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EPA 601B22001 | August 2022 | www.epa.gov/research

Toxicity Reference Database Version 2.1 User Guide

Office of Research and Development
Center for Computational Toxicology and Exposure

EPA Report Number 601B22001
August 2022

Toxicity Reference Database
Version 2.1
User Guide

by

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Purpose

The purpose of this document is to provide documentation on how to technically access and use the Toxicity Reference Database (ToxRefDB) version 2.1. The latest data can be accessed through EPA's Clowder site (*https://clowder.edap-cluster.com/datasets/61147fefe4b0856fdc65639b#folderId=62c5cfebe4b01d27e3b2d851*) . More information about ToxRefDB version 2.0 and its development can be found in the publications below.

Watford, S., Pham, L.L., Wignall, J., Shin, R., Martin, M.T., and Friedman, K.P. (2019). ToxRefDB version 2.0: Improved utility for predictive and retrospective toxicology analyses. Reproductive Toxicology, 89, 145-158. DOI: 10.1016/j.reprotox.2019.07.012

Pham, L.L., Watford, S., Friedman, K.P., Wignall, J.A., and Shapiro, A.J. (2019). Python BMDS: A Python interface library and web application for the canonical EPA dose-response modeling software. Reproductive toxicology. DOI: 10.1016/j.reprotox.2019.07.013

This user guide does not necessarily reflect U.S. EPA policy.

Abstract

ToxRefDB contains *in vivo* study data from over 5900 guideline or guideline-like studies for over 1100 chemicals. This is largely comprised of curated animal study data from repeat dose studies conducted according to Health Effects Series 870 guidelines, and many of these studies (over 3,000 of them) come from registrant-submitted toxicity studies known as data evaluation records (DERs) from the U.S. EPA's Office of Pesticide Programs (OPP). By employing a controlled vocabulary for enhanced data quality, ToxRefDB serves as a resource for study design, quantitative dose response, and endpoint testing status information given guideline specifications. The database can aid in the validation of *in vitro* high throughput screening of chemicals and serve as a resource for retrospective and predictive toxicology applications.

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Overview

The Toxicity Reference Database (ToxRefDB) serves as a resource for structured animal toxicity data for many retrospective and predictive toxicology applications. ToxRefDB contains *in vivo* study data from over 5900 guideline or guideline-like human health relevant studies for over 1100 chemicals.

The study types covered in ToxRefDB include the following repeat dose study designs utilizing various administration routes (predominantly oral): chronic (CHR; 1-2 year exposures depending on species and study design) conducted predominantly in rats, mice, and dogs; subchronic (SUB; 90 day exposures) conducted predominantly in rats, mice, and dogs; subacute (SAC; 14-28 day exposures depending on the source and guideline) conducted predominantly in rats, mice, and dogs; prenatal developmental (DEV) conducted predominantly in rats and rabbits; multigeneration reproductive toxicity studies (MGR) conducted predominantly in rats; reproductive (REP) toxicity studies conducted largely in rats; developmental neurotoxicity (DNT) studies conducted predominantly in rats; and a small number of studies with designs characterized as acute (ACU), neurological (NEU), or "other" (OTH).

Many of the studies (over 3,000) come from registrant-submitted toxicity studies known as data evaluation records (DERs) from the U.S. EPA's Office of Pesticide Programs (OPP). Since 2009, continued curation efforts have expanded ToxRefDB to include toxicity studies from ten additional sources, including the National Toxicology Program (NTP), peer-reviewed primary research articles (OpenLit), and pharmaceutical pre-clinical toxicity studies (Pfizer, Sanofi, GSK, Merck), among others (RIVM, PMRA, unpublished and unassigned sources). 90% of the studies with completed curation (processed=1) correspond pesticide actives and inerts. Although most studies in the database correspond to pesticides, curation of other study sources incorporated additional functional use types of chemicals.

ToxRefDB serves as a resource for study design, quantitative dose response, and endpoint testing status information given guideline specifications from the US Environmental Protection Agency (US EPA) and the National Toxicology Program (NTP) headquartered at the National Institute of Environmental Health Sciences. The legacy and current data curation workflow is described in more detail in later sections. An important component of ToxRefDB is its controlled vocabulary for studies and effects observed for enhanced data quality.

The first version of ToxRefDB (ToxRefDB 1.0) was initially released as a series of spreadsheets, which are still available on EPA's FTP site and referenced in FigShare (https://doi.org/10.23645/epacomptox.6062545.v1). ToxRefDB underwent significant updates that are described in the recent publication (Watford et al., 2019) and was released as ToxRefDB v2.0. ToxRefDB v2.0 and associated summary files can be found here: https://doi.org/10.23645/epacomptox.6062545.v3.

ToxRefDB v2.1 is a minor 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. The .sql export of ToxRefDB v2.is available for public download here: https://doi.org/10.23645/epacomptox.6062545. Although the overall number of studies and chemicals remains unchanged, the v2.1 update includes additional data as previously curated studies with extracted dose treatment groups and effects are now fully accessible. This added data can improve 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.

In addition to the accessing data via SQL downloads, ToxRefDB information is also summarized with calculated point-of-departure values at the chemical and study level for inclusion in the summary-level database, the Toxicity Value Database (ToxValDB), which is accessible via the CompTox Chemicals Dashboard. This list aggregates chemicals associated with curations in ToxRefDB v2.0: https://comptox.epa.gov/dashboard/chemical-lists/TOXREFDB2.ToxRefDB v2.1 values will be incorporated in the next ToxValDB release.

Summary of v2.1 Update

ToxRefDB v2.1 is a minor update to 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. ToxRefDB v2.1 contains summary information from 5986 studies for 1143 chemicals.

For ToxRefDB v2.0, quantitative (i.e. dose-response) data was extracted. This curation was completed for 3871 studies with plans to extract and release the remaining data in subsequent data releases. No additional curation was performed for the v2.1 update. To provide the reader with a summary of the scope and coverage of the database, ToxRefDB was filtered to present only data where a full curation with guideline profile observations was complete. This is achieved using a 'processed' flag set to 1 within the study table.

Table 1 is a summary table of the number of chemicals and number of studies for each study source, study type, and species. Study type abbreviations are as follows: CHR = Chronic, DEV = Prenatal-Developmental, MGR = Multigeneration Reproductive, SAC = Subacute, SUB = Subchronic.

Table 1: v2.1 Summary Statistics

Study type	Study source	Species	Number of studies	Number of chemicals
CHR	NTP	mouse	178	173
		rat	169	164
	OpenLit	mouse	4	4
		rat	5	5
	OPP DER	dog	331	298
		hamster	4	3
		mouse	342	303
		primate	1	1
		rat	398	328
Total CHR			1432	557
DEV	NTP	mouse	1	1
		rabbit	3	3
		rat	6	6
	OpenLit	rat	1	1
	OPP DER	mouse	18	16
		rabbit	431	372
		rat	508	433
	Other	mouse	1	1
		rabbit	1	1
		rat	4	4
Total DEV			974	486
MGR	OpenLit	rat	1	1
	OPP DER	mouse	2	2
		rat	339	310
	Other	rat	19	19

Total MGR			361	331
SAC	NTP	mouse	29	26
		rat	30	29
	OPP DER	dog	1	1
		mouse	3	3
		rabbit	6	6
		rat	15	13
Total SAC			84	51
SUB	NTP	hamster	1	1
		mouse	119	107
		rat	127	114
	OpenLit	mouse	2	2
		rat	4	4
	OPP DER	dog	214	195
		hamster	4	4
		mouse	123	112
		primate	3	3
		rabbit	5	4
		rat	418	335
Total SUB			1020	498
Database totals			3871	748

Figure 1 depicts a breakdown of studies by study source, study type, and species.

Figure 1: Study-Level Data Landscape

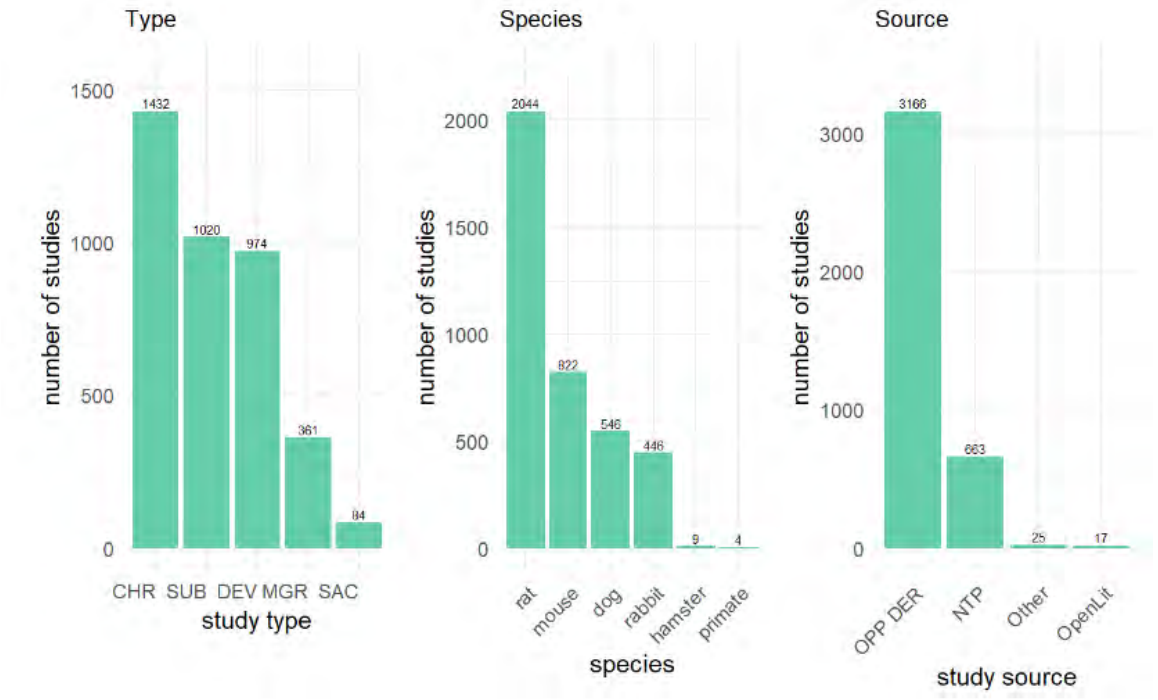
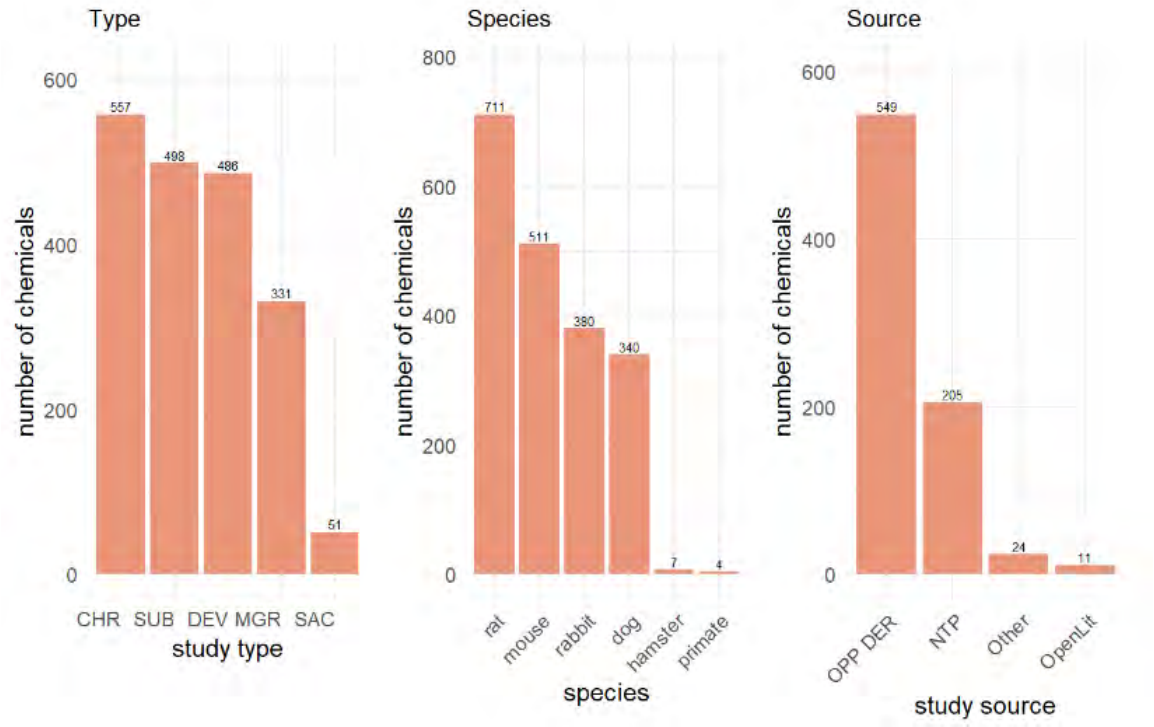


