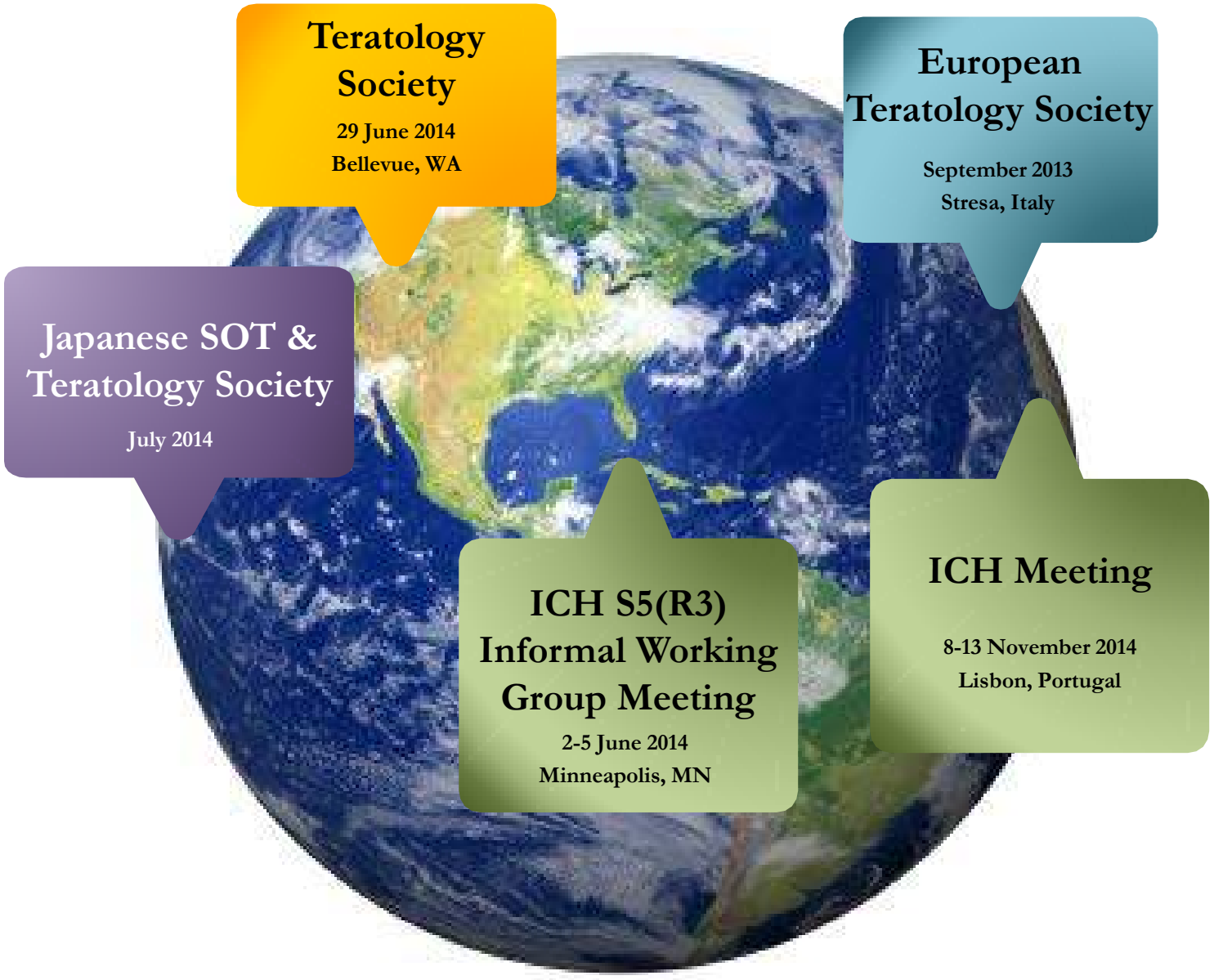
1. The **data are very COMPLEX**!

