Capturing prenatal developmental toxicity data using the Data Collection Tool (DCT): Pilot curation summary

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Rationale

- In vivo study results inform toxicity predictions as training data or may be used to build scientific confidence in the performance of new approach methodologies (NAMs).
- NAM and animal study data need to be computationally accessible and interoperable.
- An application-driven curation workflow was created to support expansion of the chemical and study data coverage in the Toxicity Reference Database (ToxRefDB).

History & Current Workflow

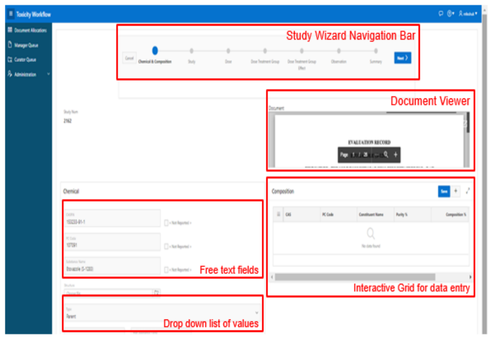
ToxRefDB contains in vivo data from over 5000 animal studies for over 1000 chemicals. This database was developed via manual curation.

The data collection tool (DCT) is an Oracle APEX software developed for curation of additional legacy documents with enhanced quality control and data provenance capabilities.

The DCT includes:

- Document allocation, curation and workflow management among users, and management review with data conflict resolution, resulting in a record that directly links quality-controlled curation to source documents.
- Curation of basic study design metadata, dose-response, treatment-related and critical effects, and endpoint testing status information (with controlled vocabulary developed for ToxRefDB).

Figure 1: Inside a DCT Curation: The study wizard navigation bar displays the sections of the curation workflow: Chemical & Composition, Study, Dose, Dose Treatment Group, Dose Treatment Group Effect, and Observation. The Chemical & Composition page (displayed) features a document viewer that allows curators to view documents on a new tab within their internet browser.



Results

Prenatal developmental (DEV) studies were selected for curation since they represent a current data gap for NAM development and validation.

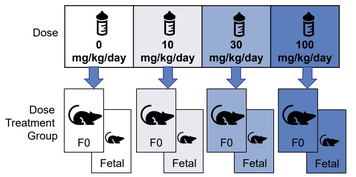
Data were extracted and made computationally accessible for 72 prenatal developmental (DEV) data evaluation records (DERs) from the EPA's Office of Pesticide Programs (OPP).

	Chemicals	Studies	Treatment Groups	Treatment Groups with Effects	Effects[a]	Critical Effects[b]	Unique Effects[c]	Unique Critical Effects[d]
Total	36	72	588	364	2079	673	155	119
Rat	35	35	290	183	1186	273	95	84
Rabbit	34	34	278	173	829	170	82	58
Mouse	3	3	20	8	64	6	22	5

Table A: Summary statistics from pilot DEV curation
The 72 DEV DERs contained 35 rat, 34 rabbit, and 2 mouse studies for 36 chemicals. Effects are defined as a combination of observation (endpoint category, endpoint type, and endpoint target) and effect description. Treatment groups *without* effects represent curated studies without significant treatment-related results. Across the 2079 effects curated, 155 unique effects were observed, of which 119 were deemed critical effects, that is, criteria for establishing NOAEL/LOAEL, in at least a single study.

a) Effects: Total number of observation (endpoint category, endpoint type, and endpoint target) and effect description combinations assigned to any treatment group. These include treatment-related effects that were statistically significant from the control.
b) Critical Effects: Effects deemed adverse by author that are criteria for establishing LOAEL
c) Unique Effects: Number of distinct effects assigned to at least one treatment group
d) Unique Critical Effects: Number of distinct critical effects assigned to at least one treatment group

Figure 2: DEV example of Dose Treatment Groups: As a prenatal developmental study design example, the number of doses administered (4) is multiplied by the number of treatment groups (2, dams and their litters) to determine the number of dose treatment groups (8) examined for effects at the time of sacrifice.



