

ToxRefDB 2.0 Overview

Toxicity Reference Database (ToxRefDB) serves as a resource for retrospective and predictive toxicology

- ToxRefDB stores large sets of guideline and guideline-like *in vivo* chemical toxicological data
 - Aids in validation of *in vitro* high throughput screening of chemicals
 - Used in predictive model development
- Challenges addressed in ToxRef 2.0:
 - Controlled effect terminology for accurate data extraction, aggregation, and integration
 - Distinctions between negative effects and not tested effects
 - Quantitative data extraction, standardization, and conversions

Figure 1. Study sources.

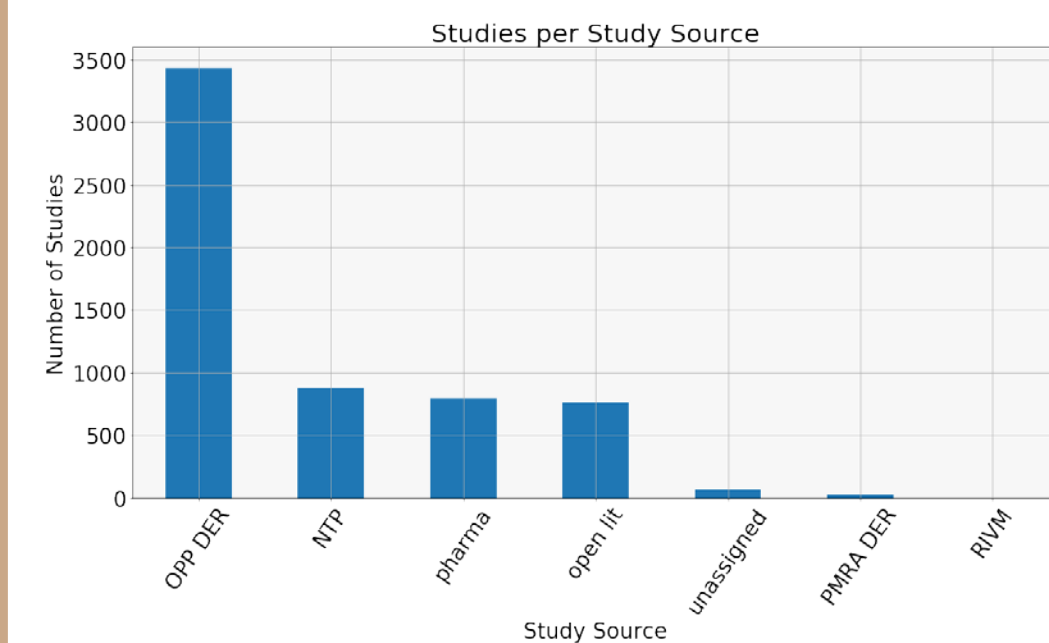


Figure 2. Study types. CHR: Chronic, DEV: Developmental, SUB: Subchronic, MGR: Multigenerational, SAC: Subacute, DNT: Developmental Neurotoxicity, REP: Reproductive, OTH: Other, NEU: Neurological, ACU: Acute

