Interagency Coordinating Committee on the Validation of Alternative Methods

Collaborative Modeling Project for Acute Inhalation Toxicity (CoMPAIT)

NICEATM

Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation
Environmental Protection Agency • Food and Drug Administration • National Institute for Occupational Safety and Health
National Institute of Standards and Technology • National Institutes of Health • National Cancer Institute • National Library of Medicine
National Institute of Environmental Health Sciences • Occupational Safety and Health Administration

Outline

Background

- ICCVAM & AcuteTox
- Agency requirements for inhalation data

The dataset

- Collection
- Curation
- Analysis (variability)

Modeling strategy

- Endpoint & challenges
- Training and validation
- Consensus

Acute Toxicity Testing

Complete – oral and dermal systemic toxicity

Evaluate the usefulness of acute oral LD50 data for classifying dermal systemic hazard of potential toxicants such as pesticides, industrial chemicals, chemical warfare agents, and household chemicals

Complete – for pesticide formulations and active ingredients; EPA published waiver guidance for formulations in 2016 and for technical chemicals in 2020

Evaluate in vitro/in silico approaches for predicting acute systemic toxicity

Modeling workshop convened – workshop report published (Kleinstreuer et al. 2018; https://doi.org/10.1016/j.comtox.2018.08.002)

Acute oral toxicity in silico models – CATMoS (Mansouri et al. 2021; https://doi.org/10.1289/EHP8495); model predictions for ICCVAM agencies

Variability analysis of the in vivo oral test method (manuscript published – Karmaus et al. 2022; https://doi.org/10.1093/toxsci/kfac042)

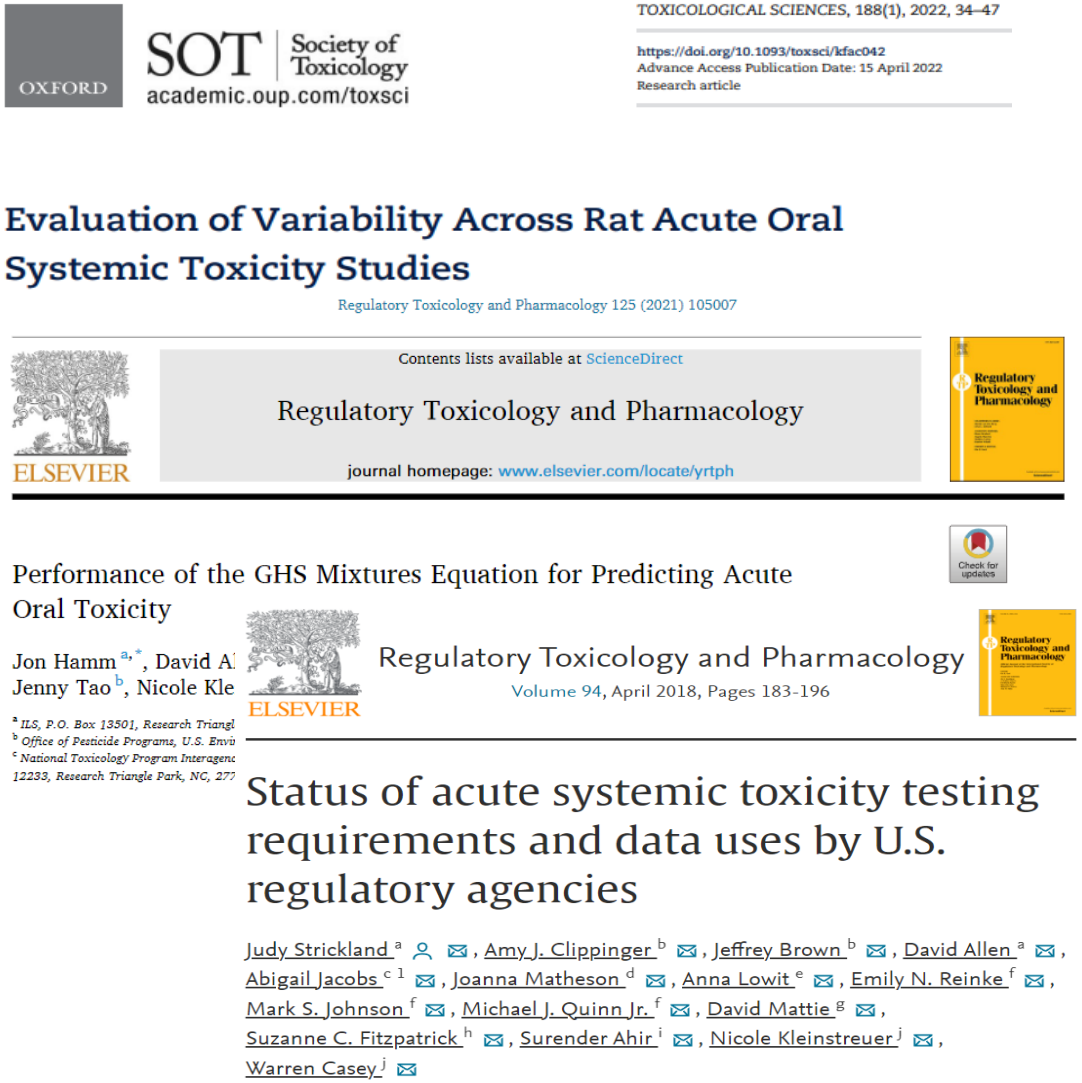
GHS additivity formula evaluation for acute systemic toxicity tests

