ToxRefDB v2.1: A Minor Update to the Toxicity Reference Database

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Overview

A component of building scientific confidence in new approach methodologies (NAMs) for toxicology is comparison to results from in vivo studies. However, these efforts require NAM and animal study data to be computationally accessible and interoperable.

The US EPA's Toxicity Reference Database (ToxRefDB) aggregates in vivo data from nearly 6000 studies for over 1000 chemicals. Developed via a manual curation workflow, ToxRefDB serves as a resource for study design, quantitative dose response, and endpoint testing status information according to guideline specifications. An important component of ToxRefDB is its controlled vocabulary for studies and effects observed for enhanced data quality. Study coverage includes a variety of repeat dose study designs utilizing various administration routes. Study sources include data evaluation records (DERs) from the US EPA's Office of Pesticide Programs (OPP), NTP reports, pharmaceutical pre-clinical studies, and guideline-like open literature.

Figure 1: Study Coverage by Study Type and Species

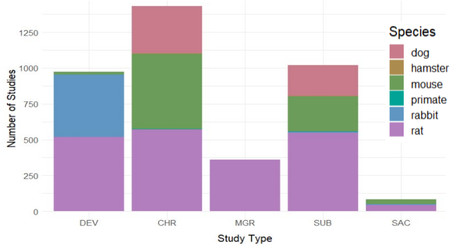
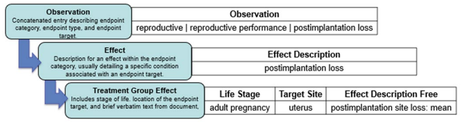


Figure 2: Example of Hierarchical Controlled Vocabulary



ToxRefDB v2.1

ToxRefDB v2.1 is a data update of ToxRefDB v2.0 to correct issues discovered with the compilation script that caused some extracted values to not import properly from AccessDB curation files, such as failure to import some effects. No additional curation was performed for the v2.1 update.

Visit this webpage to download the ToxRefDB v2.1 database package and accompanying user guide.

Version Comparison

The following table summarizes key differences between ToxRefDB v2.0 and v2.1:

Output	v2.0	v2.1	Change
Total number of studies with complete curation	3882	3871	-11
Number of studies with extracted effects	3068	3662	**594**
Total number of chemicals	748	748	0
Total database rows, including studies with no extracted effects	328623	344868	16245
Total effects extracted	313525	335281	**21756**
Dose treatment groups with effects	35679	40905	**5226**
Unique effects: Cholinesterase endpoint category	5323	6008	685
Unique effects: Developmental endpoint category	8502	9640	1138
Unique effects: Reproductive endpoint category	4691	5775	1084
Unique effects: Systemic endpoint category	284352	302674	18322
Unique critical effects: Cholinesterase endpoint category	713	796	83
Unique critical effects: Developmental endpoint category	1118	1276	158
Unique critical effects: Reproductive endpoint category	488	645	157
Unique critical effects: Systemic endpoint category	18757	20989	2232

Given the extent of added data, study and chemical-level analyses were conducted to evaluate the impact on the database, particularly in relation to aggregated points of departure (PODs). We derive PODs with qualifiers based on extracted effect data across effect profile groupings, including:

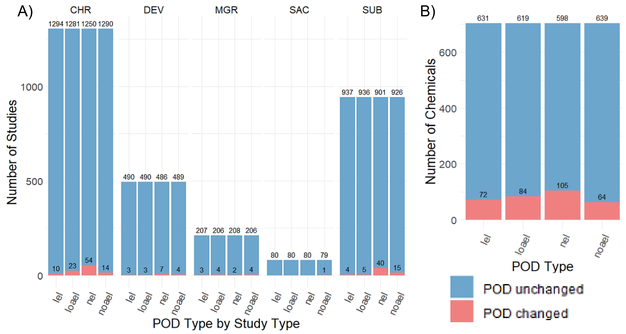
- **Lowest Effect Level (LEL):** Lowest dose with observed treatment-related effects
- **Lowest Observed Adverse Effect Level (LOAEL):** Lowest dose with observed critical effects
- **No Effect Level (NEL):** Highest dose with no observed effects, as inferred from LEL
- **No Observed Adverse Effect Level (NOAEL):** Highest dose with no observed critical effects, as inferred from LOAEL

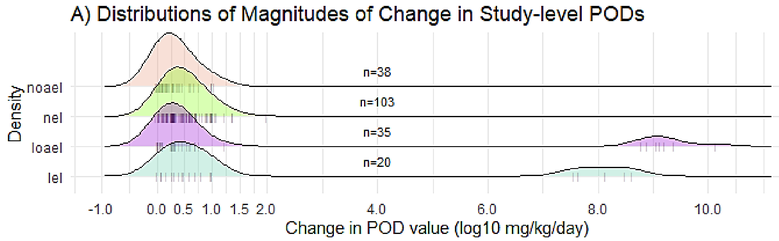
where *treatment-related* indicates effects were statistically significant from the control and *critical* designates adversity according to the study reviewer.

# of POD types changed	No change	One or more	Two or more	Three or more	All Four
All Studies	95%	5%	1%	0%	0%
All Chemicals	71%	29%	14%	2%	1%

Figure 3: POD Change: For each study and chemical, the lowest LEL, lowest LOAEL, highest NEL, and highest NOAEL were identified for comparison. A) Overall, only 5% of all studies had a change in 1 or more PODs with most change in chronic (CHR) & subchronic (SUB) study types and least change in the subacute (SAC) type. B) 29% of chemicals *across all study types* had a change in 1 or more POD types, with only 2% showing change in 3 or more.

These study-level comparisons do not consider the PODs added for the 594 studies with effects. Chemical-level change drastically decreases when subset to exclude the PODs added for the 377 DEV and 123 MGR studies that were most impacted by compilation error and have the most recovered data.





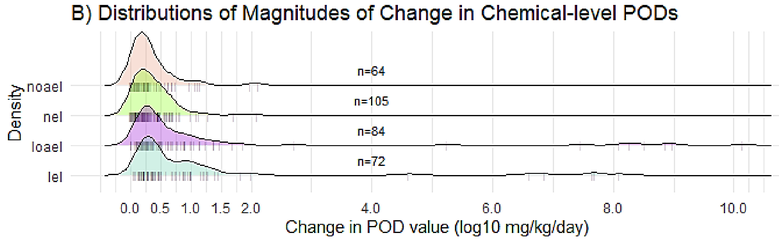


Figure 4: Magnitudes of POD Change: These density distributions show the magnitudes of the change in study-level and chemical-level PODs by pod type. A) Magnitude of change distributions across all study types could be examined to increase sample size. When all study types are combined, majority of study-level magnitude of change values fall under 1 log10-mg/kg/day. B) Majority of chemical-level magnitude of change values fall under 1 log10-mg/kg/day. Large outlying magnitude of change values can be explained by miscalculated v2.0 PODs given lack of data or new v2.1 PODs from studies with added effect data.

For more information, the complete analysis is provided within the ToxRefDB v2.1 release note.

Conclusions

This recovered data improves the utility of ToxRefDB as a resource for curated legacy in vivo information by providing more complete information of the past animal studies conducted. Moving forward, an application-driven workflow with the Data Collection Tool (DCT) will be utilized to create a more sustainable process for loading curated information to a database and support a more regular release cycle. Continued development increases ToxRefDB's utility as a resource for retrospective analyses that lay the foundation for acceptance of NAMs, as well as development of new predictive tools.

Disclaimer: This poster does not necessarily reflect U.S. EPA policy.

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