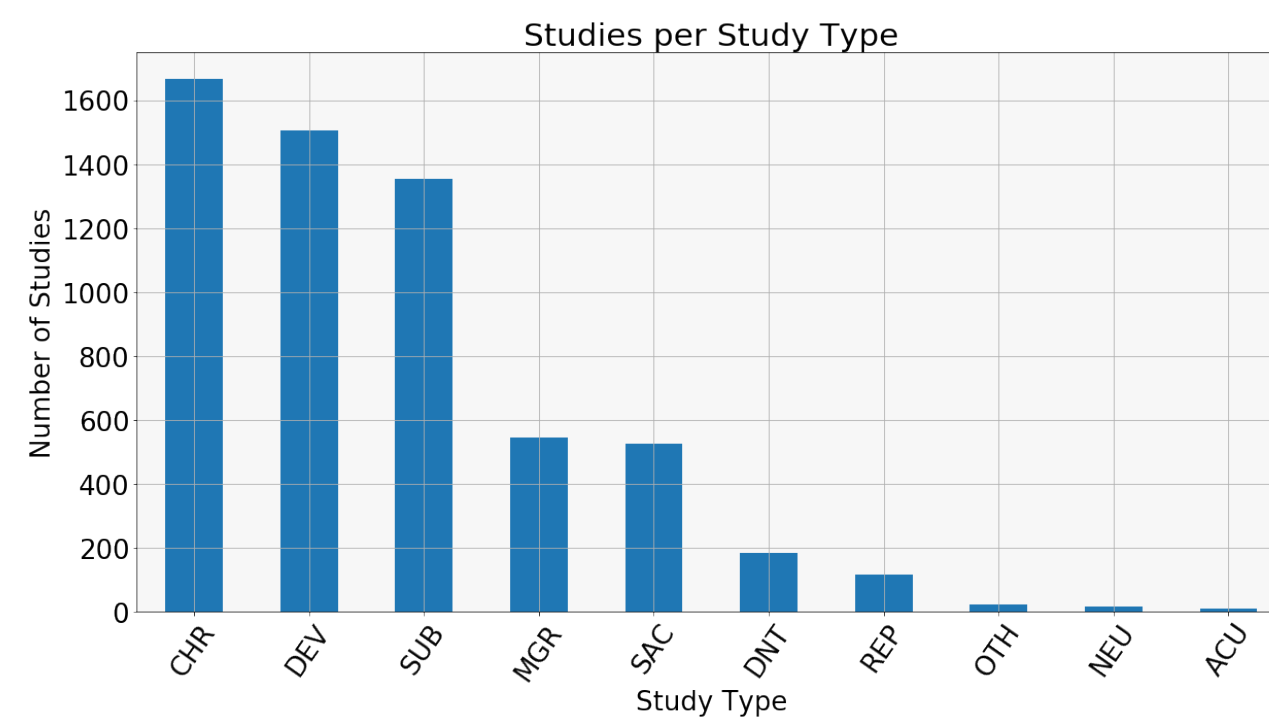


Figure 3A-C. ToxRefDB 2.0 general schema

A. Portion of ToxRefDB 1.0 that carried over to version 2.0 unchanged. B. Quantitative data was added as part of a data entry workflow. The previously extracted information from Figure 3A was checked for accuracy and modified/added for QA purposes. A three layer review process was implemented to ensure data integrity and minimize data entry error. C. Guideline profiles were developed that match language found in the studies. These guideline profiles were used for inference of negative endpoints/effects.

Endpoint Observation Status

- Endpoint observation status (not in ToxRefDB 1.0) distinguishes between negative vs. missing (not tested) effects
- Two binary fields were created to represent the testing status: "reported" and "tested"
- If an endpoint was required to be tested according to the study's specific guideline, then the database reflects this status as a 1, unless stated otherwise in the report (Table 1)

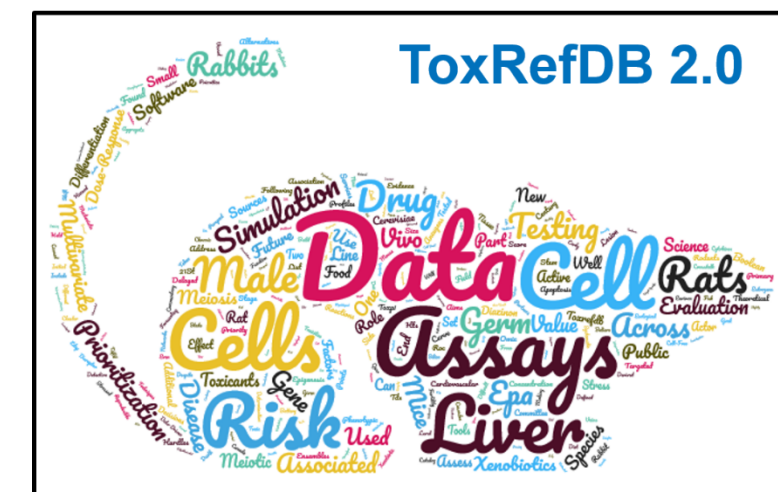
Table 1. Tested and reported status.