Manuscript published – Hamm et al. 2021; https://doi.org/10.1016/j.yrtph.2021.105007

Publish a scoping document that outlines the current requirements and testing needs for U.S. and international regulatory authorities

U.S. published (Strickland et al. 2018; https://doi.org/10.1016/j.yrtph.2018.01.022)

International published (Strickland et al., 2023; https://doi.org/10.1080/10408444.2023.2240852)



OXFORD SOT Society of Toxicology academic.oup.com/toxsci

TOXICOLOGICAL SCIENCES, 188(1), 2022, 34–47

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Research article

Evaluation of Variability Across Rat Acute Oral Systemic Toxicity Studies

Regulatory Toxicology and Pharmacology 125 (2021) 105007

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

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ELSEVIER

Performance of the GHS Mixtures Equation for Predicting Acute Oral Toxicity

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ELSEVIER Regulatory Toxicology and Pharmacology
Volume 94, April 2018, Pages 183-196

Status of acute systemic toxicity testing requirements and data uses by U.S. regulatory agencies

Judy Strickland [a], Amy J. Clippinger [b], Jeffrey Brown [b], David Allen [a], Abigail Jacobs [c 1], Joanna Matheson [d], Anna Lowit [e], Emily N. Reinke [f], Mark S. Johnson [f], Michael J. Quinn Jr. [f], David Mattie [g], Suzanne C. Fitzpatrick [h], Surender Ahir [i], Nicole Kleinstreuer [j], Warren Casey [j]

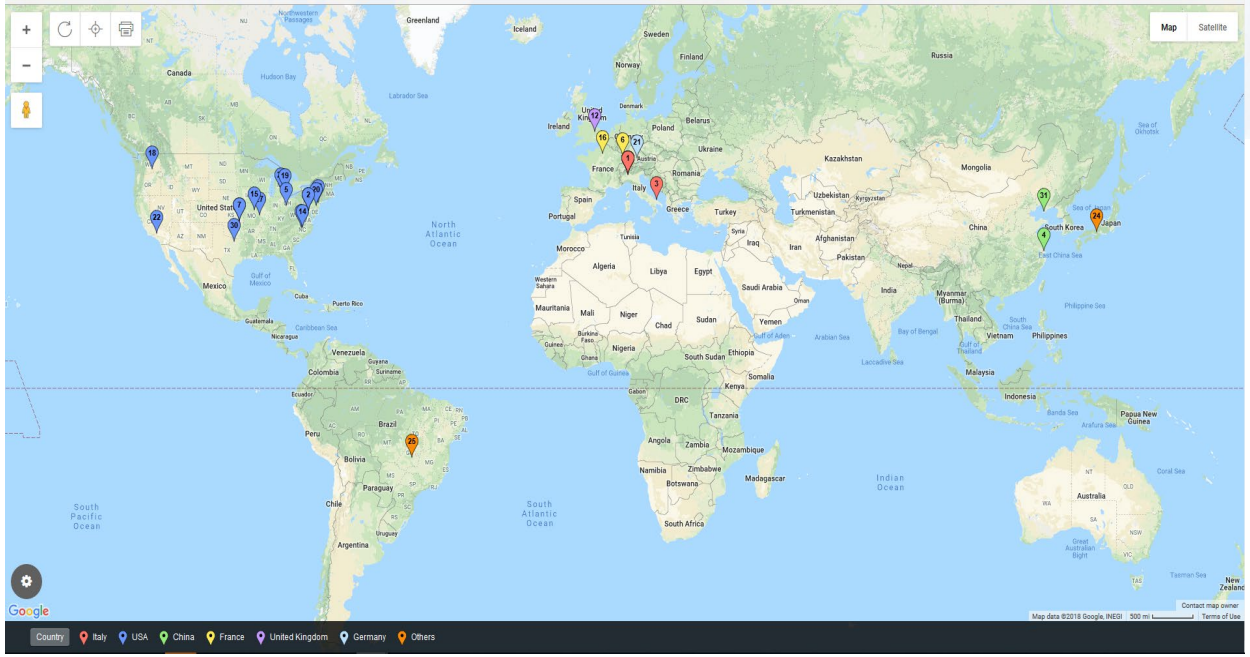
ICCVAM Agencies requirements

Multiple U.S. Federal and International agencies require inhalation data

- Determine occupational exposure safety limits
- Requirements for protective gear
- Consumer safety levels
- Packaging and transportation requirements and limits