Figure 2 depicts a breakdown of chemicals by study source, study type, and species.

Figure 2: Chemical-Level Data Landscape



In addition to the SQL downloads, ToxRefDB information is also summarized with calculated point-of-departure values at the chemical and study level for inclusion in the summary-level database, the Toxicity Value Database (ToxValDB), which is accessible via the CompTox Chemicals Dashboard. ToxRefDB v2.1 values will be incorporated in the next ToxValDB release.

Changes between v2.0 and v2.1

The following table details a summary of differences between ToxRefDB v2.0 and v2.1. ToxRefDB v2.1 is a minor update to recover thousands of extracted values that failed to import properly from the original AccessDB curation files as described in the Data Curation Process section. Although the overall number of studies and chemical remains unchanged, the v2.1 update includes additional data as previously curated studies (+594 studies with extracted effects) with extracted dose treatment groups (+5226 dose treatment groups with effects) and effects (+21756 effects) are now fully accessible. This added data can improve the utility of ToxRefDB as a resource for curated legacy *in vivo* information by providing more complete information of the past animal studies conducted.

Table 2: Changes between 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

Accessing information in ToxRefDB

A MySQL database export and summary files of ToxRefDB v2.1 are available for public download, available here. The summary spreadsheet contains study and chemical-level information for reference. ToxRefDB information is also summarized with calculated point-of-departure values at the chemical and study level for inclusion in the summary-level database, the Toxicity Value Database (ToxValDB), which is accessible via the CompTox Chemicals Dashboard. ToxRefDB v2.1 values will be incorporated in the next ToxValDB release.

Below is documentation on how to install MySQL, load ToxRefDB, and access the data using both SQL and programmatic access using either Python or R. Another useful tool to access the data is MySQL Workbench, which provides a user interface to interact with any MySQL database.

Installing MySQL and loading ToxRefDB

Steps to install MySQL load ToxRefDB are detailed below. More comprehensive documentation for using MySQL can be found online.

- Download the ToxRefDB MySQL database
- Download the latest version of the MySQL community server.
- Select the appropriate installer for your operating system
    - For Windows, download the MSI installer
    - For MAC and Linux, download the DMG installer
- The installer will walk you through the installation. During the installation, be sure to copy the temporary root password. You will need it later.
    - For Windows, MySQL should automatically be added to your PATH
    - For MAC and Linux, if MySQL was not added to your PATH automatically you will have to add it manually
- Open the terminal and type:

```
>> echo 'export PATH=/usr/local/mysql/bin:$PATH'
>> ~/.bash_profile
```

- Open the command line (Windows) or terminal (MAC and Linux) to login to the MySQL server with the command

```
>> mysql -u root –p
```

- Enter the temporary root password when prompted for a password. Change the root password following instructions detailed here.
- Create the ToxRefDB database, select it as the default database, and load the dump file following instructions detailed here:

```
mysql> CREATE DATABASE IF NOT EXISTS toxrefdb_2_0;
mysql> USE toxrefdb_2_0;
mysql> source toxrefdb_2_0.sql
```

Example queries using MySQL

Once the ToxRefDB instance is established, the user is ready to begin querying the database. These example queries can be tailored for exploratory data analysis, specific research questions based the individual's use case, or risk assessment workflows.

```
# Get number of studies per study type
SELECT study_type, COUNT(study_id) FROM study
GROUP BY study_type;

# Get number of studies per study type and species
SELECT study_type,species, COUNT(study_id) FROM study
GROUP BY study_type,species;

# Get number of studies per source
SELECT study_source, COUNT(study_id) FROM study
GROUP BY study_source;

# Get all study information for chronic studies
SELECT * FROM study WHERE study_type="CHR";

# Get all treatment group and dosing information for a single chemical
SELECT * FROM chemical
 INNER JOIN study ON chemical.chemical_id=study.chemical_id
 INNER JOIN tg ON tg.study_id=study.study_id
 INNER JOIN dose ON dose.study_id=study.study_id
 INNER JOIN dtg ON dtg.tg_id=tg.tg_id AND dose.dose_id=dtg.dose_id
WHERE casrn="42509-80-8";

# Get number of studies per endpoint
SELECT endpoint_category, endpoint_type, endpoint_target,
 COUNT(DISTINCT study.study_id) AS "number of studies" FROM  study
 INNER JOIN tg ON study.study_id=tg.study_id
 INNER JOIN tg_effect ON tg.tg_id=tg_effect.tg_id
 INNER JOIN effect ON effect.effect_id=tg_effect.effect_id
 INNER JOIN endpoint ON endpoint.endpoint_id=effect.endpoint_id
GROUP BY endpoint_category,endpoint_type,endpoint_target;

# Get all study-level LELs and LOAELs for effect profile 2
SELECT * FROM pod WHERE effect_profile_id=2 AND study_id IS NOT NULL AND pod_type IN("loael","lel");

# Get chemical-level PODs for effect profile 2
SELECT * FROM pod WHERE effect_profile_id=2 AND study_id IS NULL;

# Get study-level PODs for effect profile 2 and for a specific endpoint
SELECT DISTINCT pod.* FROM pod
 INNER JOIN pod_tg_effect ON pod.pod_id=pod_tg_effect.pod_id
 INNER JOIN tg_effect ON tg_effect.tg_effect_id=pod_tg_effect.tg_effect_id
 INNER JOIN effect ON effect.effect_id=tg_effect.effect_id
 INNER JOIN endpoint ON endpoint.endpoint_id=effect.endpoint_id
WHERE effect_profile_id=2 AND study_id IS NOT NULL
AND endpoint_target LIKE "thyroid%";

# Get all dose-response data for a study
SELECT * FROM chemical
 INNER JOIN study ON study.chemical_id=chemical.chemical_id
 INNER JOIN tg ON tg.study_id=study.study_id
 INNER JOIN dose ON dose.study_id=study.study_id
 INNER JOIN dtg ON dtg.tg_id=tg.tg_id AND dose.dose_id=dtg.dose_id
 INNER JOIN tg_effect ON tg.tg_id=tg_effect.tg_id
 INNER JOIN effect ON effect.effect_id=tg_effect.effect_id
 INNER JOIN endpoint ON endpoint.endpoint_id=effect.endpoint_id
 INNER JOIN dtg_effect ON tg_effect.tg_effect_id=dtg_effect.tg_effect_id AND dtg.dtg_id=dtg_effect.dtg_id
```

```
WHERE study.study_id=687;
```

Programmatic Access

The user is not limited to SQL queries in MySQL Workbench to access ToxRefDB. You can also programmatically access the data with several languages. Below are examples of accessing the data into datasets for further work in Python and R. You will still have to connect to the database through the language specific connector.

