Application of a Controlled Vocabulary to Curated Databases of *In Vivo* Developmental Toxicity Data

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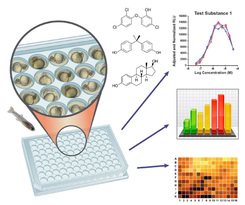
DART Test Methods: Traditional and Alternatives

- **Traditional** developmental and reproductive toxicity (DART) testing:
  - Uses animals to inform about *in vivo* risks
  - Requires significant time and resources
- **Alternative** DART testing:
  - Includes *in vitro* assays, small model organisms, and computational models
  - Can provide mechanistic insight
  - Generates large amounts of data
- Challenges to acceptance of alternatives include the need to:
  - Demonstrate scientific soundness
  - Characterize relevance and utility
  - Identify limitations and applicability domain
  - Draw valid comparisons to *in vivo* data
- *In vitro* and *in vivo* assays can provide different information on the key events underlying toxicity.
- Key events can be organized within an adverse outcome pathway (AOP) that allows for combining data from multiple tests into a testing strategy.
- However, combining data from different sources requires that these data be standardized and consistently annotated.
- This poster describes the challenges to using currently available data to validate alternatives to traditional mammalian models for DART testing, and ongoing annotation efforts.

Zebrafish as an Alternative Method

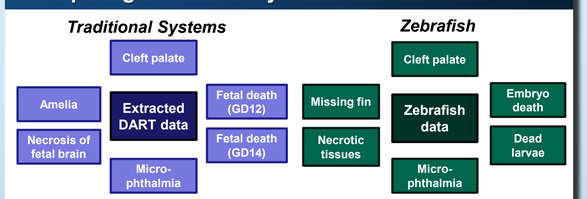
- The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) is coordinating the analysis of data being generated in multiple laboratories using an embryonic zebrafish model of developmental toxicity.
- This analysis is part of the Systematic Evaluation of the Application of Zebrafish in Toxicology effort (SEAZIT; **Poster P36**).
  - Zebrafish are promising model organisms that can be screened in a high-throughput format, making them an attractive alternative to mammals for DART testing.
  - Broader use of zebrafish in this context is hampered by a lack of harmonization in experimental data reporting, making comparisons between zebrafish and traditional mammalian tests difficult.



Evaluation of Alternative Methods

- NICEATM extracted data from *in vivo* mammalian developmental toxicity studies performed by NTP and from chemical registration dossiers available from the European Chemicals Agency (Ceger et al. 2017).
  - The extracted data were intended to be used for the evaluation of alternative methods (e.g. zebrafish), but endpoints were numerous (n > 13,000) and non-standardized, limiting their ability to be compared to data from other assays.
  - Work is ongoing to standardize the extracted data to improve utility, and to develop a mapping between controlled vocabularies.
- In order to adequately characterize the usefulness and limitations of zebrafish methods, developers and reviewers need:
  - Chemicals with well-established and understood effects on mammalian development, with consistently defined and annotated endpoints
  - A way to link zebrafish and mammalian responses

Comparing Traditional Systems with Zebrafish

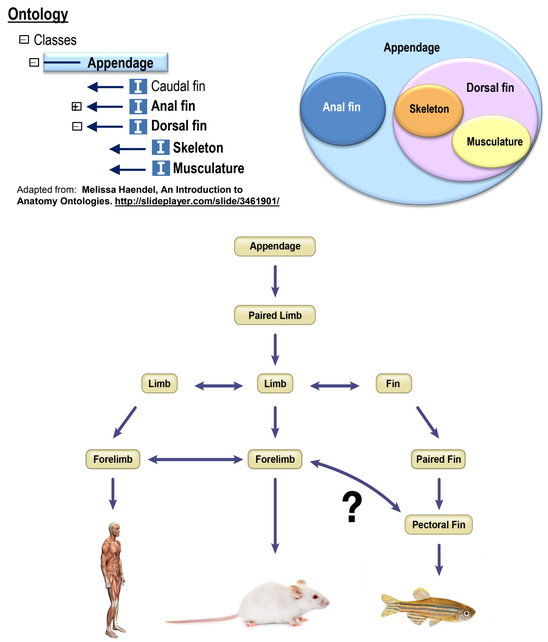


- Data in both systems are not standardized or annotated using controlled terminology, preventing easy comparisons.
- Knowledge organization systems (KOS) can be used to map endpoints, enabling comparisons between zebrafish and traditional systems.