- **Alternative Approaches for Acute Inhalation Toxicology Testing Workshop in September 2016 identified the need for 4 working groups, one of which should:**
  - Establish a database of acute inhalation toxicity tests
    - Required to build and evaluate alternative models
    - Data collection, curation, and cleanup occurred from 2018 – 2022

Global Crowdsourcing Predictive Models



- International consortium : academia, industry, govt
- Curate reference data to train & test models:
- Use molecular structure and chemical properties to predict toxicity (e.g. endocrine disruption, acute systemic effects)
- Combine best models together into “ensemble” approaches
- Create open access AI/ML modeling suite

OPERA
OPEn (q)saR App

https://github.com/NIEHS/OPERA

Kleinstreuer et al. Comp Tox (2018); Mansouri et al. J Cheminform (2018), Env Health Persp (2020, 2022)

CERAPP

Collaborative Estrogen Receptor Activity Prediction Project **(2015/16)**

Mansouri et al. (https://doi.org/10.1289/ehp.1510267)

CoMPARA

Collaborative **M**odeling **P**roject for **A**ndrogen **R**eceptor **A**ctivity **(2017/18)**

Mansouri et al. (https://doi.org/10.1289/EHP5580)

CATMoS

Collaborative **A**cute **T**oxicity **Mo**deling **S**uite **(2019/20)**

Kleinstreuer et al. (https://doi.org/10.1016/j.comtox.2018.08.002)
Mansouri et al. (https://doi.org/10.1289/EHP8495)

Endocrine Disruptor Screening Program

Acute Toxicity Workgroup: alternative methods

ICCVAM: Interagency Coordinating Committee on the Validation of Alternative Methods

Outline (2)

Background

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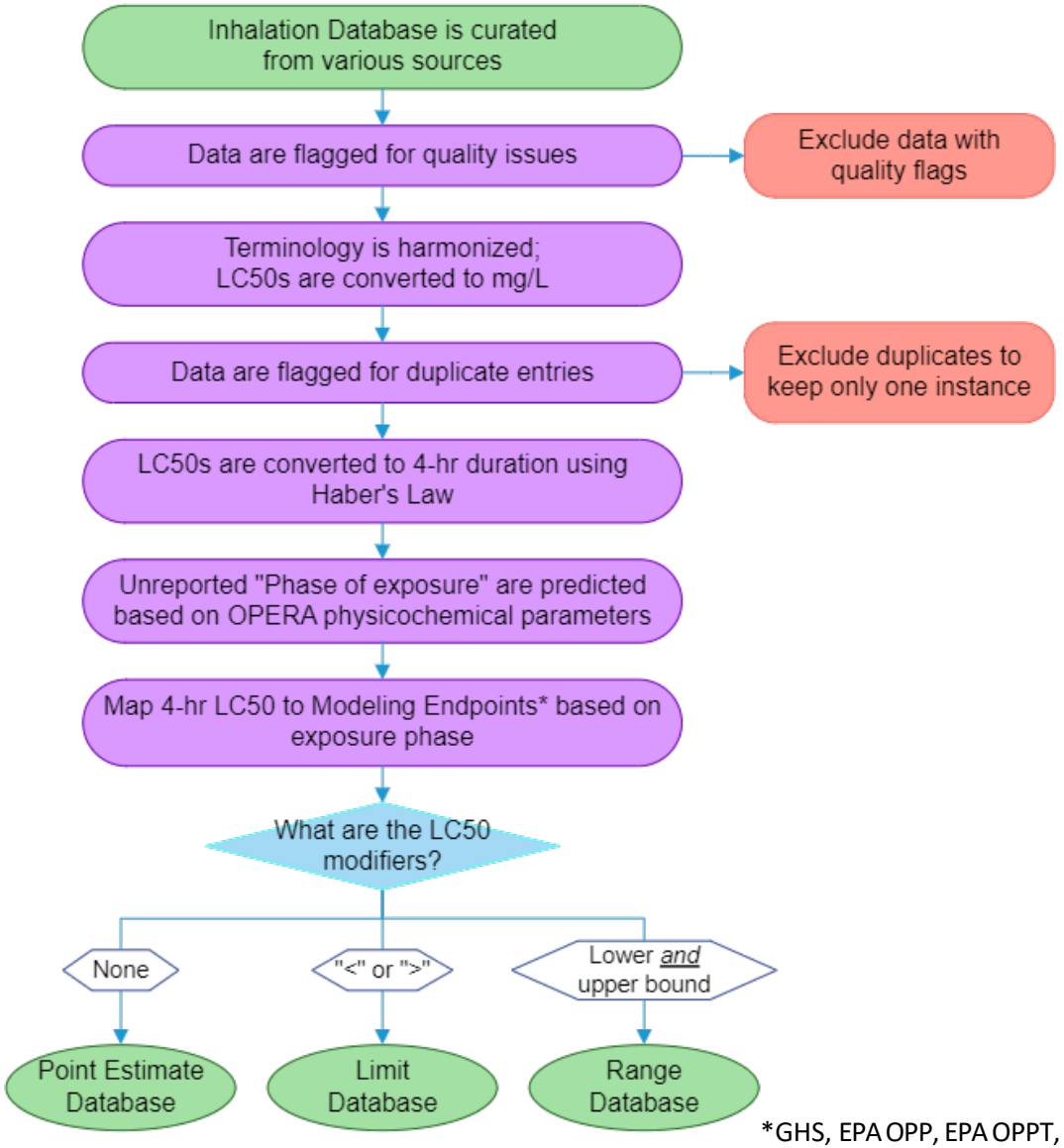
Inventory Sources and Data Collected