Effects[a] Breakdown	Count	Proportion
Maternal (F0)	1125	54.11% of effects
Systemic	960	85.33% of maternal effects
Clinical signs	234	24.38% of maternal systemic effects
Body weight	215	22.40% of maternal systemic effects
Food consumption	169	17.60% of maternal systemic effects
Reproductive	161	14.31% of maternal effects
Resorptions	47	29.19% of maternal reproductive effects
Aborted	30	18.63% of maternal reproductive effects
Post implantation loss	24	14.90% of maternal reproductive effects
Fetal	954	45.88% of effects
Developmental	804	84.28% of fetal effects
Bone	663	82.46% of developmental effects
Systemic	145	15.19% of fetal effects
Body weight	138	95.17% of fetal systemic effects

Table B: Effects breakdown by generation, endpoint category, and endpoint target
Count reflects the number of effects associated with any treatment group; *Proportion* reflects the percentage of effects within each grouping. Summarizing effects first by generation, maternal (F0) or fetal, is one logical way to array the responses among treatment groups. Effects associated with each generation can be grouped by endpoint category and further stratified by endpoint target to better understand trends in effects.

The controlled vocabulary reflect both the OCSPP Health Effects 870 series guidelines and DER summary reporting. This hierarchical relationship of effects and endpoints (Figure 3) was adapted from ToxRefDB.

Figure 3: Hierarchical terminology example for the "postimplantation loss" effect

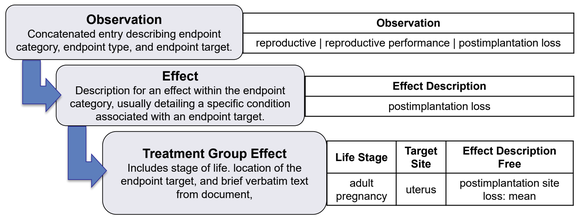
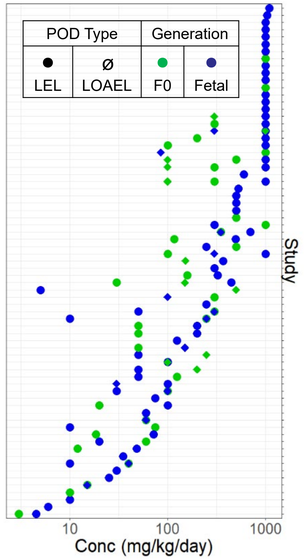


Table B examines the 2079 curated effects by generation, endpoint category, and endpoint target. The most common maternal effects include systemic effects (clinical signs, weight change and food consumption) followed by reproductive effects (resorptions and abortions). Developmental toxicity is described in terms of fetal weight reduction and skeletal variations.

Conclusions

When comparing the dose levels of the critical and treatment related effects by generation, the *maternal* (F0) lowest effect level (LEL) and lowest observed adverse effect levels (LOAEL) by study appear equal or more sensitive than the *developmental* LEL and LOAEL for approximately 82% of the 72 curated studies. The median range of difference was 40 mg/kg/day. Further analysis is needed to evaluate the chemicals flagged with developmental sensitivity compared to maternal toxicity.

Figure 4: POD Comparison by Generation: Points of departure (POD) can be derived from the dose response data. For both generations within each DEV study, the lowest effect level (LEL) was derived by identifying the lowest dose level at which treatment-related effects occur. The lowest observed adverse effect level (LOAEL) was derived by identifying the lowest dose level at which critical effects occur.



Future Directions

As curation of hundreds of additional DERs and study types (including chronic, subchronic, and multi-generational reproduction) with the DCT continues, this pilot dataset will be used to construct a sustainable pipeline for loading new legacy curations into ToxRefDB. These DEV studies will be reevaluated to understand their value added when compared to other DEV studies in future ToxRefDB releases. With ongoing curation, ToxRefDB will become a better resource for scientists and the interested public to access thousands of animal toxicity testing results, which is a crucial component in NAM validation to ultimately achieve reductions in animal testing.

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