   For example:

   - Difficulty in determining maternal & Fetal LOAEL. Changes that define Fetal LOAEL are different among studies include:
     - ✓ Morphological changes vs. fetal viability (fetal death and resorption)
     - ✓ Morphological changes vs. fetal body weight changes
     - ✓ Fetal viability vs. fetal body weight changes
     - ✓ Do all these carry the same weight? LOAELs with different severity?
   - Fetal LOAEL may be driven by maternal toxicity

2. Preliminary results show **that each species contributes different information necessary for risk assessment.**

Potential Global Impact



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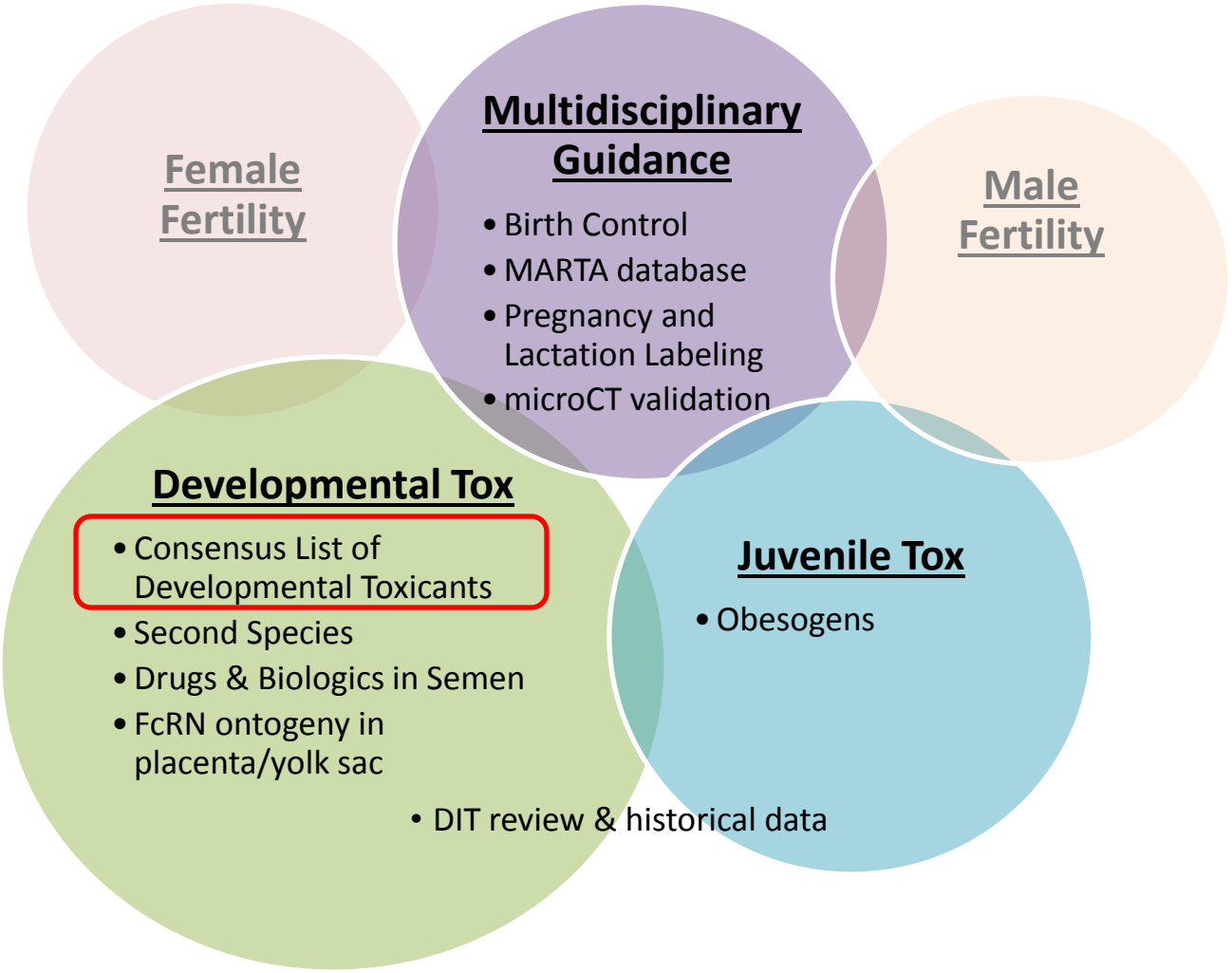
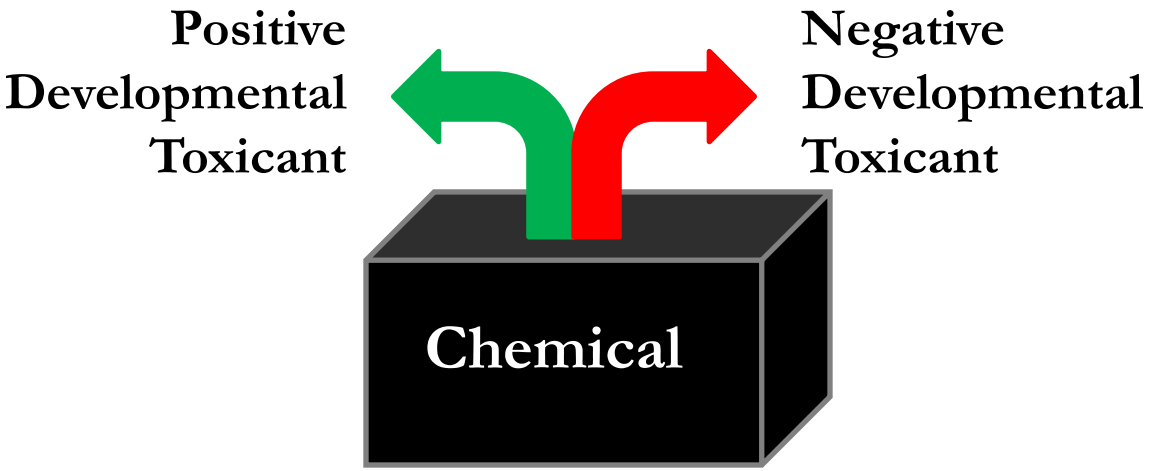