Python

In the example below, the python packages sqlalchemy, pandas, and pymysql are required. You can, however, use any type of connector. Any SQL query can replace the one provided in this example.

```
# Load libraries
import sqlalchemy as sa
import pandas as pd

# Establish connection
username = "<username>"
password = "<password>"
host = "<host>"
database = "<database>"
engine =sa.create_engine(f"""mysql+pymysql://{username}:{password}@{host}/{database}""")

# Get guideline profiles
results = pd.read_sql("""
SELECT guideline.guideline_id,
 guideline.guideline_number,
 guideline.name,
 guideline.profile_name,
 guideline.description,
 guideline_profile.guideline_profile_id,
 guideline_profile.obs_status,
 guideline_profile.description,
 endpoint.endpoint_id,
 endpoint.endpoint_category,
 endpoint.endpoint_type,
 endpoint.endpoint_target FROM guideline
INNER JOIN guideline_profile ON guideline.guideline_id=guideline_profile.guideline_id
INNER JOIN endpoint ON endpoint.endpoint_id=guideline_profile.endpoint_id
""",engine)

# Export to excel
writer = pd.ExcelWriter("guideline_profiles.xlsx")
results.to_excel(writer,index=False,merge_cells=False)
writer.save()
```

R

In the example below, the R package RMySQL required. Any SQL query can replace the one provided in this example.

```
# Load library
library(RMySQL)

# Establish connection
```

```
con <- dbConnect(drv = RMySQL::MySQL(), user="<username>",
 password = "<password>",
 host = "<host>", database =”<database>”)

# Get all ToxRefDB information for subchronic studies
output <- dbGetQuery(con, "SELECT chemical.casrn,
 chemical.preferred_name,
 study.study_id,
 study.study_type,
 study.study_year,
 study.study_source,
 study.species,
 study.strain_group,
 study.admin_route,
 study.admin_method,
 endpoint.endpoint_category,
 endpoint.endpoint_type,
 endpoint.endpoint_target,
 endpoint.endpoint_id,
 tg_effect.life_stage,
 tg_effect.tg_effect_id,
 effect.effect_id,
 effect.effect_desc,
 tg.sex,
 tg.generation,
 dose.dose_level,
 dtg.dose_adjusted,
 dtg.dose_adjusted_unit,
 dtg_effect.treatment_related,
 dtg_effect.critical_effect,
 tested_status,
reported_status FROM chemical
 INNER JOIN study ON chemical.chemical_id=study.chemical_id
 LEFT JOIN dose ON dose.study_id=study.study_id
 LEFT JOIN tg ON tg.study_id=study.study_id
 LEFT JOIN dtg ON tg.tg_id=dtg.tg_id AND dose.dose_id=dtg.dose_id
 LEFT JOIN tg_effect ON tg.tg_id=tg_effect.tg_id
 LEFT JOIN dtg_effect ON tg_effect.tg_effect_id=dtg_effect.tg_effect_id AND dtg.dtg_id=dtg_effect.dtg_id
 LEFT JOIN effect ON effect.effect_id=tg_effect.effect_id
 LEFT JOIN endpoint ON endpoint.endpoint_id=effect.endpoint_id
 LEFT JOIN obs ON obs.study_id=study.study_id AND obs.endpoint_id=endpoint.endpoint_id
WHERE study_type='SUB' ")
```

Database Structure

This entity-relationship diagram (ERD) can be used to understand the relationships between tables. BMDExpress software (Pham et al, 2019) was not run to calculate benchmark dose values for v2.1, therefore BMD tables were dropped from the v2.1 schema.

Figure 3: ToxRefDB v2.1 ERD

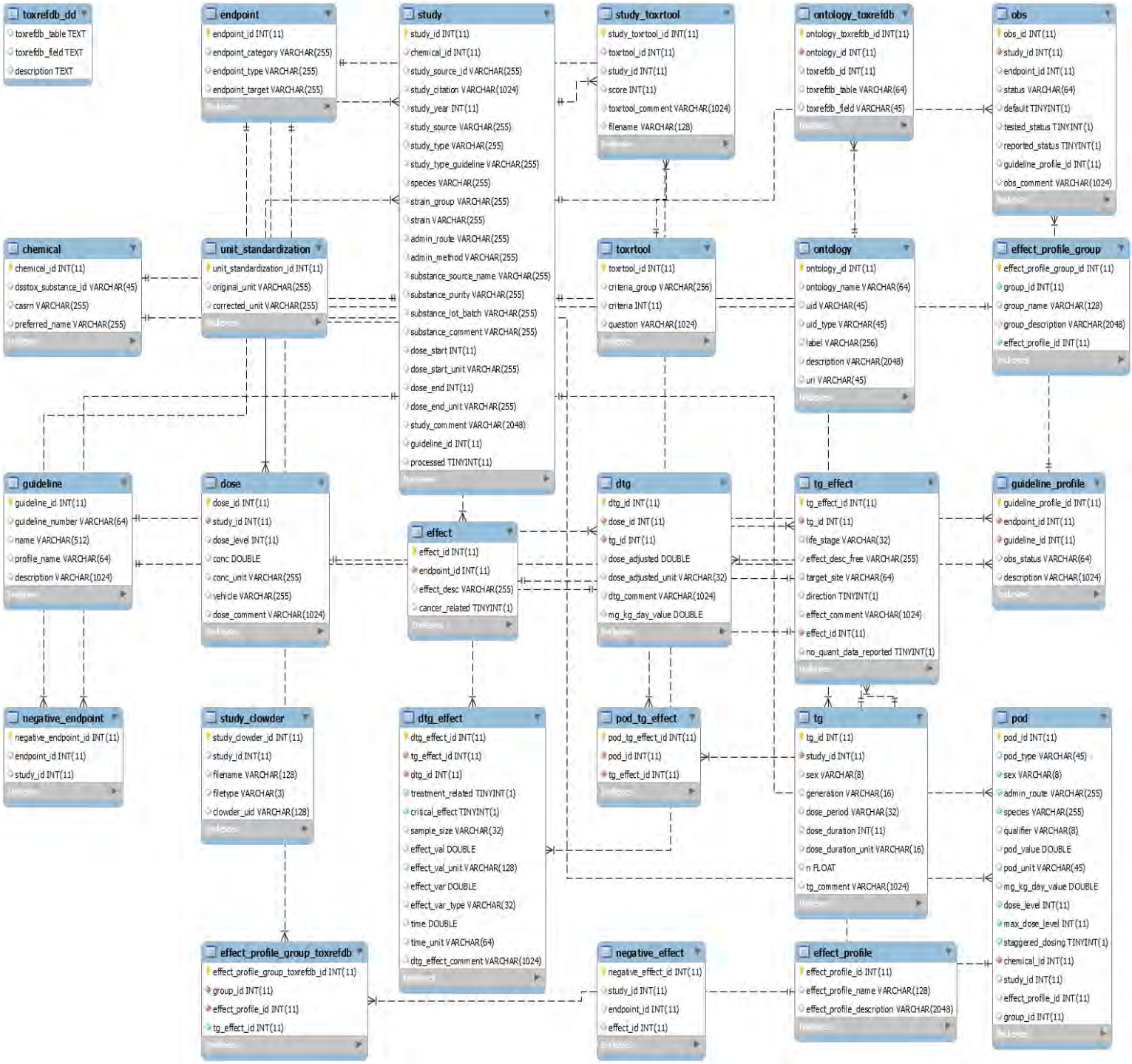
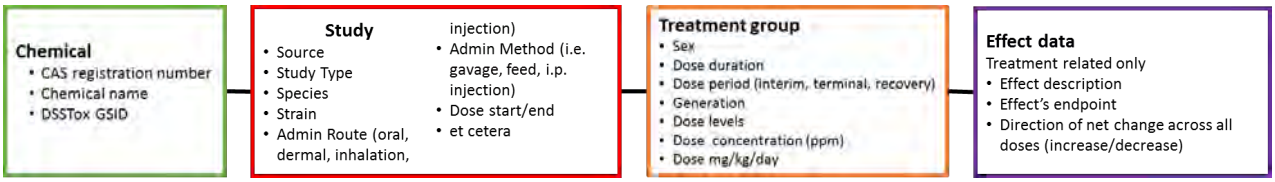


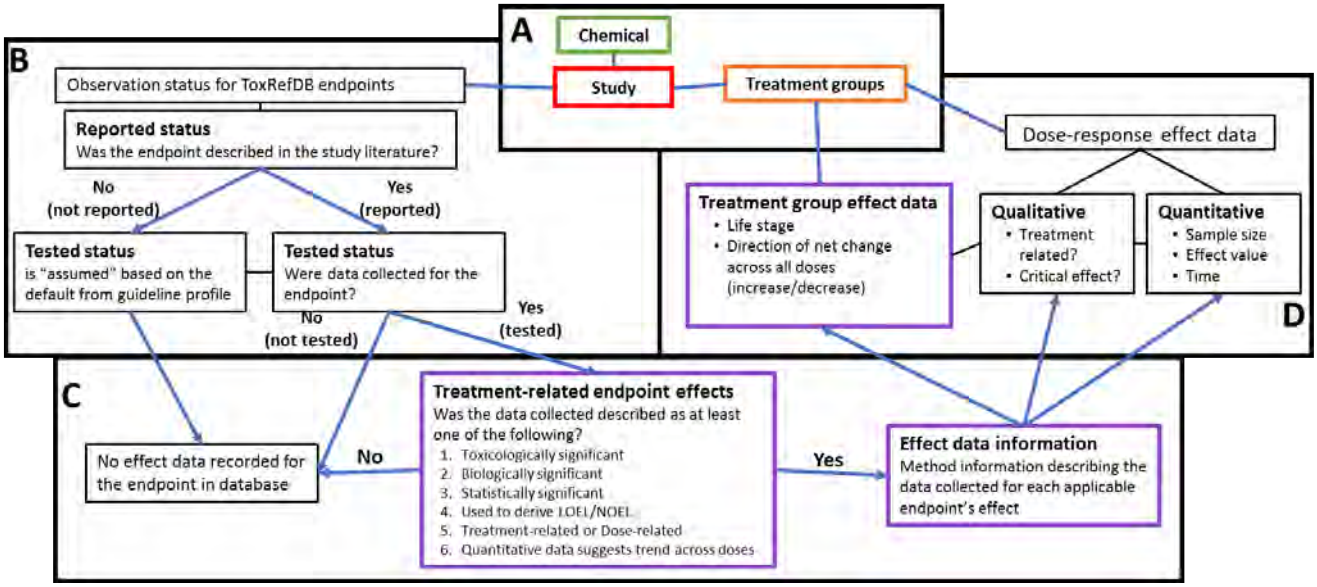
Figure 4: Schema Overview

Part 1:



Part 1 shows the basic information captured in ToxRefDB, including study design and chemical metadata, dosing, and significant treatment-related and critical effects.

Part 2:



Part 2 provides more context about the data entry method. Portion of ToxRefDB 1.0 that carried over to version 2.0 unchanged. The previously extracted information from ToxRefDBv1 was checked for accuracy and modified/added for QA purposes.

A. Curator assigns endpoint testing status according to guideline profile. Uses decision tree to classify 400 standardized endpoints as described in study reports. Guideline profiles were developed that match language found in the studies. These guideline profiles were used for inference of negative endpoints/effects.
B. Observed Endpoints classified as "tested" are evaluated for treatment-related effects. Treatment-related effects are indexed by endpoint and method information pertaining to the data collected.
C. Where available, complete dose-response effect qualitative and/or quantitative data for each dose was extracted.