Reported	Tested	Rationale
1/true	1/true	The study reported that the endpoint was tested
1/true	0/false	The study reported that the endpoint was not tested <ul style="list-style-type: none">Triggered endpoints will start with this notation, and should be updated to R1,T1 if there is evidence that the endpoint was measured.
0/false	1/true	The study did not report that an endpoint was tested. <ul style="list-style-type: none">For example, if gross pathology was tested, but specific organs were not listed – this notation is for those organs indicated as "required" by guideline
0/false	0/false	The study did not provide any information on this endpoint whatsoever and it is not required by guidelines (no assumptions to be made; not listed in a table or text at all)

Endpoint Terminology Standardization and Data Integration

Figure 4. Endpoint hierarchy and standardization.

Endpoint language was updated to adhere to series 870 Health Effects Testing Guidelines created by the Office of Chemical Safety and Pollution Prevention (OCSPP). Effect mappings and subsequent layers were maintained



Endpoint	Category	Type	Target
	Systemic	Pathology Microscopic	Liver

Effect	Description
	Hyperplasia

Treatment Group-Related Effect	Life Stage	Target Site	Description Free
	Adult	Bile duct	intrahepatic bile duct hyperplasia

Category	Type	Target	Description	UMLS Concept Name
systemic	pathology microscopic	mammary gland	adenocarcinoma	Mammary gland
systemic	pathology microscopic	mammary gland	adenocarcinoma	Histopathology Result
systemic	pathology microscopic	mammary gland	adenocarcinoma	Adenocarcinoma
systemic	pathology microscopic	mammary gland	adenocarcinoma	Breast adenocarcinoma
systemic	pathology microscopic	mammary gland	adenocarcinoma	Mammary adenocarcinoma
systemic	pathology microscopic	liver	adenocarcinoma	Liver
systemic	pathology microscopic	liver	adenocarcinoma	Adenocarcinoma
systemic	pathology microscopic	liver	adenocarcinoma	Histopathology Result

Figure 5. Unified Medical Language System (UMLS) mapping. UMLS is a service provided by National Library of Medicine (NLM) where over 150 terminologies are mapped to concepts. National Cancer Institute (NCI) maintains a subset of these terminologies within their own domain. CDISC-SEND and related CDISC terminologies are cross-referenced with NCI. Among the other terminologies are SNOMED-CT (-VET) and Medical Subject Heading (MeSH).

