NTP
National Toxicology Program

Peer Review of Draft NTP Developmental and Reproductive Toxicity Technical Reports

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NTP Technical Reports Peer Review Meeting
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National Toxicology Program (NTP) Technical Reports

- Peer-review of draft NTP Developmental and Reproductive Toxicity (DART) reports:
  - DART-01: Tris (chloropropyl) phosphate (TCPP)
  - DART-02: 4-Methylcyclohexanemethanol (MCHM)
  - DART-03: Vinpocetine
  - DART-04: Dimethylethanolamine Bitartrate (DMAE)

- These reports present Level of Evidence (LOE) conclusions from studies that evaluated potential prenatal developmental toxicity of the test article

Prenatal Developmental Toxicity Studies

- Developmental and Reproductive Toxicity studies cover a wide range of biological development and reproduction
  - These reports are focused on potential prenatal developmental toxicity and maternal toxicity
- Studies followed a typical design of dosing from implantation of the embryo to prior to delivery
  - To select doses for the main study, a dose range finding study is conducted using a smaller number of animals
- Level of evidence (LOE) conclusion was applied based on the findings in each report
  - A single LOE conclusion for each test article

- Maternal endpoints: Clinical observations, body weights, feed consumption, and uterine parameters
- Fetal endpoints: Fetal weight, external, visceral, skeletal examination, live/dead fetuses, and sex ratio

NTP DART Level of Evidence

- NTP conducts rodent studies on agents of public health concern to identify potential hazards for human health

- NTP expanded the formal evaluation to other hazard endpoints by developing Level of Evidence categories for Developmental Toxicity and Reproductive Toxicity

- These level of evidence categories follow a similar pattern as the carcinogenicity categories (e.g. clear, some, equivocal evidence), but criteria were adapted to DART data interpretation

Levels of Evidence (LOE) of Developmental Toxicity

- **Clear evidence:** A dose-related effect on one or more of its four elements (embryo-fetal death, structural malformations, growth retardation, or functional deficits) that is not secondary to overt maternal toxicity.
- **Some evidence:** Dose-related effects on one or more of its four elements (embryo-fetal death, structural malformations, growth retardation, or functional deficits), but where there are greater uncertainties or weaker relationships with regard to dose, severity, magnitude, incidence, persistence, and/or decreased concordance among affected endpoints.
- **Equivocal evidence:** Marginal or discordant effects on developmental parameters that may or may not be related to the test article.
- **No evidence:** Appropriate experimental design and conduct that are interpreted as showing no biologically relevant effects on developmental parameters that are related to the test article.
- **Inadequate study:** precludes interpretation

Factors Considered in Applying DART LOE Categories

- Dose-relationship
- Statistics
- Common versus uncommon findings
- Concurrent and historical control data
- Concordant effects
- Number of Litters affected
- Maternal Toxicity
- Findings in additional species
- Persistent vs Transient changes

https://ntp.niehs.nih.gov/testing/types/devrepro/index.html#study-criteria

DART Historical Control

- The concurrent control is more important for comparison than the historical control in interpreting findings
- However, historical control data can provide context of the findings
- NTP historical control for fetal pathology findings of Sprague Dawley (Hsd:Sprague Dawley SD) rats:
  - Publicly available: https://ntp.niehs.nih.gov/results/dbsearch/historical
  - Listed by contract lab, routes, etc
  - Provides individual study incidence and overall incidence for external, visceral, and skeletal findings
  - Additional endpoints are being added to expand the database

Charge to the Panel

- Review and evaluate the scientific and technical elements of the study and its presentation

- Determine whether the study's experimental design, conduct, and findings support the NTP's conclusions regarding the developmental toxicity of the substance tested

Questions?