Data Curation Process

Initially, ToxRefDB v1.0 provided only summary effect levels and lacked quantitative dose response information. This task initially proceeded using an Excel file-based extraction; however, the process required manual corrections after uploading study extractions to the ToxRefDB MySQL database, including inconsistent comments, different number of animals for the same treatment group, and added effects outside of the controlled terminology. The quantitative information and its application in ToxRefDB v2.0 served as a strong impetus to re-extract the studies.

An Access database file was generated from the MySQL database for each study in v1.0, and this approach offered several improvements including standardized options for more consistent reporting in some fields, such as the units on time and dose, dose-treatment group, and effect information; checkbox reporting for observation status on each endpoint and effect; and a log for tracking changes and facilitating QA. Nearly 32% of the studies were extracted using the Excel-based approach, with the remaining studies extracted using the Access database approach. Switching to Access database files from Excel files significantly reduced errors and increased standardization of reporting items such as units, endpoints, and effects.

Figure 5: Data Extraction and Review Workflow

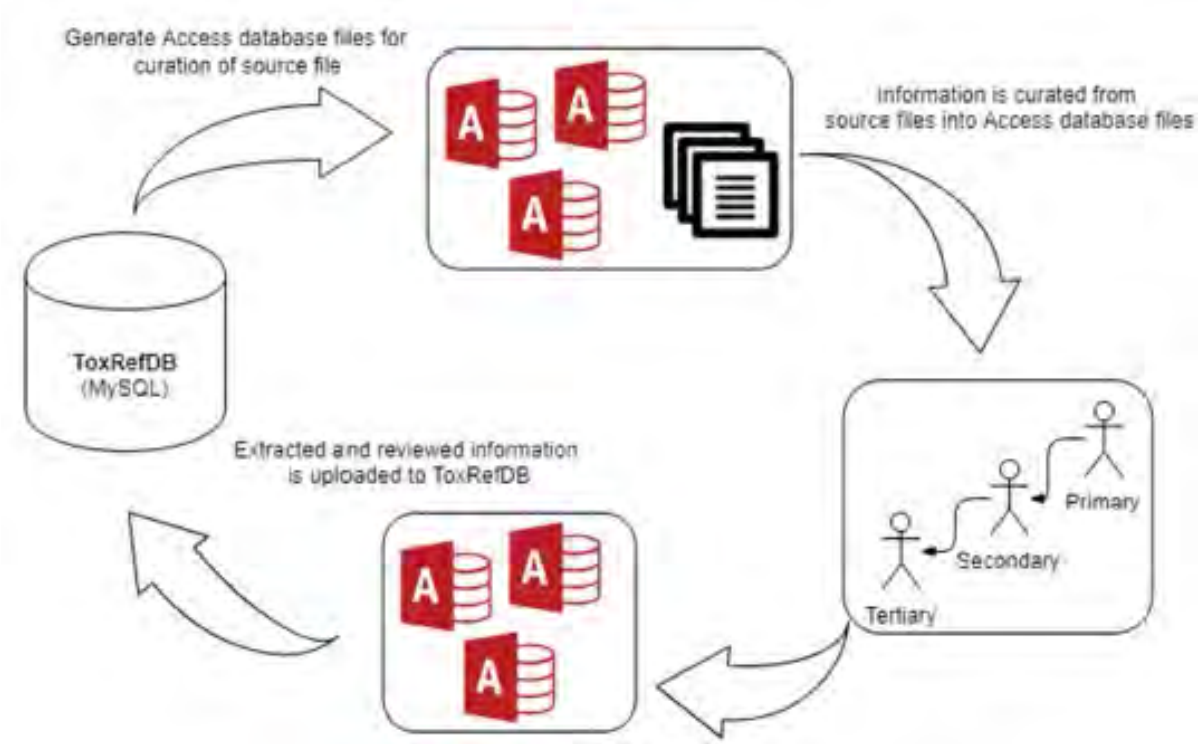


Figure 5 details the workflow of the overall data extraction process for ToxRefDB v2.0. Access databases files were generated for each study in ToxRefDB v1.0 and bundled with the corresponding source files for data extraction. The data in the Access databases are curated with additional data extracted from the source files with up to three levels of review. The Access databases are returned by the reviewers and the data is imported back into the MySQL database with the study table designation of processed=1.

ToxRefDB v2.0 curation also included the implementation of guideline profiles to guide curation. Endpoints were annotated (e.g. “required”, “not required”) according to guidelines for subacute, subchronic, chronic, developmental, and multigenerational reproductive designs, distinguishing negative responses from untested. Implementation of controlled vocabulary improved data quality; standardization to guideline requirements and cross-referencing with United Medical Language System (UMLS) connects ToxRefDB v2.0 observations to vocabularies linked to UMLS, including PubMed medical subject headings (MeSH). The endpoint terminology and its hierarchical nature is described in later sections.

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. The DCT improves upon the legacy ToxRefDB curation workflow to provide document allocation, curation and workflow management among users, and management review with data conflict resolution, resulting in records that directly link quality-controlled curations to source documents. The DCT offers flexibility via its modular workflow for curating the heterogeneous and complex *in vivo* study designs.

A multi-layer review process will continue to be implemented with the DCT to ensure data integrity and minimize data entry error.

Quality Assurance in Data Extraction

Guidance for data extraction was stratified first according to study type (e.g., CHR, SUB, DEV, MGR) then by study source (e.g., OPP DER and NTP) because of the differences in both study design and adverse effects required for reporting as stated in guidelines. The process used to extract study information was also an important aspect of QA efforts for ToxRefDB v2.0. First, a primary reviewer extracted study, dose, treatment group, effect, and endpoint observation information. The instructions detailed how to review the toxicological data and extract it from the original data sources consistently across reviewers using the Access database. This was reviewed by a second, senior reviewer, who was asked to review all extracted information as if they were extracting it again and, also, to review the comment log from the primary reviewer. Finally, if either the primary or secondary reviewer noted that it was necessary, an additional senior toxicologist reviewed the comment logs, extracted information, and resolved any conflicts or questions prior to finalization of the extraction. The final, tertiary review occurred for approximately 10% of the studies. Review by a manager to resolve any differences between the primary and secondary reviewer serves to inform any training needs or gaps for the reviewers. During this process, subject matter experts can also be consulted to resolve questions. For release of ToxRefDB v2.0, the full quantitative data extraction for all CHR and SUB studies were completed, with quantitative data extraction completed for many other study types and sources as well.

Efforts to Reduce Error Rate

Error rate is an inherent problem for legacy databases as much of the source information was entered manually and human errors resulting from transcription are impossible to completely avoid. However, as part of the ToxRefDB v2.0 curaion effort, more robust QA processes were implemented to promote greater fidelity of the information extracted and numerous quality control (QC) checks to verify data integrity.

First, studies were extracted utilizing a defined QA process, with multiple levels of review and Access form-based entry (described previously) to prevent extraction errors. Upon uploaded into ToxRefDB v2.0, these extractions were required to pass specific QC checks because, although the Access database files enforce the MySQL database constraints as well minimize data entry error by standardizing vocabulary used, logical errors can persist. After the extracted data was uploaded through the import script, a series of potential logical errors were identified through unit tests where their curated value could be assumed. Flagged logical errors that have been corrected included:

- Dose level numbering did not correspond to the total number of doses;
- Duplication of concentration/dose values, including two control doses;
- No concentration and no dose adjusted value for a reported effect (possible extraction error or possibly that the effect was qualitatively reported);
- The critical effect level is at a dose below where treatment-related effects were observed; and/or,
- The control was incorrectly identified as a critical effect level.

Any of these issues that could not be resolved systematically were flagged to undergo a second round of extraction and review to correct. Though QC is an ongoing and evolving process, these QC checks are serving as an improvement to the overall database and database development process.

Unit Standardization

An additional ongoing problem for reporting quantitative data from clinical or related laboratory findings is unit standardization. No guidance is provided on how to report findings in the OCSPP guidelines nor from any other sources, so units were extracted exactly as they were presented in the reports. The units were standardized by eliminating duplicate entries for the same units that were originally entered differently or with typographical errors. Units were only standardized, and no conversions were introduced in the current database. Ongoing efforts include further standardization of units and defining conversions that cannot be systematically automated.

Study Reliability with ToxRTool

Most studies referenced within ToxRefDB were extracted via summaries from OPP DERs, and these studies typically follow OCSPP 870 series Health Effects Testing Guidelines. As ToxRefDB was expanded, additional studies needed to be assessed for reliability and guideline adherence.

The Toxicological Data Reliability Assessment Tool (ToxRTool) was adapted for reliability assessment. ToxRTool is an Excel application that includes questions across 5 criteria with numerical responses that are summed to lead to a Klimisch score: a score ranging from 1-4 that captures an overall assessment of reliability.

A total of 522 OpenLit studies were assessed with the ToxRTool with scores ranging from 8 to 23. As explained in the table below, most studies reviewed for ToxRefDB v2.0 corresponded to Klimisch quality scores of 1 (ToxRTool score of ≥ 18) or 2 (ToxRTool score of 13-18). The ToxRTool scores could be used as a quality flag both to qualify and prioritize studies for the extraction process, or by users who are performing reviews of information on a single chemical basis.

Table 3: ToxRTool Guideline Adherence Score

Score	Description
5	Adheres to modern* OECD/EPA guideline for repeat-dose toxicity studies (explicitly stated by authors; broad endpoint coverage and ability to assess dose-response)
4	Adheres to an existing or previous guideline (explicitly stated by authors; previous version of OECD/EPA guidelines or FDA guidelines)
3	Not stated to adhere to guideline but guideline-like in terms of endpoint coverage and ability to assess dose-response (e.g., NTP). Please see Quick Guide to EPA Guidelines for chronic and subchronic studies. In this table, you can easily assess whether the study was guideline-like in terms of the animals used (species, sex, age, number), dosing requirements, and reporting recommendations.
2	Unacceptable adherence to guideline (intended to adhere to guideline but had major deficiencies)
1	Unacceptable (no intention to be run as a guideline study, purely open literature or specialized study)

A study is considered as adhering to “modern” OECD/EPA guidelines if it was published after 1998, which is the date that many Health Effect 870 series guidelines were re-published. Note that many of the studies extracted, particularly from sources like the NTP and OpenLit, were never intended to adhere to a guideline and as such “unacceptable” in this case only refers to their guideline adherence and not the study design itself.