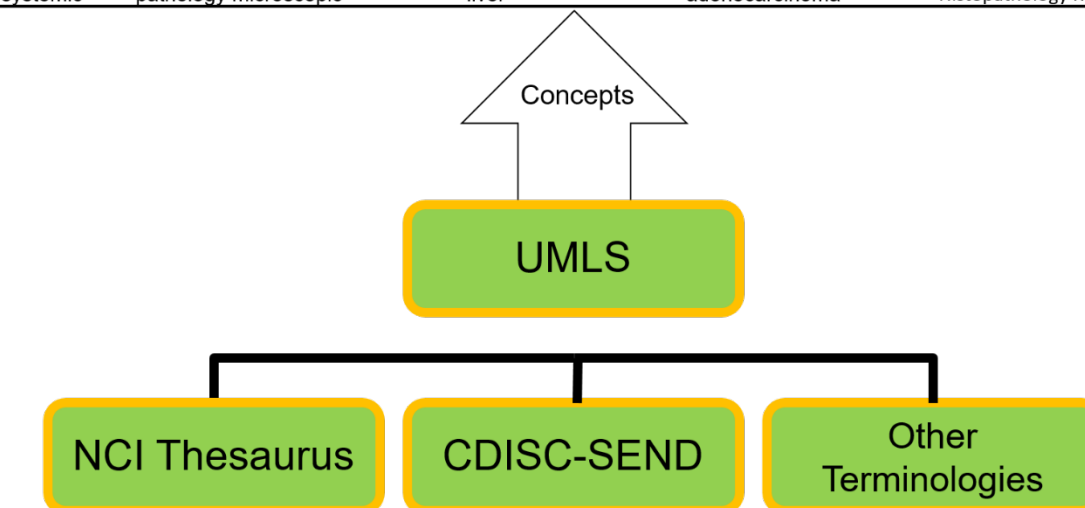


Table 2. ToxRefDB 2.0 endpoint and effects mapped to UMLS concepts. UMLS concepts are uniquely identified with a Concept Unique Identifier (CUI) and have a preferred name (UMLS Concept Name). UMLS Metathesaurus was searched using the endpoint and effect terminology to identify the best matching concept. Each endpoint and effect can be mapped to many different concepts.

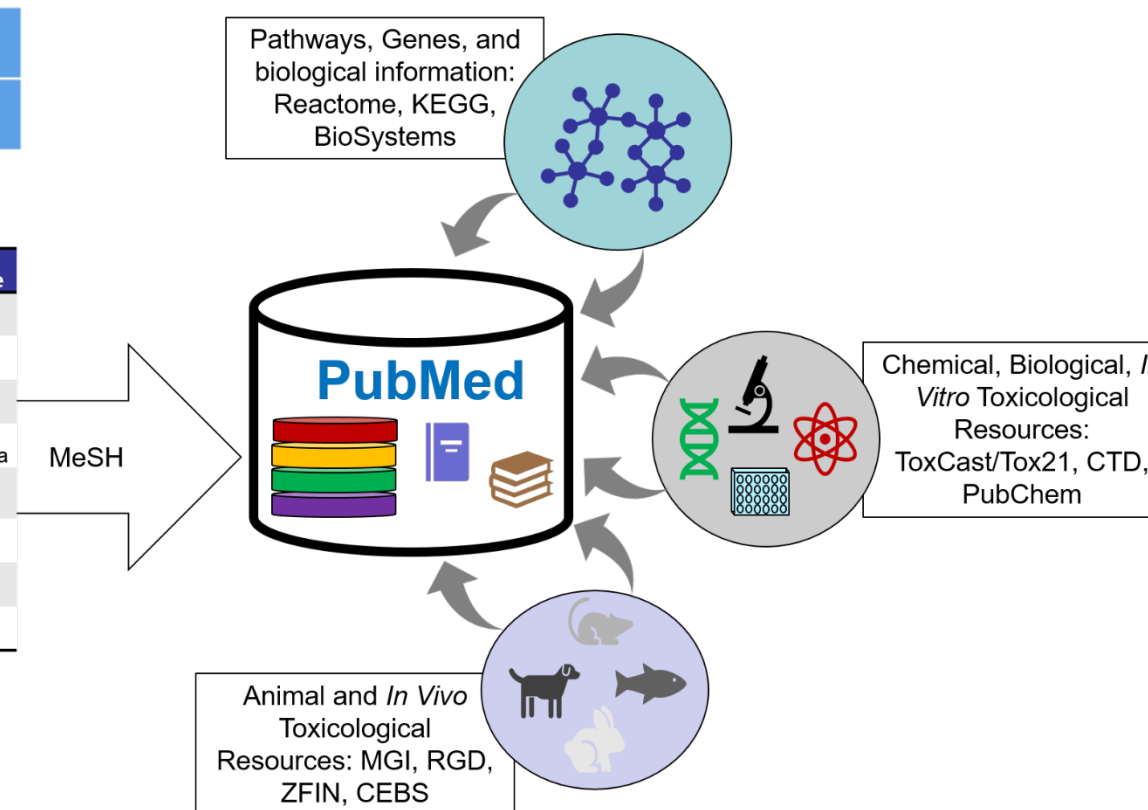


Figure 6. MeSH cross-references allow literature integration. MeSH are keywords that categorize articles by topic and are used by PubMed to index articles. By cross-referencing ToxRefDB endpoints and effects with MeSH, we can effectively map any other entities from numerous resources.