- **ChemIDplus**
  - Data Rows: 2036
  - Unique Substances: 1249
- **NIOSH Pocket Guide**
  - Data Rows: 136
  - Unique Substances: 649
- **ECHA REACH Database**
  - Data Rows: 3016
  - Unique Substances: 611
- **EPA AEGL**
  - Data Rows: 1682
  - Unique Substances: 271
- **Department of Defense**
  - Data Rows: 47
  - Unique Substances: 13

- **Data Types Collected**
  - Chemical ID information
    - Name, CASRN, DTXSID, SMILES, Inchikey
  - Chemical type information and source
  - Species/Strain/Sex
  - Route/Phase of Exposure (aerosol, gas, vapor)
  - Exposure type (nose only or whole body)
  - Vehicle
  - Duration
  - Concentration (mg/L, ppm, mg/m^3)
  - Additional clarifying data

Data curation



Data Quality Flags (examples)
Missing or incorrect units
Missing study duration
Species other than rat
Incorrect route of administration
Study type indicated as read across
Deduplication Requirements
Difference in LC50 values ≤ 0.1 mg/L
Duration is equal or unreported
Sex is the same or unreported
Route of administration matches

*GHS, EPA OPP, EPA OPPT, CPSC, etc.

Data distribution

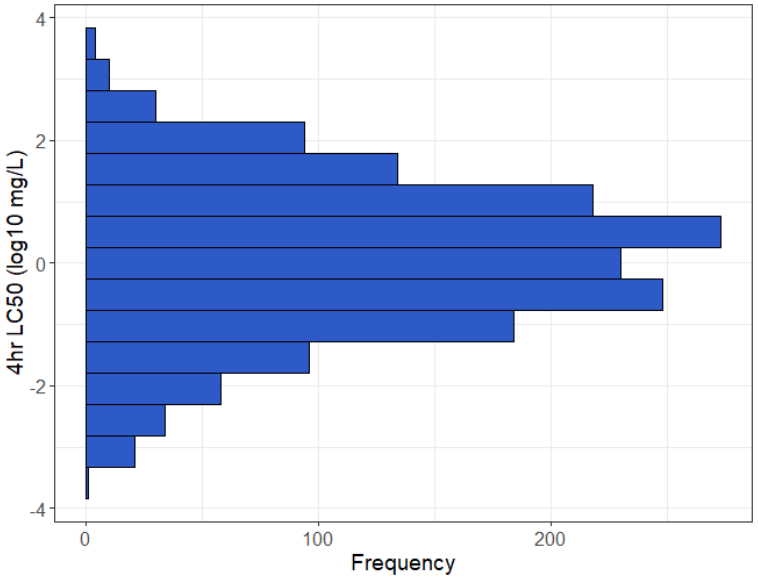
2109 entries, 1025 chemicals

98 chemicals overlap

343 chemicals (14 overlap)