Guideline Profiles

Within a curation, study records are linked to a guideline profile. OPP DERs follow the Series 870 - Health Effects Test Guidelines, described here. NTP reports follow NTP specifications. Other subsources cannot be uniformly mapped, but some curations may be assigned a guideline profile based on how closely the study design adheres to a guideline.

Guideline profiles for study endpoints were created from the Office of Chemical Safety and Pollution Prevention (OCSPP) series 870 Health Effects Testing Guidelines and NTP specifications (Table 2). This allows for analysis of guideline adherence for both guideline and non-guideline studies.

Table 4: Guideline Profile Coverage
Additional efforts are underway to develop new profiles. The Guideline Profile column is a concatenated entry of ToxRefDB's guideline id, guideline number (usually OCSPP Guideline No. or NA for NTP specifications), guideline name, and abbreviated guideline profile name.

Study Type	Guideline Profile	Guideline Profile Description
CHR - Carcinogenicity	• 9 | 870.42 | Carcinogenicity | CHR_carc	The objective of a long-term carcinogenicity study is to observe test animals for a major portion of life span for development of neoplastic lesions during or after exposure to test substance by an appropriate route of administration. The dose period generally lasts a year or longer, typically 12, 18, or 24 months, and observations will exclude developmental and neurological effects. See OPPTS 870.4200 Carcinogenicity.
CHR - Chronic Toxicity	• 17 | NA | 2 - Year Toxicity | CHR_ntp • 8 | 870.41 | Chronic Toxicity| CHR_chr_tox	The objective of a chronic toxicity study is to determine the effects of a substance in a mammalian species following prolonged and repeated exposure. A chronic toxicity study should generate data to identify chronic effects and define long-term dose-response relationships. The dose period generally lasts a year or longer, typically 12, 18, or 24 months, and observations will exclude developmental and neurological effects. See OPPTS 870.4100 Chronic Toxicity.
CHR - Combined Chronic Toxicity / Carcinogenicity	• 10 | 870.43 | Combined Chronic Toxicity / Carcinogenicity | CHR_chr_canc	The objective of a combined chronic toxicity/carcinogenicity study is to determine the effects of a substance in a mammalian species following prolonged and repeated exposure. Following updates to the 870 Series Health Effects Guidelines in 1998, this combined study was preferred to separate submissions of 870.4100 and 870.4200. The design and conduct should allow for the detection of neoplastic effects and a determination of the carcinogenic potential as well as general toxicity. The dose period generally lasts a year or longer, typically 12, 18, or 24 months, and observations will exclude developmental and neurological effects. See OPPTS 870.4300 Combined Chronic Toxicity/Carcinogenicity.
DEV - Prenatal Developmental Toxicity Study	• 6 | 870.37 | Prenatal Developmental Toxicity Study | DEV_pren_dev	This guideline for developmental toxicity testing is designed to provide general information concerning the effects of exposure of the pregnant test animal on the developing organism; this may include death, structural abnormalities, or altered growth and an assessment of maternal effects. The dose period is usually gestational (in utero) and the animal is sacrificed prior to delivery. See OPPTS 870.3700 Prenatal Developmental Toxicity Study

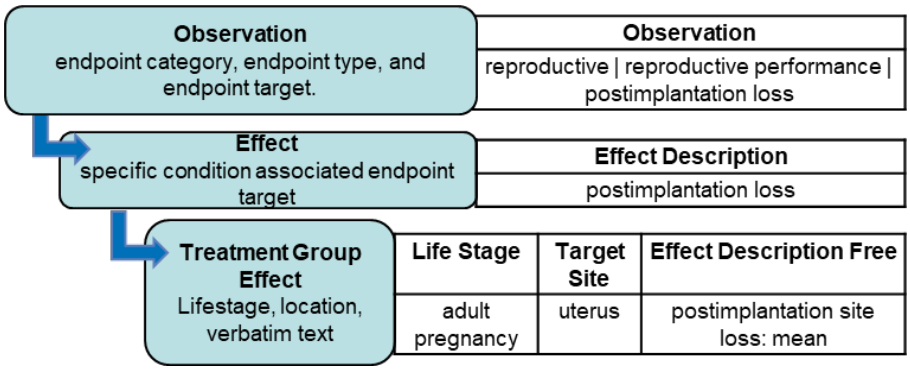
MGR – Multi-generational reproductive toxicity study	• 7 | 870.38 | Reproduction and Fertility Effects | MGR_rep_fert • 13 | 13 | 870.38 | Reproduction and Fertility Effects | MGR_rep_fert_pre98 Note: There are two guideline profiles due to a 1998 guideline change. The post-1998 guideline was likely used for MGR studies that started in 1996.	This guideline for two-generation reproduction testing is designed to provide general information concerning the effects of a test substance on the integrity and performance of the male and female reproductive systems, including gonadal function, the estrous cycle, mating behavior, conception, gestation, parturition, lactation, and weaning, and on the growth and development of the offspring. The study may also provide information about the effects of the test substance on neonatal morbidity, mortality, target organs in the offspring, and preliminary data on prenatal and postnatal developmental toxicity and serve as a guide for subsequent tests. Additionally, since the study design includes in utero as well as postnatal exposure, this study provides the opportunity to examine the susceptibility of the immature/neonatal animal. The dose period begins in adolescent F0 males and females and continues until the terminal generation. Some of the litters deliver their pups, while others may be sacrificed prior to delivery. See OPPTS 870.3800 Reproduction and Fertility Effects.
REP - Fertility (Segment I)	• 5 | 870.355 | Reproduction/Development Toxicity Screening Test | REP_rep_dev	This guideline is designed to generate limited information concerning the effects of a test substance on male and female reproductive performance such as gonadal function, mating behavior, conception, development of the conceptus, and parturition. This screening test guideline can be used to provide initial information on possible effects on reproduction and/or development, either at an early stage of assessing the toxicological properties of chemicals, or on chemicals of high concerns focused on early postnatal evaluation, with sacrifice of dams and offspring at postnatal day 4. See OPPTS 870.3550 Reproduction and Fertility Effects.
REP - Peri- and post-natal toxicity study (Segment III)	• 5 | 870.355 | Reproduction/Development Toxicity Screening Test | REP_rep_dev	The study may provide information about the effects of the test substance on neonatal morbidity, mortality, target organs in the offspring, and preliminary data on prenatal and postnatal developmental toxicity and serve as a guide for subsequent tests. Additionally, since the study design includes in utero as well as postnatal exposure, this study provides the opportunity to examine the susceptibility of the immature/neonatal animal (F1 generation). See OPPTS 870.3550 Reproduction and Fertility Effects.
REP – Reproductive / developmental toxicity screening test	• 5 | 870.355 | Reproduction/Development Toxicity Screening Test | REP_rep_dev	This guideline is designed to generate limited information concerning the effects of a test substance on male and female reproductive performance such as gonadal function, mating behavior, conception, development of the conceptus, and parturition. This screening test guideline can be used to provide initial information on possible effects on reproduction and/or development, either at an early stage of assessing the toxicological properties of chemicals, or on chemicals of high concern. See OPPTS 870.3550 Reproduction and Fertility Effects.
SAC – Sub-acute dermal toxicity	• 3 | 870.325 | 90-day Dermal Toxicity | SUB_sub_derm	A 21/28 day repeated dose dermal study will provide information on possible health hazards likely to arise from repeated dermal exposure to a test substance for a period of 21/28 days. Dose period is typically 21-28 days with dermal exposure route, and observations will exclude developmental and neurological effects. See OPPTS 870.3200 21/28-Day Dermal Toxicity.
SAC – Sub-acute repeat dose toxicity	• 14 | 870.305 | 28-day Oral Toxicity in Rodents | SAC_oral_rode_28 • 15 || 14-day Toxicity in Rodents | SAC_ntp	The objective of a sub-acute repeat dose toxicity study is to determine the adverse effects of a substance in a mammalian species occurring after short-term dosing duration. Determination of acute toxicity is usually an initial step in the assessment and evaluation of the toxic characteristics of a substance. Dose period is typically 21-28 days with varied exposure routes, and observations will exclude developmental and neurological effects. See https://www.regulations.gov/document/EPA-HQ-OPPT-2009-0156-0009

SUB - Subchronic dermal toxicity	• 16 | | 13-Week Toxicity in Rodents | SUB_ntp • 3 | 870.325 | 90-day Dermal Toxicity | SUB_sub_derm	The subchronic dermal study has been designed to permit the determination of the no-observed-effect level (NOEL) and toxic effects associated with continuous or repeated exposure to a test substance for a period of 90 days. It can provide useful information on the degree of percutaneous absorption, target organs, the possibilities of accumulation, and can be of use in selecting dose levels for chronic studies and for establishing safety criteria for human exposure. The dose period is typically 90 days or 13 weeks, but may be as long as 6 months, via dermal routes of exposure. Observations will exclude developmental and neurological effects. See OPPTS 870.3250 90-Day Dermal Toxicity.
SUB - Subchronic inhalation toxicity	• • 4 | 870.3465 | 90-Day Inhalation Toxicity | SUB_sub_inha	The subchronic inhalation study has been designed to permit the determination of the no-observed effect-level (NOEL) and toxic effects associated with continuous or repeated exposure to a test substance for a period of 90 days. It will provide information on target organs and the possibilities of accumulation, and can be used to select concentration levels for chronic studies and establishing safety criteria for human exposure. The dose period is typically 90 days or13 weeks, but it may be as long as 6 months, via inhalation routes of exposure. Observations will exclude developmental and neurological effects. See OPPTS 870.3465 90-Day Inhalation Toxicity.
SUB - Subchronic oral toxicity in nonrodent	• 2 | 870.315 | 90-day Oral Toxicity in Nonrodents | SUB_oral_nonr	The subchronic oral study has been designed to permit the determination of the no-observed-effect level (NOEL) and toxic effects associated with continuous or repeated exposure to a test substance for a period of 90 days. It provides information on target organs, the possibilities of accumulation, and can be of use in selecting dose levels for chronic studies and for establishing safety criteria for human exposure. The dose period is typically 90 days or 13 weeks, but it may be as long as 6 months, via oral routes of exposure in any nonrodent species. Observations will exclude developmental and neurological effects. See OPPTS 870.3150 90-Day Oral Toxicity in Nonrodents.
SUB – Subchronic oral toxicity in rodents	• 1 | 870.31 | 90-day Oral Toxicity in Rodents | SUB_oral_rode • 16 | | 13-Week Toxicity in Rodents | SUB_ntp	The subchronic oral study has been designed to permit the determination of the no-observed-effect level (NOEL) and toxic effects associated with continuous or repeated exposure to a test substance for a period of 90 days. It provides information on target organs, the possibilities of accumulation, and can be of use in selecting dose levels for chronic studies and for establishing safety criteria for human exposure. The dose period is typically 90 days or 13 weeks, but may be as long as 6 months, via oral routes of exposure in rodent species, typically rats and mice. Observations will exclude developmental and neurological effects. See OPPTS 870.3100 90–Day Oral Toxicity in Rodents.