Identification of Negative Endpoints and Effects

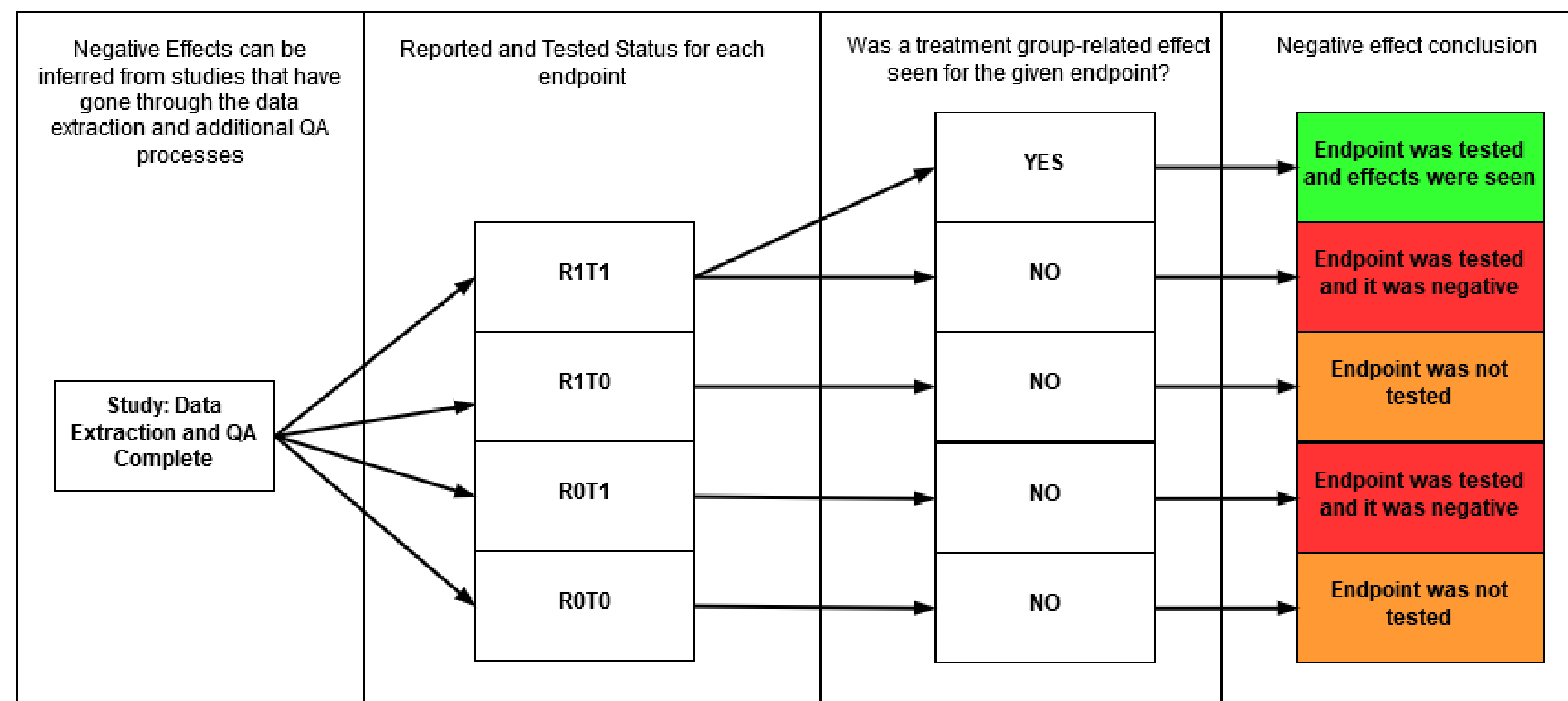


Figure 7. Decision tree for identification of negative endpoints and effects.

Negative endpoints and effects can only be identified in studies that have gone through data extraction and any subsequent QA processes because this ensures confidence in decisions made about the adherence and/or deviations from the corresponding guideline profiles. We can infer negatives based on whether or not an endpoint was tested and no treatment group-related effects were seen.