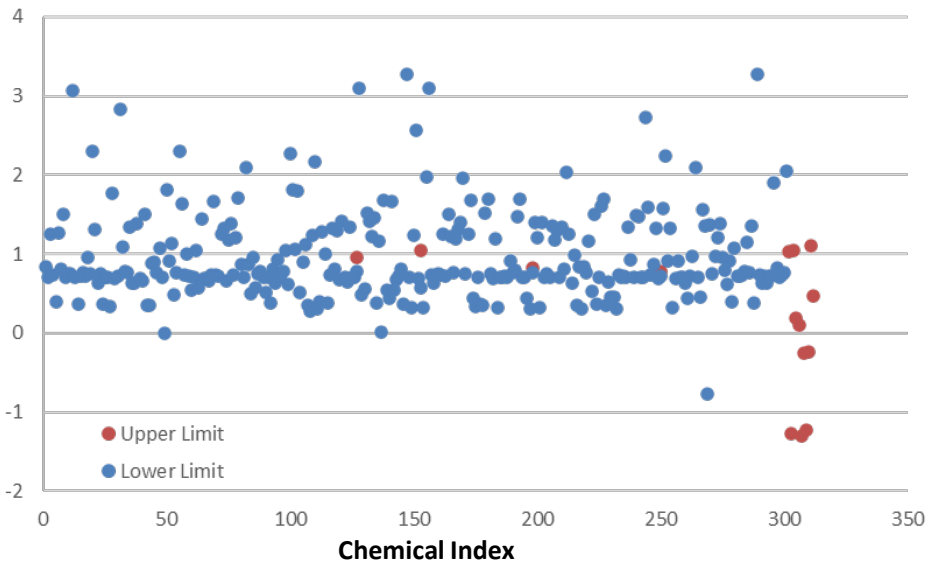
76%

Mean = 35.75 mg/L , SD = 253 mg/L



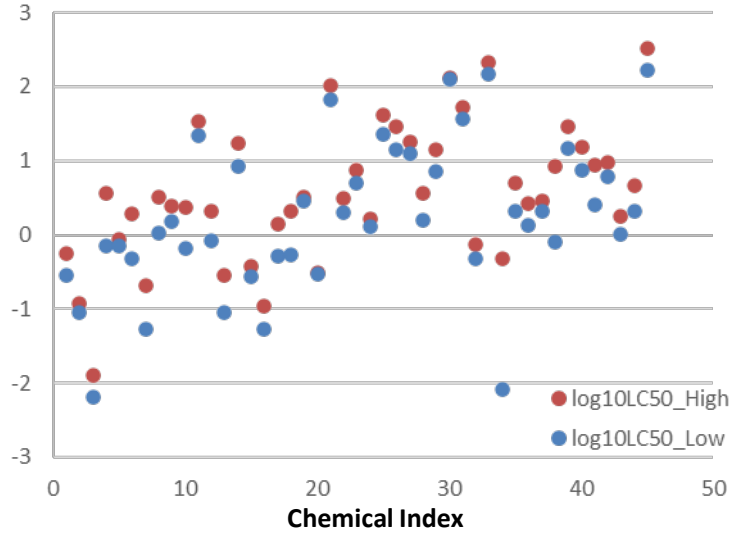
LC50 entries: 1635; chemicals: 780

20%



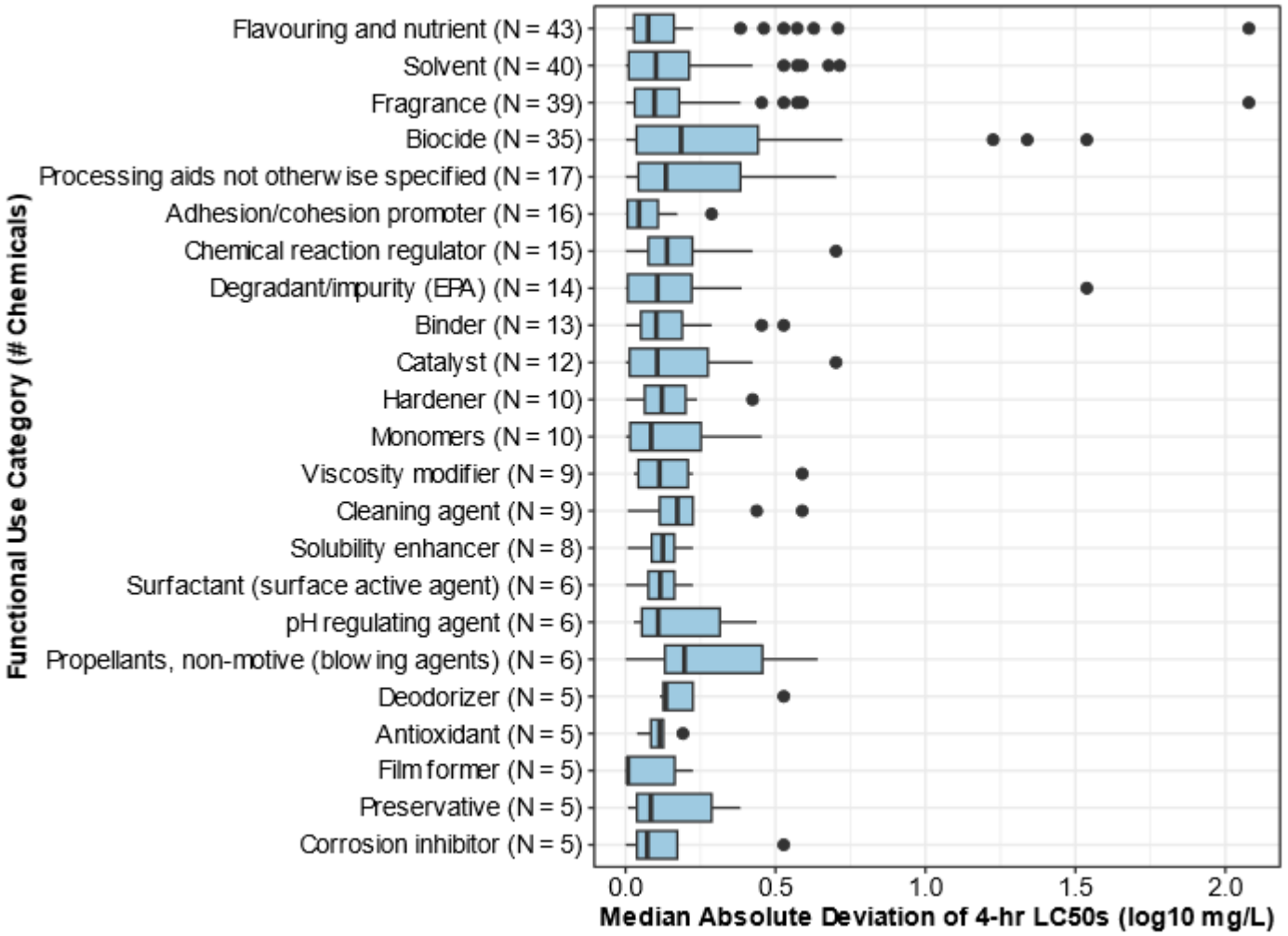
Limit test entries: 420; Chemicals: 312
(lower: 301 ; upper: 15)