Endpoint Terminology

ToxRefDB employs controlled terminology standardized to better reflect both the OCSPP Health Effects 870 series guidelines and DER summary reporting. This hierarchical relationship of effects and endpoints was adapted from the vocabulary developed for earlier versions of ToxRefDB based on the data types curated. Novel values can be added when found during a curation.

Figure 6: Hierarchical endpoint terminology example



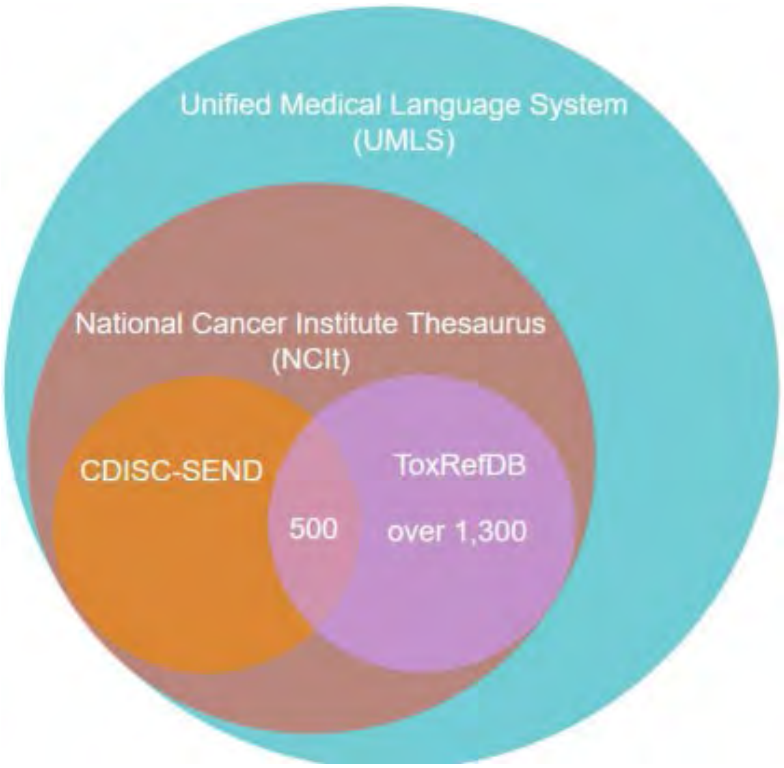
An example of the terminology hierarchy is demonstrated for an effect described as “postimplantation loss”. The finding is recorded as is in the “effect description free” field, which is the verbatim wording used in the study report. The remaining fields are part of the ToxRefDB controlled terminology. The endpoint category is reproductive, the endpoint type is reproductive performance, the endpoint target is postimplantation loss, the effect description is postimplantation loss, and the specific observation of “postimplantation loss” was made in the adult pregnancy life-stage at the specific target site, the uterus.

Ontology mappings

It is increasingly apparent that many toxicology research questions will require the integration of public data resources, both with those containing the same types of information, as well as with other databases to connect different kinds of information. ToxRefDBv2.0 allows for increased connections to other resources, which has greatly enhanced its quantitative and qualitative utility for predictive toxicology.

For example, efforts linking *in vitro* effects in ToxCast to *in vivo* outcomes using predictive models may help to identify rapid, more efficient chemical screening alternatives. To connect the ToxRefDB endpoint and effect terminology with other resources, the ToxRefDB terminology was standardized and cross-referenced to the United Medical Language System (UMLS). UMLS cross-references enable mapping of *in vivo* pathological effects from ToxRefDB to PubMed (via Medical Subject Headings or MeSH terms), which may be relevant for toxicological research and systematic review. This enables linkage to any resource that is also connected to PubMed or indexed with MeSH.

Figure 7: Cross-referenced Terminology Sources
Over 1,800 UMLS concept codes were mapped to endpoints and effects in ToxRefDB via a manual process. Only 500 of those concept codes are a part of the CDISC-SEND terminology. All of the concept codes are a part of vocabularies within both National Cancer Institute Thesaurus (NCIt) as well as UMLS.



Additionally, the Entity MeSH Co-occurrence Network (EMCON) consists of ranked lists of genes for a given topic. This resource can be used to identify genes related to adverse effects observed in ToxRefDB. Subsequently, ToxCast can be integrated since the intended targets are mapped to Entrez gene IDs.

The result of updating the ToxRefDB terminology and linking to the UMLS concepts is that ToxRefDB may be used to better anchor or compare to new approach method (NAM) information, including data from ToxCast or structure-activity relationship models, as well as other *in vivo* databases of toxicological information, such as eChemPortal, and e-TOX. Integration of these data resources is a major hurdle toward to evaluating the reproducibility and biological meaning of both traditional, legacy toxicity information and the data from NAMs.

Additional work may be performed to link to other ontologies and to assist stakeholders in mapping their ontologies to the ToxRefDB and UMLS ontologies.

Negative Endpoints and Effects

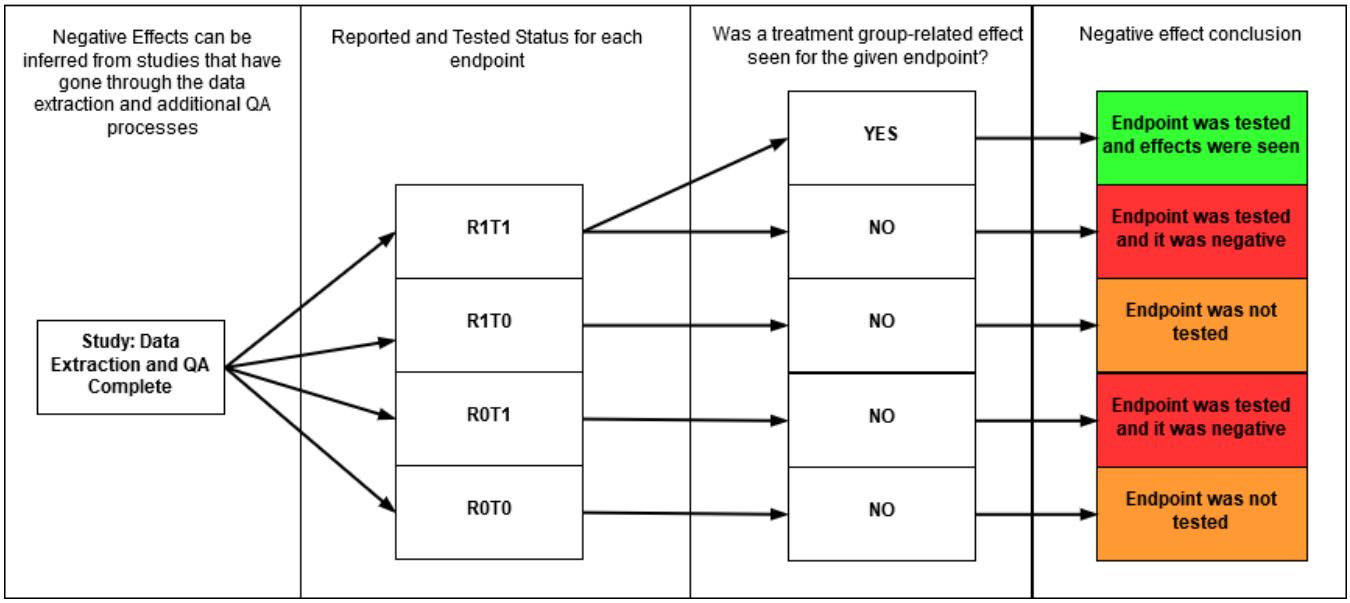
As part of the v2.0 update to ToxRefDB, negative endpoints and effects can be inferred from guideline profiles and the testing and reporting statuses of endpoints. Given the list of all observations required for the relevant guideline profile, the curator indicates which endpoints were missing (meaning not tested) or negative (meaning tested with no effect observed) by setting tested and reported status accordingly. Endpoint observation status enables automated distinction of true negatives and a better understanding of false negative effects. Users can access the current inferred negatives and calculate inferences for a specific subset.

The MySQL database has inferred study-level negative effects and negative endpoints available in two tables: “negative_effect” and “negative_endpoint”. These tables were created from stored procedures (repopulate_negative_effect and repopulate_negative_endpoint) that are also available with the full MySQL database. The logic for the stored procedures follows the inference workflow seen in Figure *6*. Endpoint Observation Status distinguishes negative and missing (not tested) effects based on the study’s specific guideline requirements. An effect is negative if the study has gone through the data extraction process, the effect was tested (regardless of being reported), and no effect was seen in the study. An endpoint is negative for a study if all effects for that endpoint are also negative in the study.

