Characteristics and Applications of the ToxRefDB In Vivo Datasets from Chronic, Reproductive and Developmental Assays
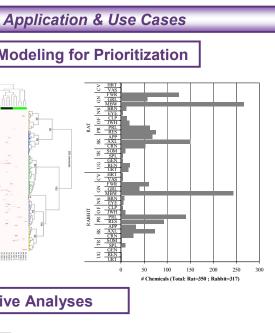
Matthew T. Martin, Richard S. Judson, Daniel M. Rotroff, Ann M. Richard, Imran Shah, Thomas B. Knudsen, Robert J. Kavlock, David J. Dix

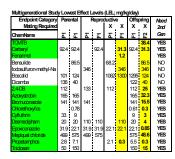U.S EPA, ORD, Computational Toxicology Research Program

research&development
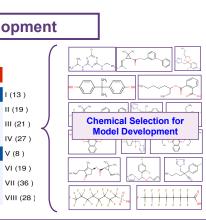
CompTox
Computational Toxicology
Program Review

Science Question

Following years of work in database design, vocabulary development, data curation and entry, and quality control, can the outputted data from ToxRefDB inform or advance major scientific efforts and research questions, including:

- Can unstructured legacy toxicity data be captured in a manner conducive to large-scale computation and modeling?

- Can *in vitro* data combined with chemical descriptors be used to predict detailed or summarized *in vivo* endpoints?

- What is the optimal level of *in vivo* endpoint aggregation for model development, and can model success be an indicator of appropriate level of endpoint summarization?

- How has this total data set, and specific study design components, impacted chemical regulation, and can it inform future study design considerations?

Research Goals

- Develop a highly normalized and structured relational database capable of storing chemical toxicity data from *in vivo* animal studies

- Appropriately aggregate and summarize detailed endpoints based on known biological systems & relationships, study design & animal group characteristics, or disease progression & severity

- Make ToxRef chemical inventory and summary data available in a variety of formats for internal and external modeling applications

- Develop computational tools available to the public to query and analyze ToxRefDB data

Methods/Approach

Database Construction & Publication

Data Curation & Entry

ToxRefDB Entry Interface

Data evaluation records

Chemical & Data Coverage

2073 Studies Entered For 480 Chemicals

CHR = Chronic/Cancer
SUB = Sub-chronic
DEV = Prenatal Developmental

A = Rat
B = Mouse
C = Rabbit

21 ToxCast Chemicals of No Studies

Public Availability

ToxRefDB Intranet

EPA ACToR Data Collection

EPA DSSTox Chemical Inventory & Summary Data Files

External Internet Resources

PubChem ChemSpider

Endpoint Summary & Aggregation

Biological Systems

target: kidney
description: absent renal papilla
code: UG_REN_3.1060.5013

target: sternebra
description: incomplete ossification
code: SK_AXL_2.1099.5130

target: hindpaw
description: polydactyly (digit I)
code: SK_APP_2.1061.5234

Images from www.DevTox.org

ToxRefDB
387 chemicals
751 prenatal studies
988 effects annotated
(enhanced DevTox.org)

Study Design

- Parental
- Reproductive
- Offspring

N = Necropsy
S = standardize Litters
P = Parental System / Body Weight (extends to N)
TO = Target Organ (Non-Reproductive Tract)
F = Fertility
M = Mating
G = Gestation
L = Lactation
RP = Reproductive Performance (includes F, M, & G)
RT = Reproductive Tract Organs (includes SA)
SA = Sperm Assessment

RO = Reproductive Outcome/ Early Offspring Survival
ES = Estrous Cyclicity (part of RT)
OW = Offspring Weight
DO = Developmental Malformations
OD = Late Offspring Survival
DL = Developmental Landmarks
PPS = Preputial Separation (part of SDL)
VO = Vaginal Opening (part of SDL)
AGD = Anogenital Distance (part of SDL)
SDL = Sexual Developmental Landmark (includes AGD)

Adapted from Tyl (RTI)

Disease Progression

Stage (i) → Stage (ii) → Stage (iii)

Necrosis / Apoptosis / Inflammation / Hypertrophy → Hyperplasia / Preneoplastic Foci → Adenoma / Carcinoma

Mouse | Rat
i ii iii | i ii iii

Chemical A
Chemical B

Lesion Progression Vectors

Application & Use Cases

Predictive Modeling for Prioritization

Chemicals (Total: Rat=350 ; Rabbit=317)

Retrospective Analyses

Chemicals (Total: 316)

- 1st Generation Only (F1 Adult to P1 Juvenile)
- 1st & 2nd Generation (P/F1 Adult to F1/2 Juvenile)
- 2nd Generation Only (F1 Adult to F2 Juvenile)

Gestational Interval / Fertility / Mating / Implantations / Litter Size / Lactation Index / Live Birth Index / Viability Index / PPS / VO / Prostate / Testis / Epididymis / Thyroid / Adrenal / Ovary / Pituitary / Kidney / Liver / Uterus / Spleen

Multigenerational Study Lowest Effect Levels (LEL; mg/kg/day)

Chemicals	Parental		Reproductive		Offspring		Need 2nd Gen

PPS = Preputial Separation
VO = Vaginal Opening

Systems Model Development

Mouse | Rat
i ii iii | i ii iii

I (13)
II (19)
III (21)
IV (27)
V (8)
VI (19)
VII (36)
VIII (28)

Chemical Selection for Model Development

Results/Conclusions

High quality data has been captured in ToxRefDB for over 400 chemicals across 5 major study types

Grouping highly descriptive effects into meaningful aggregated endpoints proves useful and necessary across all applications

Resulting endpoints have been successfully used as anchoring endpoints in building specific predictive toxicology models (e.g., liver proliferative lesions and liver tumorigenicity)

Impact and Outcomes

Digitized 30 years and >$2Billion worth of laboratory animal toxicology data

Being used as primary resource for predictive modeling efforts within ToxCast and externally (e.g., QSAR models from LHASA)

Enabling large-scale retrospective analysis of current and past study guidelines and chemical regulation based on these studies (e.g., OECD EOGRTS)

Provided data for pesticides causing "Rodent-Only Tumors", being incorporated into larger analysis (NHEERL & OPP)

Future Directions

- Capturing all available chemical registration data, including studies from additional pesticidal actives, antimicrobials, and inerts, along with industrial chemicals
- Expanding beyond guideline studies into open literature
- Expanding to other study types (e.g., DNT, Immunotoxicity studies)
- Capturing incidence data, especially for organ pathology
- Making database web available and searchable
- Publishing chemical inventory & summary activities in DSSTox, ACToR and External Internet resources.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

COMPUTATIONAL TOXICOLOGY

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