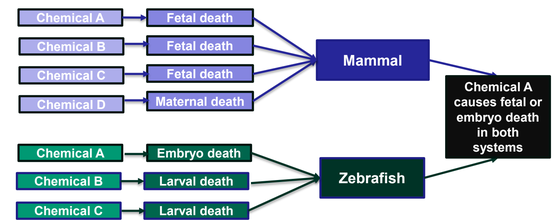
KOS Facilitate Analyses

- **Knowledge organization systems** (KOS):
  - Include levels that increase in complexity from controlled vocabulary through ontology to meta-models
  - Allow for the application of standardized vocabulary terms to facilitate comparisons within and between systems
  - Provide information on linkages within and between systems
  - Link chemical exposures to phenotypic endpoints/adverse events
  - Help map molecular, cellular, and tissue-level changes, as well as phenotypic adverse events, to AOPs

Using KOS to Relate Mammalian to Zebrafish Data



Using KOS to Relate Chemical Effects in Mammals and Zebrafish



Internal Standardization and Mapping

- Determine whether an endpoint contains multiple pieces of data
  - Break out each piece of data, e.g., "Fetal death (Gestational Day 12)" becomes "Fetal death, GD12"
- Identify related terms and synonymous endpoints
- Curate to standardized controlled vocabularies
- Map terms to relevant thesauri or ontologies

Extracted DART Data
Amelia
Necrosis of the fetal brain stem
Cleft palate
Microphthalmia
Fetal death (GD12)
Fetal death (GD14)

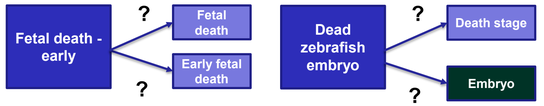
Original Endpoint	Endpoint Modifier	Curated Endpoint	Ontology
Amelia	NA	Amelia	MedDRA
Necrosis of the fetal brain	Fetus	Brain necrosis	IOBC
Cleft palate	NA	Cleft palate	SnoMed CT
Microphthalmia	NA	Microphthalmia	MedDRA
Fetal death (GD12)	GD12	Fetal death	SnoMed CT
Fetal death (GD14)	GD14	Fetal death	PLOS Thesaurus

Zebrafish Data
Missing fin
Necrotic tissues
Cleft palate
Microphthalmia
Embryo death
Dead larvae

Original Endpoint	Endpoint Modifier	Curated Endpoint	Ontology
Missing fin	NA	Fin absent, abnormal	ZPO
Necrotic tissues	NA	NA	NA
Cleft palate	NA	Cleft palate	Uberon
Microphthalmia	NA	Eye abnormal	ZPO
Embryo death	Embryo	Death	Uberon
Dead larvae	Larva	Death	Uberon

Issues with Standardization and Mapping

- Some steps require expert judgment.
  - For example, should "fetal death - early" be mapped as "fetal death" or "early fetal death"?
- Some KOS are purpose-driven; not all endpoints are represented.
- Some KOS are species-driven; not all endpoints are represented for all species.
- Certain endpoints may need to be mapped to more than one term. There is no one term for zebrafish embryo death, so it needs to be mapped to "embryo" and to "death."
- Cross-species KOS are still in early development.



Conclusions

- Developing alternatives to traditional *in vivo* DART tests presents many challenges, including access to standardized and annotated reference data so that *in vivo* endpoint descriptions are sufficiently homogeneous to be integrated across sources.
- Standardization and annotation requires use of KOS, however:
  - Curation of the data requires expert knowledge, both of the subject matter and of KOS.
  - KOS are purpose- and species-driven; a given system may not contain all relevant endpoints for all relevant species.
  - Cross-species KOS are still in early development.
- Method developers working with KOS developers can increase usability of models and KOS.
- Use of KOS by alternative method developers can add clarity and context to *in vivo* relationships and increase usability of the alternative methods.

Future Directions

- Consult with subject matter experts to improve term standardization and mapping.
- Work with KOS developers to improve endpoint representation within and between species.
- Compare mammalian and zebrafish developmental assay data.
- Make curated and annotated datasets available to the public.

References

Ceger P., Choksi N., Hamm J., Truax J., Daniel A., Allen D., Sutherland V., McIntyre B., Foster P., Maull E., Casey W. Development of a Curated Database of In Vivo Developmental Toxicity Data. 56th Annual Meeting of the Society of Toxicology, Baltimore, MD. 2017

Noy NF, Shah NH, Whetzel PL, Dai B, Dorf M, Griffith N, et al. 2009. BioPortal: ontologies and integrated data resources at the click of a mouse. Nucleic Acids Res 37:W170–W173; doi:10.1093/nar/gkp440.

Xiang Z, Mungall C, Ruttenberg A, He Y. Ontobee: A Linked Data Server and Browser for Ontology Terms. Proceedings of the 2nd International Conference on Biomedical Ontologies (ICBO), July 28-30, 2011, Buffalo, NY, USA. Pages 279-281.

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