4%



Range entries: 54 ; chemicals: 45

Functional use categories



- To determine potential associations between functional use and LC50 variability, data were obtained from EPA's Chemicals and Products Database (CPDat v4.0.0.alpha) accessed through ChemExpo (https://comptox.epa.gov/chemexpo/).
  - CPDat contains reported functional uses harmonized to 107 functional use categories defined by the Organisation for Economic Co-operation and Development (OECD).
- Of the 231 chemicals with at least two LC50 point estimates, 142 had an OECD functional use in CPDat.
  - These chemicals span 61 of the 107 functional use categories in CPDat.
  - Chemicals had as many as 20 functional uses (n=20 for 2-butoxyethanol)

Median absolute deviation of 4-hour LC50s for functional use categories with at least five unique chemicals.

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Endpoints of interest

- Continuous: LC50 (mg/L), 4-hour exposure
- Categorical: hazard category schema
  - GHS
  - EPA OPPT
  - EPA OPP
  - CPSC
  - DoT

GHS Categories

GHS Category	Gases (ppm)	Vapors (mg/L)	Dust and Mists (mg/L)
1	LC50 ≤ 100	LC50 ≤ 0.5	LC50 ≤ 0.05
2	100 < LC50 ≤ 500	0.5 < LC50 ≤ 2.0	0.05 < LC50 ≤ 0.5
3	500 < LC50 ≤ 2500	2.0 < LC50 ≤ 10.0	0.5 < LC50 ≤ 1.0
4	2500 < LC50 ≤ 20,000	10.0 < LC50 ≤ 20.0	1.0 < LC50 ≤ 5.0
Not classified	LC50 > 20,000	LC50 > 20.0	LC50 > 5.0

EPA OPPT Categories

Hazard Ranking	Gas/Vapor (mg/L)	Dust and Mists (mg/L)
3 (high)	<2.0 < LC50 ≤ 10	<0.5 < LC50 ≤ 1.0
2 (moderate)	10.0 < LC50 ≤ 20.0	1.0 < LC50 ≤ 5.0
1 (low)	LC50 > 20.0	LC50 > 5.0

EPA OPP Categories

EPA Category	Criteria	Entries	Chemicals
I	LC50 ≤ 0.05	212	86
II	0.05 mg/L < LC50 ≤ 0.5	425	212
III	0.5 mg/L < LC50 ≤ 2.0	273	165
IV	LC50 > 2.0	1165	641

CPSC Categories

Category	Gas or Vapor (ppm)	Dusts/mists (mg/L)
Highly toxic	LC50 ≤ 200	LC50 ≤ 2
Toxic	200 < LC50 ≤ 20,000	2 < LC50 ≤ 200
Nontoxic	LC50 > 20,000	LC50 > 200

Endpoints of interest (2)

- Continuous: LC50 (mg/L), 4-hour exposure
- Categorical: hazard category schema
  - 5 categories — GHS: 3 phases (gas, vapor, aerosol)
  - 3 categories — EPA OPPT: 2 phases (gas, aerosol)
  - 4 categories — EPA OPP: No phases
  - 3 categories — CPSC: 2 phases (gas, aerosol)
  - 5 categories — DoT: 2 phases (gas, aerosol)

Total 11 endpoints if modeled separately!

