NTP
National Toxicology Program

Peer Review of Draft NTP Developmental and Reproductive Toxicity (DART) Reports

Chad Blystone, PhD, DABT
Division of the National Toxicology Program
National Institute of Environmental Health Sciences

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

- NTP conducts rodent developmental and reproductive toxicity (DART) studies on agents of public health concern to identify potential hazards for human health.
- NTP DART reports describe the methods, results, and NTP conclusions as “levels of evidence” under the specific conditions of the study. These two reports are the first NTP Modified One Generation (MOG) studies to be peer-reviewed.
- Peer-review of draft DART Reports:
  - Draft NTP DART Report on 2-Hydroxy-4-methoxybenzophenone (2H4MBP)
  - Draft NTP DART Report on 2-Ethylhexyl p-Methoxycinnamate (EHMC)
- These reports present Level of Evidence (LOE) conclusions for Reproductive and Developmental toxicity based on pre-determined criteria.
  - One set of criteria for *Reproductive Toxicity* and another set of criteria for *Developmental Toxicity*

https://ntp.niehs.nih.gov/whatwestudy/testpgm/devrepro/index.html

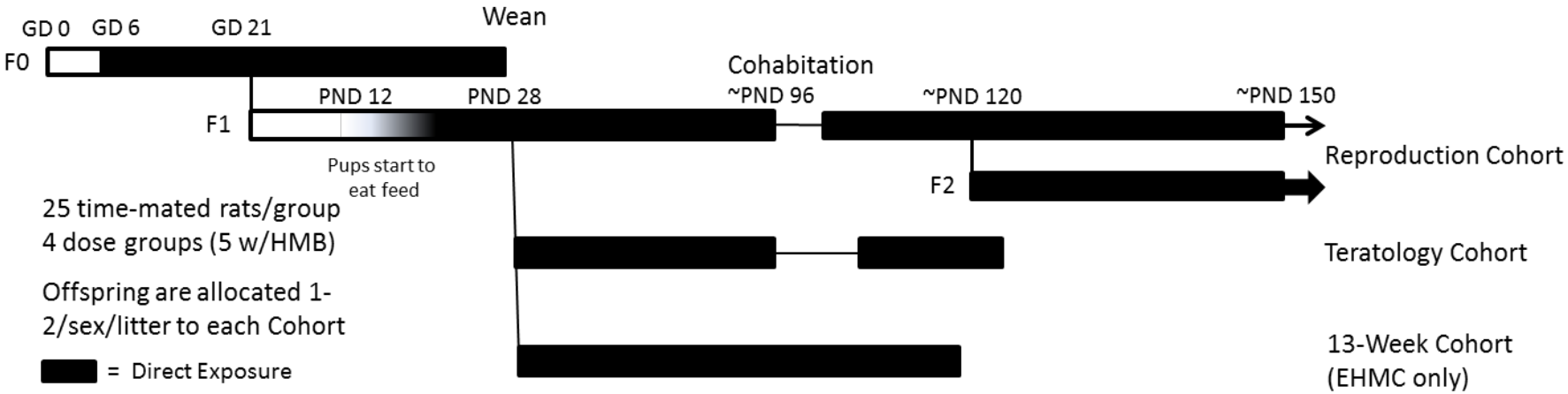
Modified One Generation Study Design

Multiple goals:

- Study test agent exposure during critical periods of development (i.e., *in utero*, postnatal, sexual maturation)
- Use multiple F_1 cohorts to assess potential areas of toxicity (e.g., reproduction, teratology, general toxicity):
  - Provides information on multiple endpoints which the inter-relationship can be assessed
  - Makes the best use of the animals produced
- Power the cohorts to provide definitive hazard identification and dose-response information
  - Cross “cohort” comparisons allow for robustness of subtle effects