Benchmark Dose Modeling for ToxRefDB

- Calculate BMD and BMDL(U) for all effects, not just critical effects.
- Batch BMDs with python package bmds (<https://github.com/shapiromatron/bmds>)
- In the current pipeline, BMR=10% was used and all corresponding results were stored.

A

Dose	Sample Size	Mean	Standard Deviation
0	25	2.61	0.81
10	25	2.61	1.19
50	24	2.96	1.37
150	24	4.66	1.72
400	24	11.23	2.84

B

Model Name	BMD	BMDL	AIC	Recommended
Linear	51.12	42.90	228.24	FALSE
Polynomial	88.35	61.52	221.68	FALSE
Power	94.74	66.75	221.89	FALSE
Hill	94.78	67.27	223.89	FALSE
Exponential	93.78	82.45	220.02	TRUE

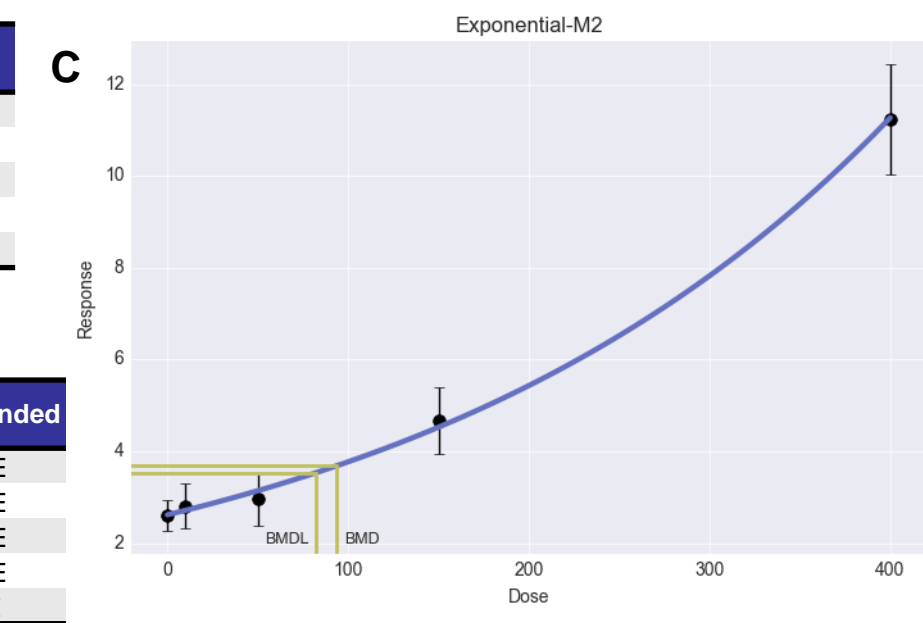


Figure 8: BMD example. (A) Input data for kidney weight percentage relative to body weight. (B) Five of the 10 modeled outputs from BMDs. (C) Plot of the recommended model output.

BMD Summary Statistics

- Quantitative data extraction and QA has been completed for over 3700 studies
 - Includes CHR/SUB OPP DERs and NTP studies