Determining Exposure Phase

- The phase of exposure is necessary for mapping to many of the toxicity endpoints (cutoffs are determined by phase)

- We consider 3 phases for inhalation:
  1. **Gas**
  2. **Vapor**
  3. **Aerosol** (includes Dust and Mist)

- Limited data had phase reported (28%)
  - We harmonized reported phase to gas, vapor, and aerosol
  - Some studies report both vapor and aerosol for a chemical

Predict Phase of Exposure Using OPERA

Melting point (MP), boiling point (BP), and vapor pressure (VP)

Physical State Rules	Physical State	Atmospheric State Rules	Atmospheric State	Exposure Phase Justification	Exposure Phase
MP ≤ 25ºC	liquid	VP ≤ 10^{-8} mmHG	particulate	atmospheric state is particulate	aerosol
MP > 25ºC	solid	VP ≤ 10^{-8} mmHG	particulate	atmospheric state is particulate	aerosol
MP ≤ 25ºC	liquid	10^{-8} mmHG < VP < 10^{-4} mmHG	vapor and particulate	atmospheric state is vapor and particulate	aerosol;vapor
MP > 25ºC	solid	10^{-8} mmHG < VP < 10^{-4} mmHG	vapor and particulate	atmospheric state is vapor and particulate	aerosol;vapor
BP ≤ 25ºC	gas	VP ≥ 10^{-4} mmHG	vapor	physical state is gas	gas
MP ≤ 25ºC	liquid	VP ≥ 10^{-4} mmHG	vapor	atmospheric state is vapor and physical state is liquid	aerosol;vapor
MP > 25ºC	solid	VP ≥ 10^{-4} mmHG	vapor	atmospheric state is vapor and physical state is solid	aerosol;vapor

Limited data had phase reported (28%)
715 rows out of ~2500 have an extracted phase

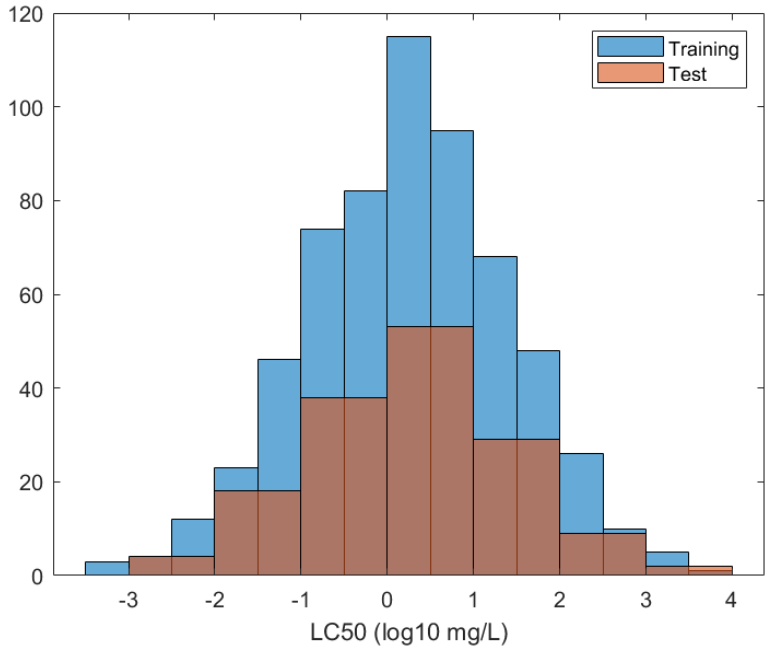
Phase	# Rows Reported	# Correctly Predicted
Gas	43	30 (69.7%)
Vapor	374	369 (98.7%)
Aerosol	303	302 (99.7%)

Proposed endpoint to be modeled

LC50 point estimate in **mg/L** and **ppm** (After modeling, select 1 or consensus of both)

- **Training and test sets:**

765 chemicals (with QSAR-ready structures)



- 80% training set: 612 chemicals
- 20% evaluation set: 153 chemicals

- **Prediction set:**

48137 QSAR-ready structures to be predicted (CATMoS list).

Included Lists:

- ToxCast/Tox21
- EDSP
- TSCA
- Substances on the market (EPA)

Proposed modeling strategy

1. Modeling step:

Endpoints to be modeled:
- LC50 values (2 units)

2. Consensus model:

- Combine the single models into consensus
- Apply WoE for consistency

3. Physical forms:

- Physicochemical properties to assign physical states
- Convert specific predictions (units)

4. Regulatory systems:

- Apply the corresponding thresholds for the different regulatory classification systems