Table 5: Endpoint Observation Status

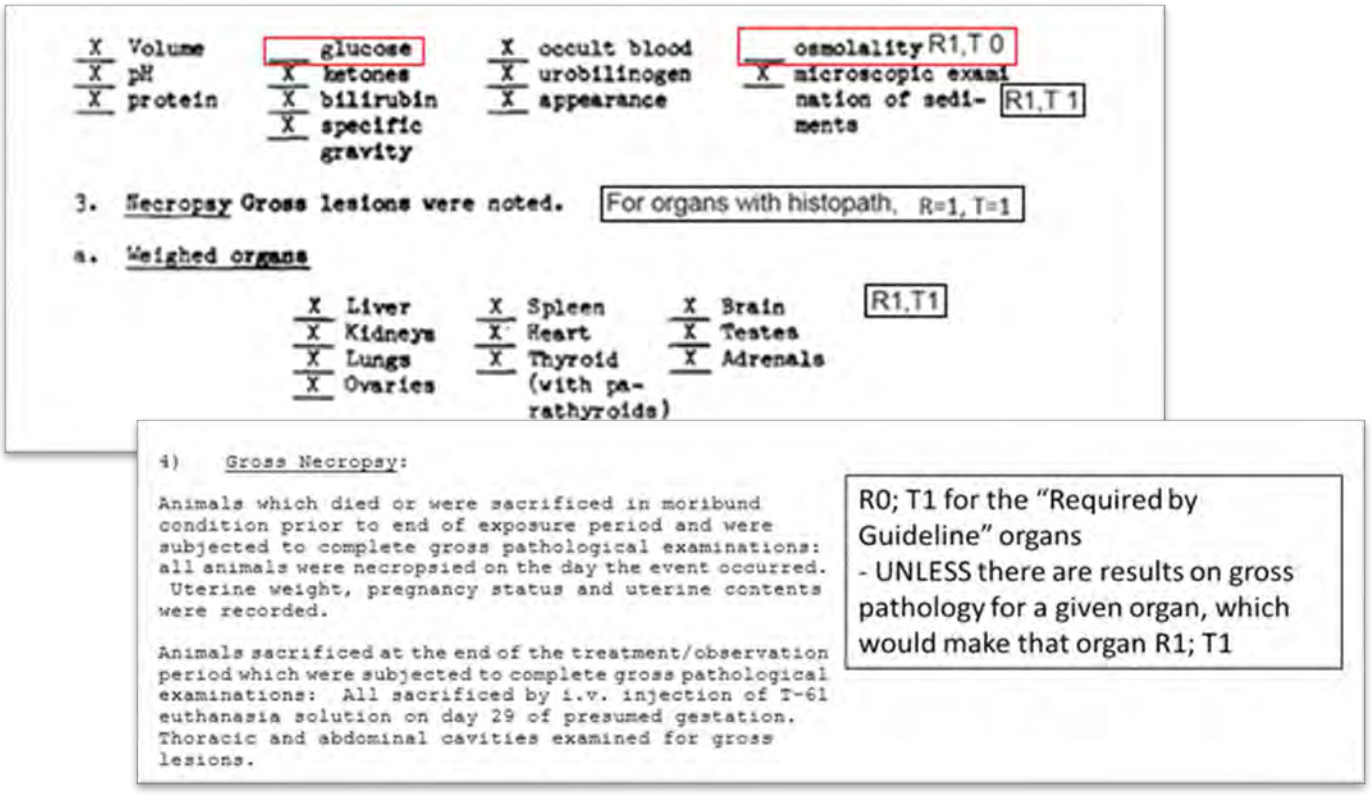
Tested Status	Reported Status	Assumption
Yes	Yes	The text of the study document explicitly stated the endpoint was measured, or data was presented in tables for the endpoint. This is the combination if required by the guideline for that study type and data is provided within the document, even the effects measured were not significant.
No	Yes	This is the combination if the study document explicitly states the endpoint was not measured or data was not collected, even though the endpoint was required by the study guidelines.
Yes	No	The text of the study document does not state the endpoint was measured and data for the endpoint is not present. However, other evidence suggests that the endpoint was measured. *This is the default for endpoints required by the study guideline and should only be changed in the face of direct evidence from the document.*
No	No	Within the long table of observations from all study guidelines, this is the default setting for the endpoints not required by the alternative study guidelines and they should not be changed. Interpret these observations as irrelevant since they are not serving the selected guideline, therefore not required to be tested nor reported.

Figure 8: 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. The example below shows how reported results are intrepreted given the study's guideline profile.

Figure 9: Example Observation Status Interpretation



Ongoing Work

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. The technical requirements of this application are that it:

- Replicate extraction of all of the data fields from ToxRefDB's legacy AccessDB curation system;
- Include a "wizard" to walk the data curator through entry of study meta-data, chemical composition information, dose information, dose-treatment group information, quantitative data extraction for dose-treatment groups, and evaluation of the endpoint observation status according to guideline specification;
- Offer flexibility for curating the heterogeneous and complex *in vivo* study designs via a modular workflow;
- Continue to implement and improve controlled vocabularies for experimental design elements as well as endpoint and effect language;
- Provide document allocation, curation and workflow management among users (internal and external) with manager review and data conflict resolution for data provenance and progress tracking;
- Link a quality-controlled curation to Clowder source documents; and
- Create a sustainable pipeline for data integration.

There are several critical advantages inherent in the success of this application. Automating the data extraction creates a new more systematic and sustainable workflow. Following data curation, ETL could be managed using Pentaho for direct loading to a database. Overall, this effort would allow for the continued expansion of the ToxRefDB resource by providing a more efficient process for curation of study information.

Following conclusion of the initial development phase, curation of developmental toxicity (DEV) data evaluation records (DERs) from recent pesticide submissions were the selected focus for Phase I DCT extraction. Future curation efforts were prioritized from the DER documents from an initial web scrape of all documents that were published since 2008, adhering to existing guideline profiles, and not currently captured in ToxRefDB. Additional extraction may include studies previously extracted using Excel and AccessDB files followed by comparison of the results to look for accuracy, as well as new study types following the generation of new guideline profiles and vocabularies. Feedback from data curators will help inform further development enhancements.

Future versions with expanded chemical and study data collected via its new application-driven curation workflow (DCT) and the creation of a ToxRefDB dashboard will increase ToxRefDB's utility. Standardization efforts will continue to provide more detailed effect and study-level information and will allow for more streamlined interoperable database efforts.

Without a user interface, ToxRefDB information is only accessible from the MySQL database download or via ToxValDB hazard summary section. Complete ToxRefDB information will soon be integrated into the CompTox Chemicals Dashboard and available via batch search functionality.

Data Dictionary

A data dictionary is found in the database in the toxrefdb_dd table.

ToxRefDB Table	Field	Field Description
chemical	chemical_id	PK: Autoincremented unique identifier for a chemical
	dsstox_substance_id	Unique identifier from DSSTox
	casrn	CAS Registry Number
	preferred_name	Preferred name of the chemical substance tested in the study.
dose	dose_id	PK: Autoincremented unique identifier for a dose
	study_id	FK: A unique numeric identifier for each study in the database.
	conc	Concentration of a test chemical, typically reported in ppm within the exposure matrix (e.g., feed or water).
	conc_unit	Unit associated with a concentration of a test chemical, typically reported as ppm.
	dose_comment	This field can be used to explain any differences in dosing over the dosing interval or provide clarifying comments on how the dose was administered. Specific concentrations of the vehicle should be listed here when relevant. For example, if methylcellulose was used as a vehicle, the concentration of methylcellulose may be included in the comment field (e.g., 0.5% w/v aqueous methylcellulose).
	dose_level	Numeric rank indicating the level of dose administered to test animals, with lower dose levels indicating lower concentrations of a chemical (e.g., 0 = vehicle, 1 = lowest dose, etc.). The dose level for some studies may be staggered since concentrations may vary by sex (e.g., male treatment group: 0 = vehicle, 1 = lowest dose, 3 = second lowest dose, etc.).
	vehicle	The media used in administration of chemical
dtg	dtg_id	PK: Autoincremented unique identifier for a dosed-treatment group
	dose_id	FK: A unique numeric identifier for each dose in the database.
	tg_id	FK: A unique numeric identifier for each treatment group in the database.
	dose_adjusted	The amount of the chemical administered in mg/kg of body weight/day (mg/kg/day). This value is typically different between male and female groups receiving the same dose concentration (conc) due to differences in bodyweight. If dose_adjusted values were not

		provided in a study, then they were calculated using species scaling factors (FAO/WHO, 2000).
	dose_adjusted_unit	Unit associated with the adjusted dose of a chemical, typically reported in mg/kg/day.
	dtg_comment	NULL if no additional comment needed; explains any difference in the dose-treatment-group over the course of the study (i.e., interim sacrifice or changes due to toxicity and/or morbidity); quality assurance (QA) flags indicate discrepancies between the reported and correct values for the study; differences in any dose_adjusted calculations are provided.
	mg_kg_day_value	The mg/kg/day species-specific, converted value from ppm concentration
dtg_effect	dtg_effect_id	PK: Autoincremented unique identifier for a dosed-treatment group effect
	dtg_id	FK: A unique numeric identifier for each dosed treatment group in the database.
	tg_effect_id	FK: A unique numeric identifier for each treatment group effect in the database.
	critical_effect	Binary description (0,1) for an effect by dose treatment group. “1” corresponds to a toxic or adverse effect denoted in the study summary or via expert judgement using a weight-of-evidence approach. “0” indicates that although an effect is produced at this level, it is not considered adverse, nor immediate precursors to specific adverse effects. If there are several critical effects, the no observed adverse effect level (NOAEL) is determined from the highest dose level without critical effects. The lowest dose level at which the critical effect was observed in a study is the lowest observed adverse effect level (LOAEL.)
	dtg_effect_comment	NULL if no additional comment needed; provides additional explanation of the dose-treatment-group-effect row in the table, including statistical significance.
	effect_val	Numeric value of a measured effect, can be continuous or dichotomous (incidence) data.
	effect_val_unit	Unit associated with the effect value.
	effect_var	Measurement of the variance for a set of data associated with a measured effect, generally reported as the standard deviation (SD) or standard error (SE).
	effect_var_type	Name of the variance metric used to determine the effect variance, typically the standard deviation (SD) or standard error (SE). Other effect_var types include: interquartile range, 95% confidence limit, and none.
	sample_size	Number of animals used for an examination for a particular effect.