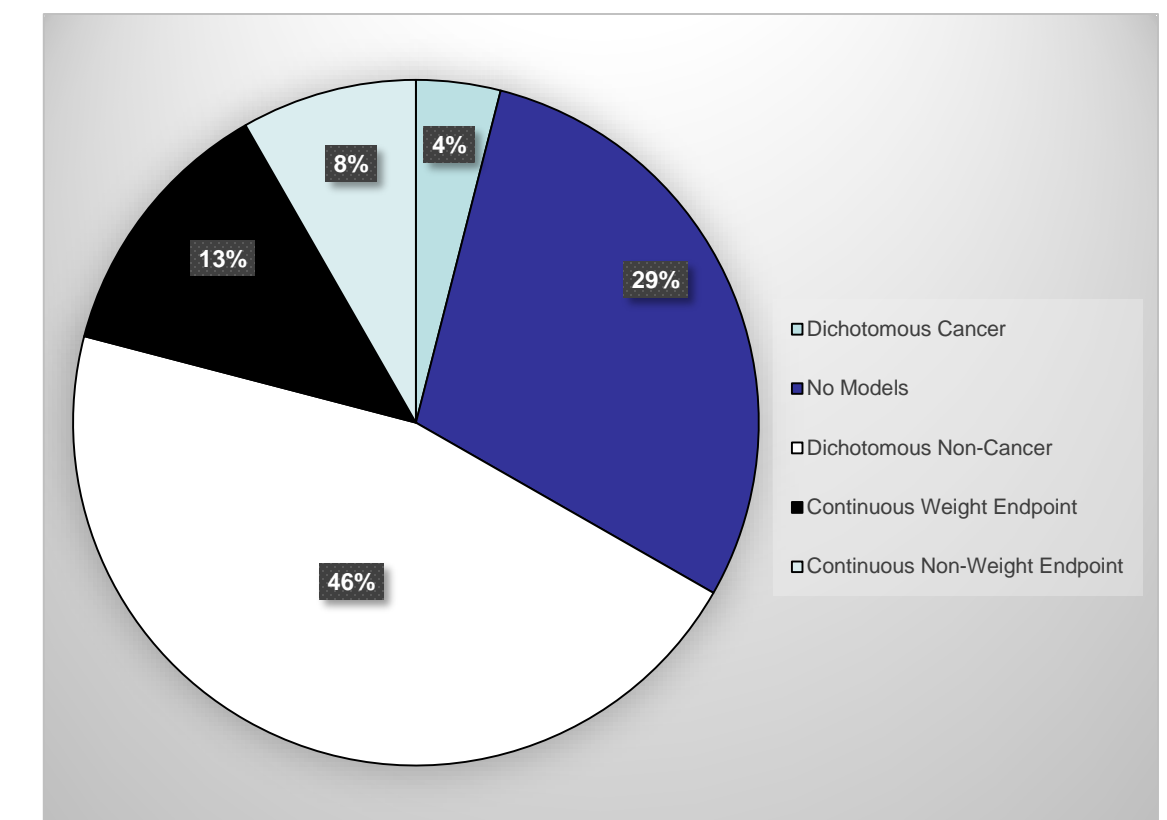
Table 3: Unit standardization for incidence data

Units	Notes and Conversions
"incidence", "Incidence", "incidences", "incidence ", "incidents", "incidence", " incidence"	All the variations of incidence in the database
"% incidence"	Can convert to incidence unit
"incidence survival "	Can convert to incidence unit
"cumulative incidence"	Cannot be converted to incident units

Table 4: Summary of BMD amenable datasets

Data Types	Number of Datasets
Total Datasets	10,104
Cancer Data	402
Dichotomous	4,627
Continuous (BW & OW)	1,279
Continuous (Non-BW & OW)	837

Figure 9: ToxRefDB Effects for BMD. BMDs requires studies that have completed extraction and subsequent QA (~3700 studies). The modeled effects are separated by data type. The cancer effects were manually identified as neoplastic effects. The weight endpoints are from any body weight or organ weight endpoint. For any given topic of interest, endpoints and effects can be manually grouped through expert review.



Conclusions and Future Directions

- Quantitative improvements:**
 - Quantitative data entry completed for SUB and CHR studies, with MGR and DEV to be completed soon.
 - Batch BMD pipeline for BMD modeling of quantitative data provides a modeled point-of-departure for a large portion of the database.
- Improvements in data interpretation:**
 - Guideline profiles enable balanced reference chemical sets for predictive toxicology via distinction between endpoints with no observed treatment related effects and endpoints that were simply not tested.
 - Default testing status generated from guideline profiles will allow for systematic evaluation of guideline adherence for any study in the database.
- Improvements in ontology and interconnectivity of the resource:**
 - Linking ToxRefDB to UMLS concepts provides a standardized language for collaboration between many organizations and regulatory agencies.
 - UMLS mappings cross-reference to numerous other terminologies including NCI, CDISC-SEND, and MeSH
 - These cross-references aid in data integration efforts, specifically using PubMed.