Evaluation Criteria

The five OECD principles for QSAR validation to be considered as guidance:

1. **A defined endpoint**
   - Separate models should be submitted corresponding to the five endpoints defined above.
2. **An unambiguous algorithm**
   - Ensure transparency in the description of the model algorithm. Preference will be given to models using **simple algorithms and open-source code.**
3. **A defined domain of applicability**
   - Define limitations in terms of the types of chemical structures, physicochemical properties and mechanisms of action for which the models can generate reliable predictions. Including ability to characterize uncertainty/confidence is a plus.
4. **Appropriate measures of goodness-of–fit, robustness and predictivity**
   - Quantitative performance, including cross-validated training set performance and external test set performance (will be recalculated by the project organizers).
5. **Mechanistic interpretation, if possible**
   - Mechanistic associations between the descriptors used in a model and the endpoint (mode of action) being predicted.

Timeline

- July 1st: Access to training and prediction sets (Box folder)
- Oct 1: Modeling results, predictions, and summary/description
- Oct 15: Access granted to test/evaluation set identifiers
- Nov 30: Organizing committee evaluation results, detailed documentation
- Dec 30: Corrections and additional documentation to models
- Jan 30: Consensus model and evaluation
- Mar 30: Drafting manuscript
- June 30: Submit manuscript

Participating groups

CDC ATSDR AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

BHSAI BIOTECHNOLOGY HPC SOFTWARE APPLICATIONS INSTITUTE

SimulationsPlus

UNIVERSITA' DEGLI STUDI DI MILANO BICOCCA

CAAT Johns Hopkins Center for Alternatives to Animal Testing

UFG UNIVERSIDADE FEDERAL DE GOIÁS

IMN ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

Insilica.co

NIH National Center for Advancing Translational Sciences

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

FDA U.S. FOOD & DRUG ADMINISTRATION NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

UNIVERSITÉ DE STRASBOURG

UCLA

AFRL THE AIR FORCE RESEARCH LABORATORY LEAD | DISCOVER | DEVELOP | DELIVER

HELMHOLTZ MUNICH

Pacific Northwest NATIONAL LABORATORY

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

The NICEATM Group (2024)

ICCVAM (ATWG & EcoWG)
EPA EFED
All international collaborators

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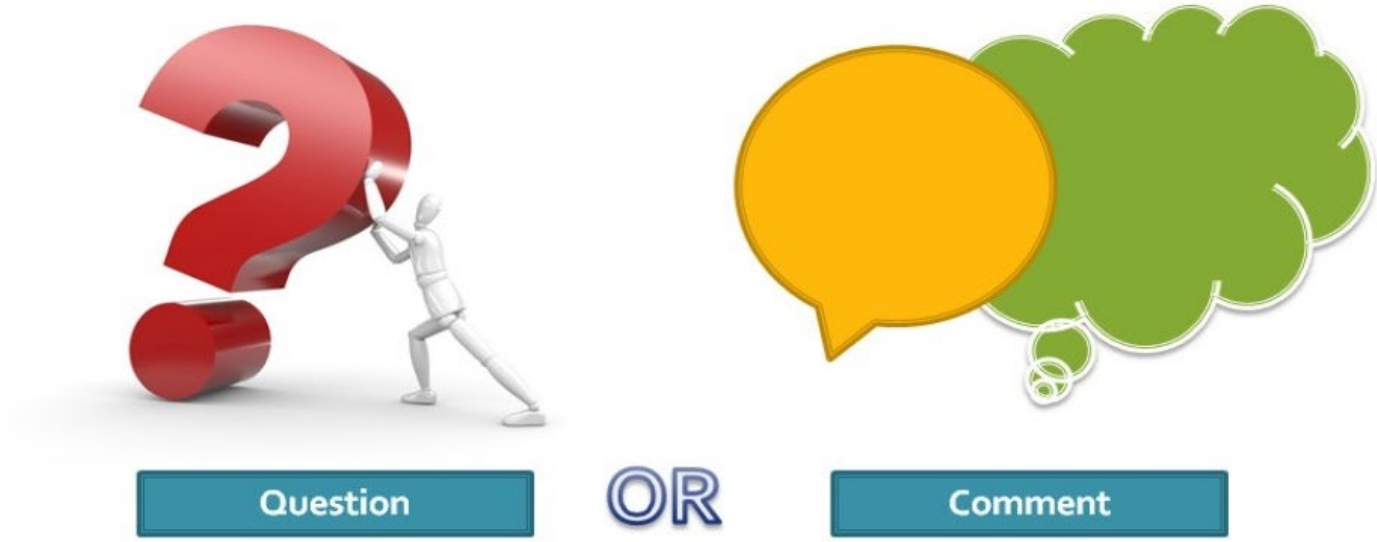

Acknowledgments:

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