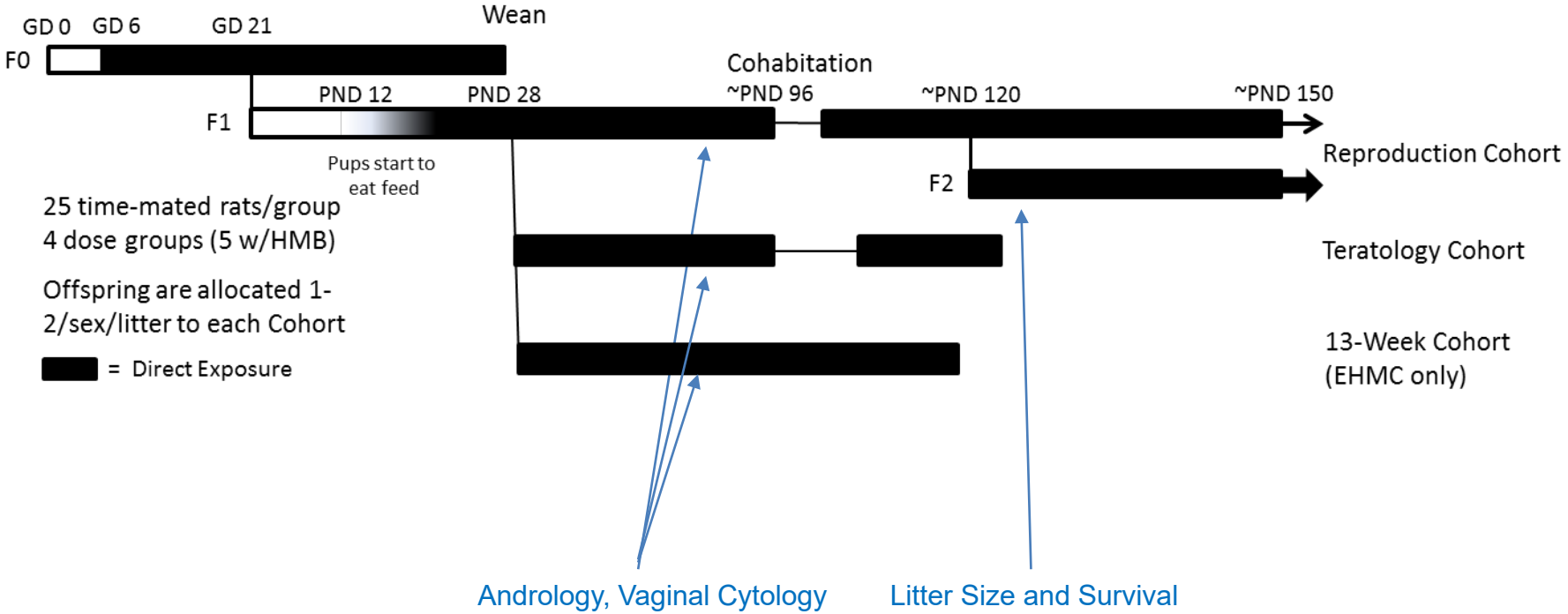
Modified One Generation Study Design

Multiple Cohorts



Modified One Generation Study Design

Reproductive Toxicity



Levels of Evidence (LOE) of Reproductive Toxicity

- **Clear evidence of reproductive toxicity**
  - Dose-related effect on fertility or fecundity, or by changes in multiple interrelated reproductive parameters of sufficient magnitude that by weight of evidence implies a compromise in reproductive function

- **Some evidence of reproductive toxicity**
  - Effects on reproductive parameters, the net impact of which is judged by weight of evidence to have potential to compromise reproductive function. Relative to clear evidence of reproductive toxicity, such effects would be characterized by greater uncertainties or weaker relationships with regard to dose, severity, magnitude, incidence, persistence, and/or decreased concordance among affected endpoints

- **Equivocal evidence of reproductive toxicity**
  - Marginal or discordant effects on reproductive parameters that may or may not be related to the test article