	time	Numeric value associated with the duration of the exposure at which a particular effect was measured or observed, typically reported in hours, days, weeks, or months.
	treatment_related	Binary description (0,1) for an effect by dose treatment group. “1” indicates there was a statistically significant difference from the control group for the effect; “0” indicates there was no difference from control group. The highest dose level at which no significant observable adverse effects were observed corresponds to the no effect level (NEL). The lowest effect level (LEL) can be inferred by treatment related effects.
effect	effect_id	PK: Autoincremented unique identifier for an effect
	endpoint_id	FK: A unique numeric identifier for each endpoint in the database.
	effect_desc	More specific description for an effect than endpoint_category, usually detailing a specific condition associated with an endpoint_target (e.g. dysplasia, atrophy, necrosis, etc.).
effect_profile	effect_profile_id	PK: Autoincremented unique identifier for an effect profile
	effect_profile_description	Description of the effect profile
	effect_profile_name	Name of the effect profile
effect_profile_group	effect_profile_id	FK: A unique numeric identifier for each effect profile in the database.
	group_id	Unique identifier for a group
	group_description	The description of a group
	group_name	The name of a group
endpoint	endpoint_id	PK: Autoincremented unique identifier for an endpoint
	endpoint_category	The broadest descriptive term for an endpoint. Possible endpoint categories include: systemic, developmental, reproductive, and cholinesterase.
	endpoint_target	Describes more specific information than endpoint_type, indicating where/how the sample was collected to supply data for a particular endpoint. Typically describes an organ/tissue or metabolite/protein measured.
	endpoint_type	The subcategory for endpoint_category, which is more descriptive for a particular endpoint (e.g. pathology gross, clinical chemistry, reproductive performance, etc.)
guideline	guideline_id	PK: Autoincremented unique identifier for a guideline
	description	Information pertinent to a study guideline. For example, MGR studies conducted post-1998 required the testing of developmental landmarks, which is notable for observation status.
	guideline_number	Number associated with the particular guideline. that a study adheres to or most closely adheres

		to. OPPTS/OCSPP guideline numbers are differentiated by the distinct number proceeding 870, as dictated by the Office of Chemical Safety and Pollution Prevention (OCSPP)
	name	Name of the particular Office of Chemical Safety and Pollution Prevention (OCSPP) guideline that a study adheres to or most closely adheres to.
	profile_name	Abbreviated name of the particular Office of Chemical Safety and Pollution Prevention (OCSPP) guideline that a study adheres to or most closely adheres to. See abbreviations section for profile_name list.
guideline_profile	guideline_profile_id	PK: Autoincremented unique identifier for a guideline profile
	endpoint_id	FK: A unique numeric identifier for each endpoint in the database.
	guideline_id	FK: A unique numeric identifier for each guideline in the database.
	description	Provides a description of the rationale for an endpoint observation status.
	obs_status	Indicates whether or not an endpoint is required to be tested according to the particular guideline a study adheres to. The observation status for an endpoint can be required, not required, or triggered.
obs	status	The status regarding whether or not an endpoint was tested and reported in a study. Assumes that an endpoint was tested if the guideline the study adheres to requires that endpoint to be tested.
	default	An endpoint is considered tested and reported if the endpoint appears in the text of the study source indicating that data was collected. If an endpoint is required to be tested by the guideline, tested and reported are the defaults.
	tested_status	Indicates if an endpoint was tested (1) or not tested (0). If an endpoint was tested, it was examined or measured.
	reported_status	Indicates if an endpoint was reported (1) or not reported (0). If an endpoint was reported, it appears somewhere in the text of the report.
ontology	ontology_id	PK: Autoincremented unique identifier for an ontology class
	description	The associated description for the identifier
	label	The associated label for the identifier
	uid	Unique identifier from respective terminology resource
	uid_type	Type of identifier
	uri	Uniform resource identifier
ontology_toxrefdb	ontology_toxrefdb_id	PK: Autoincremented unique identifier for an ontology class associated with a concept in ToxRefDB

	ontology_id	FK: A unique numeric identifier for each ontology class in the database.
	toxrefdb_table	The associated table in ToxRef
	toxrefdb_field	The associated field from toxrefdb_table linked to a term
	toxrefdb_id	Primary key from associated toxrefdb_table
pod	pod_id	PK: Autoincremented unique identifier for a point of departure or associated effect level
	chemical_id	FK: A unique numeric identifier for each chemical in the database.
	effect_profile_id	FK: A unique numeric identifier for each effect profile in the database.
	group_id	FK: A unique numeric identifier for each effect profile group in the database.
	study_id	FK: A unique numeric identifier for each study in the database.
	dose_level	Dose level at which the POD was seen
	max_dose_level	Maximum dose level tested with relation to where the POD was captured
	mg_kg_day_value	Converted mg/kg/day value
	qualifier	<, <=, >, >=, =
	pod_type	LEL, NEL, LOAEL, or NOAEL
	pod_value	Value of the POD or associated effect level
	pod_unit	Corresponding unit of the POD or associated effect level
pod_tg_effect	pod_tg_effect_id	PK: Autoincremented unique identifier for a POD associated with a treatment group effect
	pod_id	FK: A unique numeric identifier for each POD or associated effect level in the database.
	tg_effect_id	FK: A unique numeric identifier for each treatment group effect in the database.
study	study_id	PK: Autoincremented unique identifier for a study
	chemical_id	FK: A unique numeric identifier for each chemical in the database.
	guideline_id	FK: A unique numeric identifier for each guideline in the database.
	admin_method	Describes specifically how the chemicals were administered via the route (e.g., capsule, diet, gavage, topical, etc.)
	dose_end	Time during an animal's life that the administration of a test substance stopped.
	dose_end_unit	Unit of time associated with the end of the dose (dose_end).
	dose_start	Time during an animal's life that the administration of a test substance began.
	dose_start_unit	Unit of time associated with the start of the dose (dose_start).
	species	Species of the animal test subject used in a study.
	strain	Intraspecific description of group of animals used in a study; generally, a stock of animals that

		share a uniform morphological or physiological character, or group that is genetically uniform.
	strain_group	Descriptive category for a group of test animals that is more general than the strain.
	study_comment	Pertinent information the curator deemed helpful to be noted about the study in general, such as poor document quality (e.g., poor scan), missing pages, etc.
	study_type	Classification to describe animal toxicity testing that was conducted. ACU (acute): Dose period typically a day or less. Excludes developmental and neurological studies.; SAC (subacute): Dose period is typically 21-28 days. Excludes developmental and neurological studies.; SUB (subchronic): Dose period is typically 13 weeks, but may be as long as 6 months. Excludes developmental and neurological studies.; CHR (chronic): Dose period is typically 12, 18, or 24 months (generally any dosing lasting a year or longer). Excludes developmental and neurological studies.; DEV (developmental): Gestational (in utero) dose period. Sacrificed prior to delivery.; MGR (multigenerational reproductive): Dose period begins in adolescent F0 males and females and continues until terminal generation. At least some of the litters deliver their pups, some may be sacrificed prior to delivery.; NEU (neurological): Study contains functional observation battery or other battery of behavioral testing that occurs during or after dosing. Pathology has specific interest in the brain (i.e. regions, morphology, biochemistry, et cetera). excludes developmental studies; DNT (developmental neurotoxicity): dose period occurs anytime during development (i.e. in utero, lactational, adolescent [after weaning, before adulthood]). Study contains functional observation battery or other battery of behavioral testing that occurs during or after dosing, typically during adulthood. Pathology has specific interest in the brain (i.e. regions, morphology, biochemistry, etc.)
	study_type_guideline	Description that combines the study_type and guideline name for a study.
	substance_comment	Pertinent information regarding a substance's origin (generally the manufacturer/importer that produced the substance), purity, or other notable information about the substance in general.
	substance_lot_batch	Identifier specific to the origin of a batch of the test substance used in a study.
	substance_purity	Percentage of the administered solution that is composed of the chemical to be tested after dilution.

	substance_source_name	Name of the supplier that provided the chemical substance for testing during the study.
tg	tg_id	PK: Autoincremented unique identifier for a treatment group
	study_id	FK: A unique numeric identifier for each study in the database.
	dose_duration	Amount of time a group is dosed. This varies within studies depending on the dose period of a particular treatment group.
	dose_duration_unit	Unit of time associated with the dose duration. Typically in days or months.
	dose_period	Time point that best characterizes when the treatment group was evaluated for effects. Interim: Group sacrificed and examined within the dosing period. Terminal: Group sacrificed and examined at study completion and after the dosing period. These animals are not mated. Recovery: Group examined after a recovery period that followed the dosing period at the study end. Post first mating: Group examined after first mating. Post second mating: Group examined after second mating. Post third mating: Group examined after third mating. Satellite: Group of animals included in the design and conduct of a toxicity study, treated, and housed under conditions identical to those of the main study animals, but used primarily for some separate purpose to be defined as needed in the Comment section. Other: Group of animals that may have deviated from the full study design, to be defined as needed in the Comment section.
	generation	Generation of the test animal group. F0 is the default choice for animals exposed in non-reproductive studies (chronic CHR, subchronic SUB, subacute SAC), dams in reproductive DEV studies, and the first-generation mating group for multigenerational MGR studies. F1 is the second-generation, born to F0. F2 is the third-generation, born to F1. F3 is the fourth-generation, born to F2. The fetal generation is the group produced by F0 matings in DEV studies, typically removed from a female via cesarean section. Pups from live births are not fetal.
	sex	Sex of a test animal group. The gender of fetal groups is denoted as MF for both males and females.
	tg_comment	NULL if no additional comment needed; contains information that the extractor/curator found helpful in describing issues related to a treatment-group (e.g. animals dosed via capsule so concentration not reported, added recovery groups, etc.).

tg_effect	tg_effect_id	PK: Autoincremented unique identifier for a treatment group effect
	effect_id	FK: A unique numeric identifier for each effect in the database.
	tg_id	FK: A unique numeric identifier for each treatment group in the database.
	direction	Description of the net change across all doses that indicates whether the numerical data increased, decreased, or stayed the same. This can also be used to describe effects that did not have numerical data, but were still described in the study source.
	effect_comment	NULL if no additional comment needed; contains information that the extractor/curator found helpful in describing issues related to a treatment-group-effect (e.g. units not reported, effect only reported for certain treatment groups, etc.).
	effect_desc_free	Brief verbatim text from study file that was entered if the effect description differed from predetermined endpoint terminology.
	life_stage	Stage of life that a measurement was taken. CHR, SUB, and SAC studies typically only have adult for life_stage, whereas DEV and MGR studies will always be characterized by multiple life stages. The different life stages in the database include: fetal, juvenile, adult, adult-pregnancy and pregnancy.
	target_site	A more specific description than effect_target. Can describe a specific tissue within an organ, type of cell, etc.
toxrtool	toxrtool_id	PK: Autoincremented unique identifier for a toxrtool question
	criteria	The ToxRTool comprises a list of evaluation criteria to assess study reliability that are subdivided into five groups: test substance identification, test system characterization, study design description, study results documentation, and plausibility of study design and data.
	question	Question used as part of the ToxRTool evaluation criteria to assess study reliability.
	question_number	Number indicating the question as part of the ToxRTool evaluation criteria to assess study reliability.
study_toxrtool	study_toxrtool_id	PK: Autoincremented unique identifier for a ToxRTool question associated with a study
	toxrtool_id	FK: A unique numeric identifier for each ToxRTool question in the database.
	study_id	FK: A unique numeric identifier for each study in the database.
	score	The associated score for the ToxRTool question
	toxrtool_comment	The corresponding comment further describing the score

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