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
• 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
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
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](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
• 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?