Consensus List of Developmental Toxicants

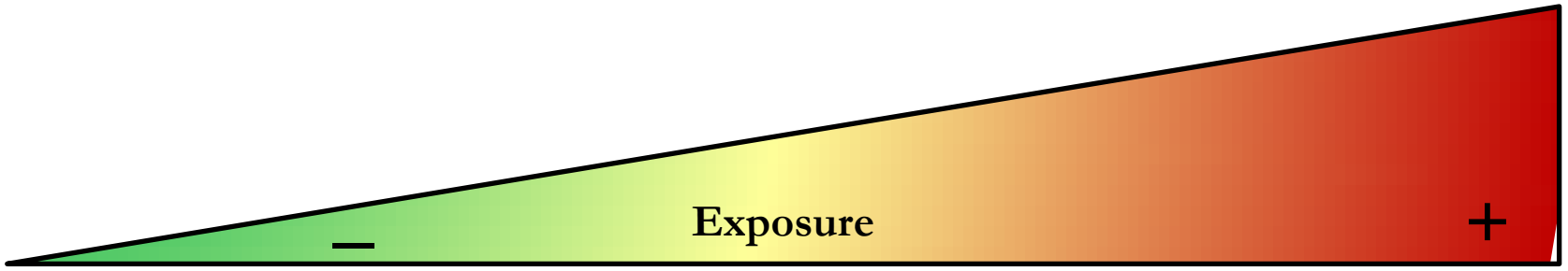
Background

- **<u>Rationale:</u>** Address the continued development and validation of alternative tests for developmental toxicity that would ultimately decrease the time, expense and use of vertebrate animals



Alternative Approach:

Chemical + Exposure



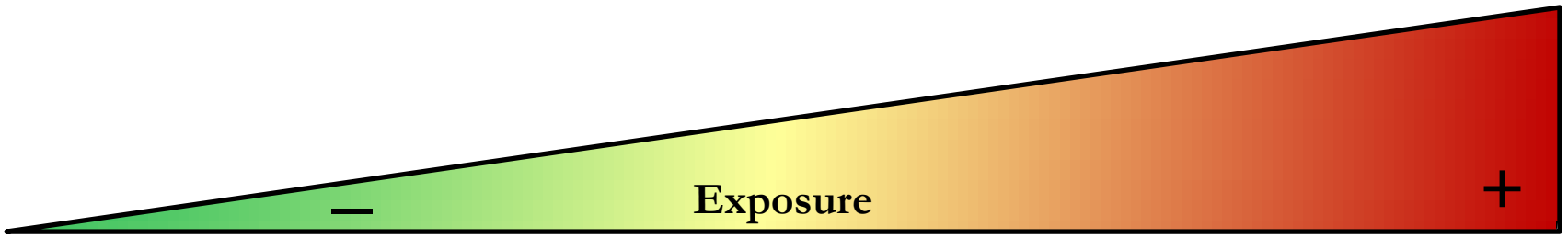
Developmental Non-Toxicant → ? ? ? → **Developmental Toxicant**

Permanent Adverse Effect

Unambiguous endpoints:

- embryo-fetal death
- structural malformation

Constructing the "Gold Standard" List



- **Exposure at the maternal Maximally Tolerated Dose that produces no adverse effects in the offspring (or) lower and ineffective dose of a compound that is toxic at higher concentrations**
- Benchmark dose approach (rather than NOAEL)

- **Internal dose metric (levels of active agent in maternal blood or embryo) linked to adverse outcome**
- Based on:
  - Mammalian dev tox studies
  - Human data
- Peak exposure (default) or AUC

Birth Defects Research (Part B) 89:526–530 (2010)

Original Article

A Different Approach to Validating Screening Assays for Developmental Toxicity

George P. Daston,[1*] Robert E. Chapin,[2] Anthony R. Scialli,[3] Aldert H. Piersma,[4] Edward W. Carney,[5] John M. Rogers,[6] and Jan M. Friedman[7]

[1]Procter & Gamble, Cincinnati, Ohio
[2]Pfizer Global R&D, Groton, Connecticut
[3]Tetra Tech Sciences, Arlington, Virginia
[4]RIVM, Bilthoven, The Netherlands
[5]The Dow Chemical Company, Midland, Michigan
[6]Toxicity Assessment Division, NHEERL, ORD, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina
[7]Department of Medical Genetics, University of British Columbia, and Child & Family Research Institute, Vancouver, British Columbia, Canada

Workshop on the Consensus List of Developmental Toxicants

May 17-18, 2011
Washington, DC

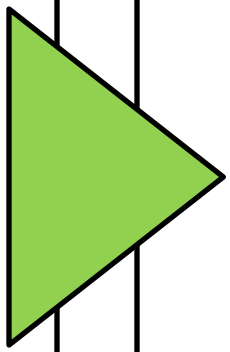
<u>Charge:</u> Determine positive or negative exposures based on existing data sets through focused break-out group discussions

<u>Criteria:</u>

- ✓ Adequate toxicity and kinetic data to identify exposure levels based on maternal or fetal concentrations
- ✓ Rat studies
- ✓ Positive response = increase in EFD structural malformation

Key Workshop Learning

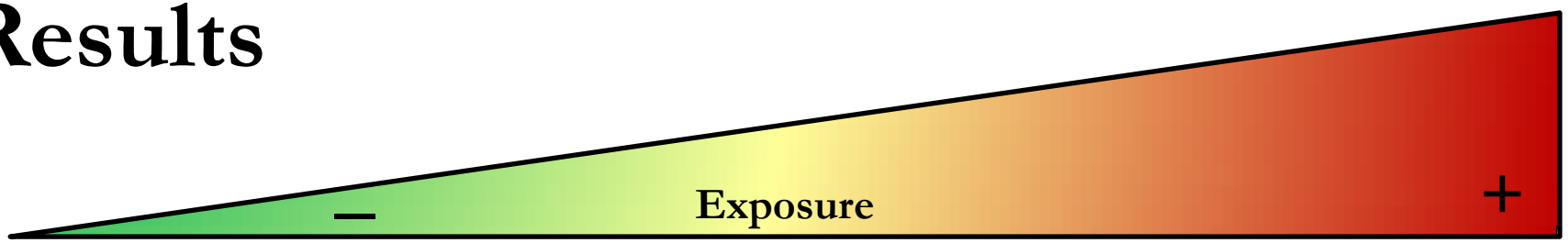
- Many data sets lack adequate kinetic data



Follow-Up Literature Searches

- NLM data bases
- NTP reports
- Publically available FDA documents

Results



Developmental Non-Toxicant → ? ? ? Permanent Adverse Effect → **Developmental Toxicant**

SB-209770

Hydroxyurea

Salicylic acid

Dabigatran

Fingolimod

Abacavir

Sodium saccharin

Artesunate

Valproate

Ethylene glycol

Acetazolamide

Ramelteon

Methylmercury

Nilotinib

Zidovudine

Acetazolamide

D,L-3-hydroxy-3-ethyl-3-phenylpropionamide (HEPP)

Caffeine

Methoxyacetic acid

Glycolic acid

MEHP

Methanol

All-trans-retinoic acid

Butylparaben

Propylene glycol

Oseltamivir

Tapentadol

Next Steps

- Publish Validation List:

  Daston GP, Beyer BK, Carney EW, Chapin RE, Friedman JM, Piersma AH, Rogers JM and Scialli AR. **Exposure-Based Validation List for Developmental Toxicity Screening Assays.** (*in review*)