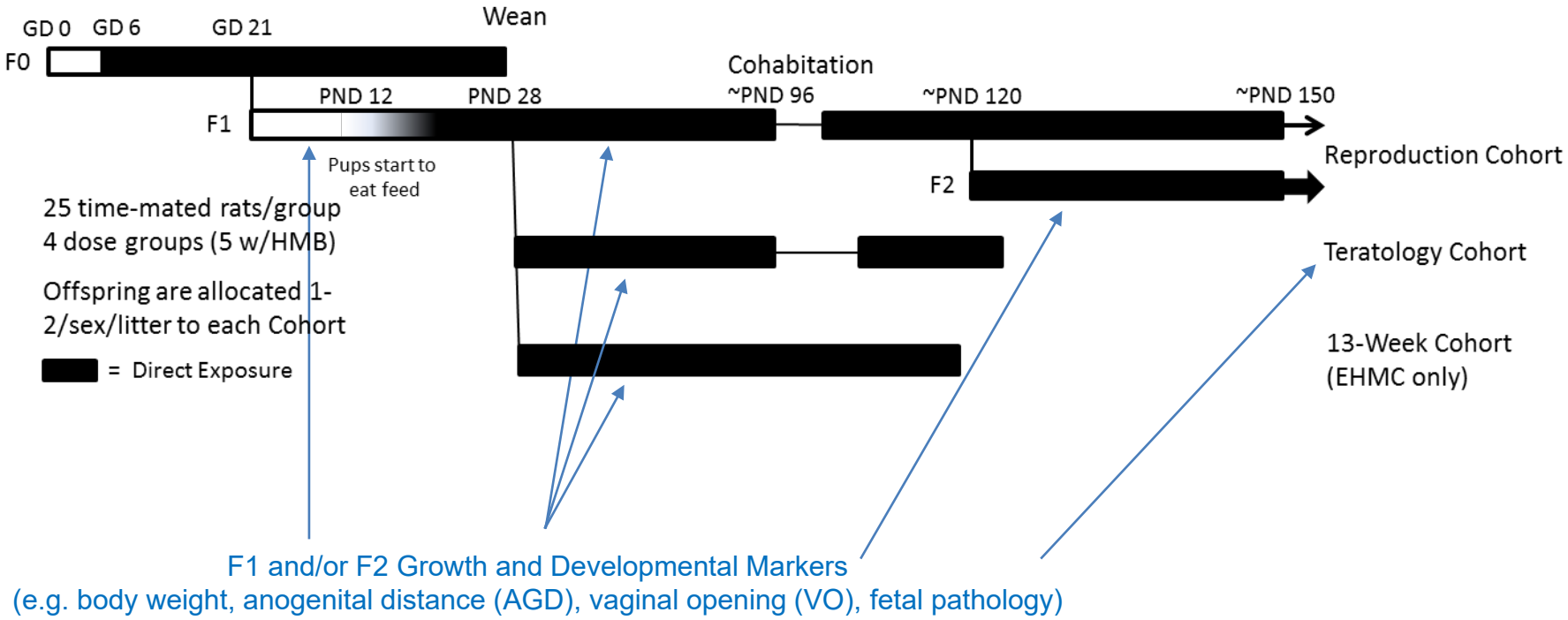
- **No evidence of reproductive toxicity**

- **Inadequate study**

https://ntp.niehs.nih.gov/ntp/htdocs/levels/09_3566_ntp_reprotox_r1.pdf

Modified One Generation Study Design

Developmental Toxicity



Levels of Evidence (LOE) of Developmental Toxicity

- **Clear evidence of developmental toxicity**
  - 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 of developmental toxicity**
  - 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 of developmental toxicity**
  - Marginal or discordant effects on developmental parameters that may or may not be related to the test article
- **No evidence of developmental toxicity**
- **Inadequate study**

https://ntp.niehs.nih.gov/ntp/test_info/ntp_devtox20190628.pdf

Examples of Factors considered in applying LOE

- Dose-relationship
- Common versus uncommon lesions
- Statistics
- Concurrent and historical control data (fetal pathology)
- Concordant effects and relationships among findings
- Number of animals and/or litters affected
- Confounding findings: maternal toxicity
- Persistent vs transient changes
- Insights from supportive studies (e.g., toxicokinetic, mechanistic, structure-activity)

https://ntp.niehs.nih.gov/ntp/htdocs/levels/09_3566_ntp_reprotox_r1.pdf
https://ntp.niehs.nih.gov/ntp/test_info/ntp_devtox20190628.pdf

Questions?

Charge for the Peer-Review Panel

- Review and evaluate the scientific and technical elements of each study and its presentation.
- Determine whether each study's experimental design, conduct, and findings support the NTP's conclusions for reproductive and developmental toxicity under the conditions of each study.

Questions?