- New workgroup convening to validate the compounds across different *in vitro* systems

	Gold Standard: Developmentally Toxic Exposure	
In Vitro Assay	Yes	No
Positive	True +	False +
Negative	False –	True –

Sensitivity = TP/(TP+FN)
Specificity = TN/(TN+FP)

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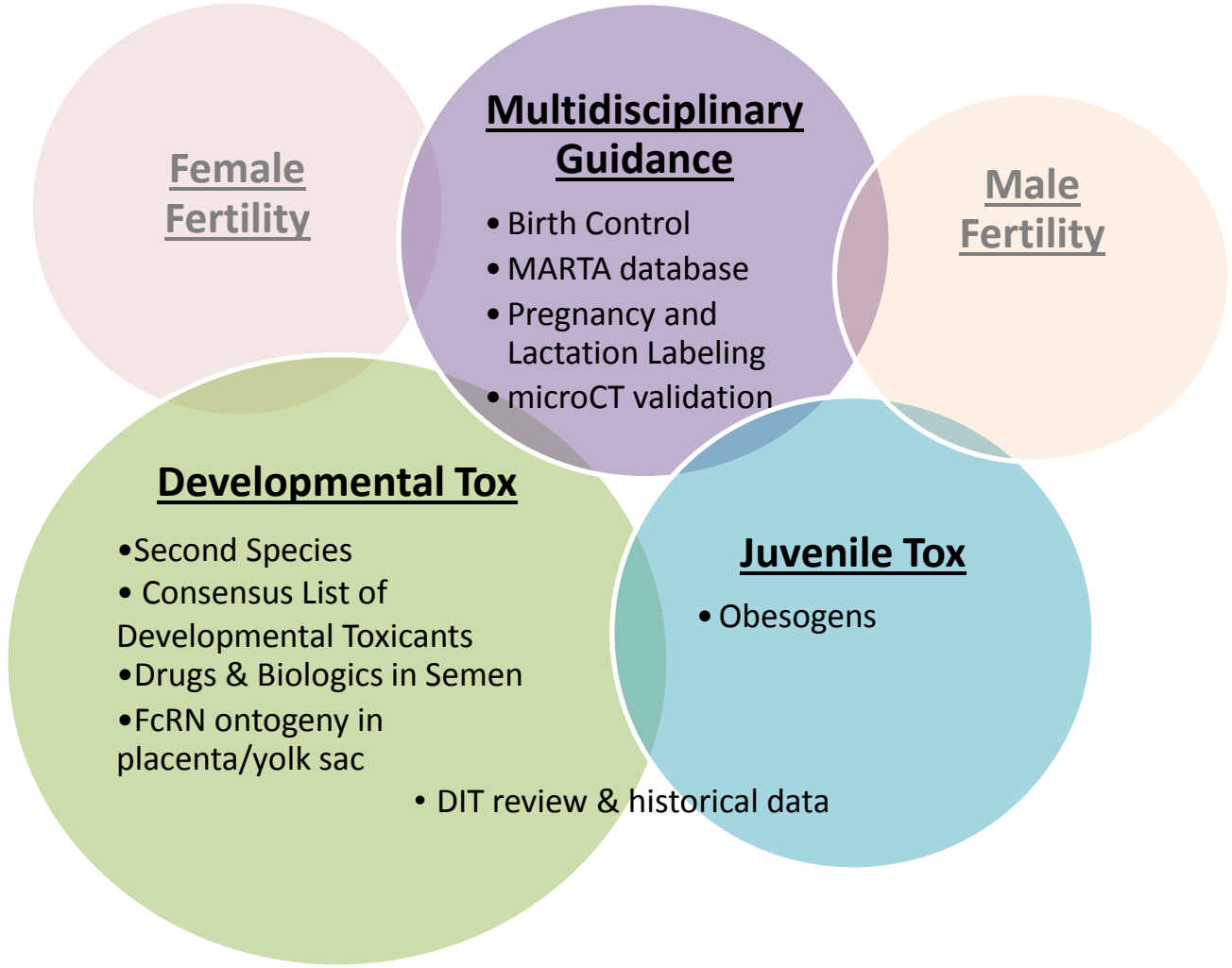

Thank you!

For questions or additional information about DART Technical Committee activities, contact:

Connie Chen (cchen@hesiglobal.org)