

Compilation and Standardization of Rat Acute Inhalation Study Data to Support Predictive Modeling Victoria Hull¹, Emily N. Reinke¹, Amber B. Daniel¹, Kimberly T. To¹, Agnes L. Karmaus^{1*}, David G. Allen¹, Kamel Mansouri², Nicole C. Kleinstreuer² ¹Inotiv, Research Triangle Park, NC; ²NIH/NIEHS/DTT/NICEATM, Research Triangle Park, NC

Introduction

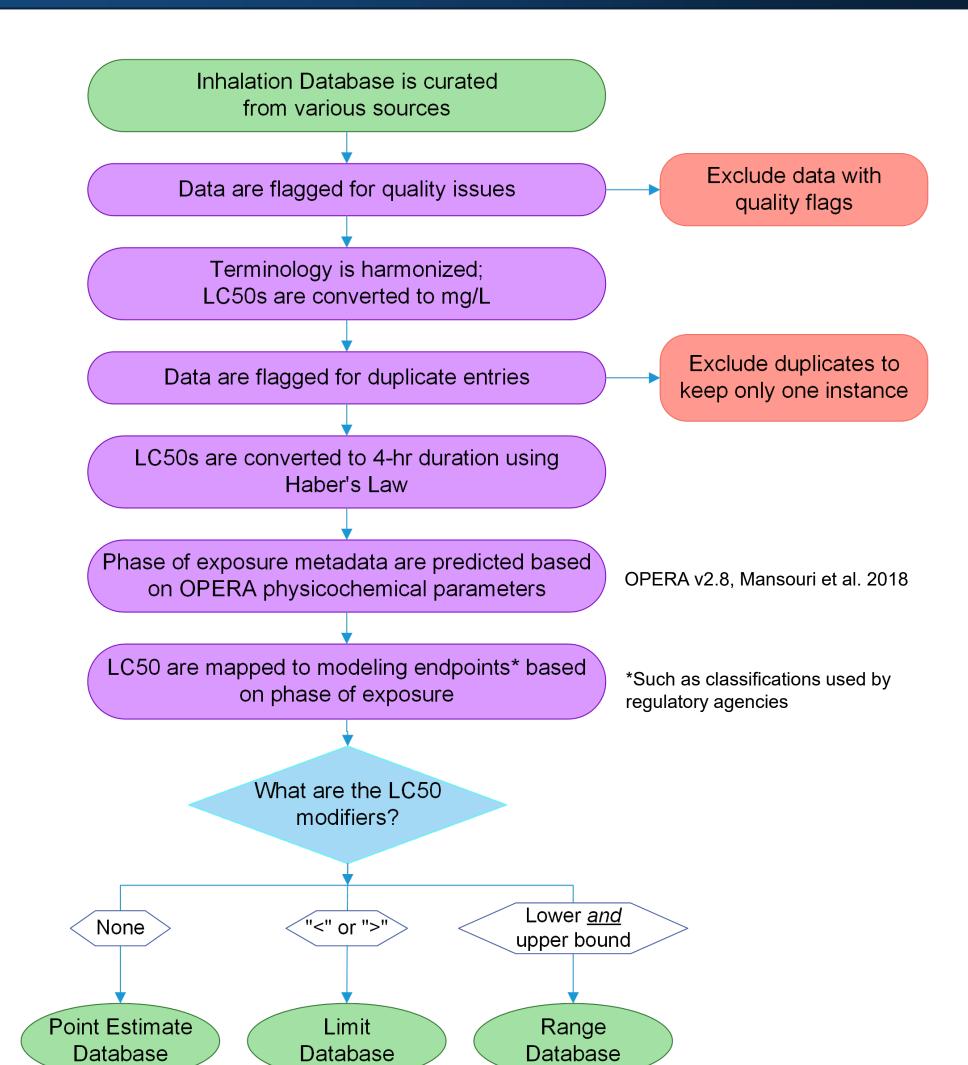
- Multiple U.S. federal and international agencies require acute inhalation toxicity data to determine occupational exposure safety limits, personal protective equipment, consumer safety levels, and packaging and transportation requirements.
- Computational models to predict acute inhalation toxicity have been proposed as alternatives to animal tests to support regulatory decision-making. • Developing such models requires robust, well-curated, and chemically diverse training data that is easily accessible.
- A working group established at an "Alternative Approaches for Acute Inhalation Toxicology Testing Workshop" (Clippinger et al. 2018) was tasked with establishing an acute inhalation toxicity database both to address agency information needs and support modeling efforts.
- The working group asked the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) to compile a rat acute inhalation toxicity database.
- This poster describes the database, which contains data from about 1200 chemicals.
- This data are available in the Integrated Chemical Environment (ICE; https://ice.ntp.niehs.nih.gov). ICE is an open-access resource developed by NICEATM to provide toxicologically relevant data and computational tools.
- To assess reproducibility of LC50 point estimates and U.S. Environmental Protection Agency (EPA) Office of Pesticide Programs (OPP) hazard categorizations, we analyzed variability in this database for chemicals having at least two reported LC50 values.

Methods: Data Sources

Data Source	Data Records	Unique Substances
Legacy data from ChemIDplus (now integrated into PubChem)	2036	1249
National Institute for Occupational Safety and Health (NIOSH) Pocket Guide	136	649
European Chemicals Agency (ECHA) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Database	3016	611
Environmental Protection Agency (EPA) Acute Exposure Guideline Levels (AEGL)	1682	271
Department of Defense	3016	13

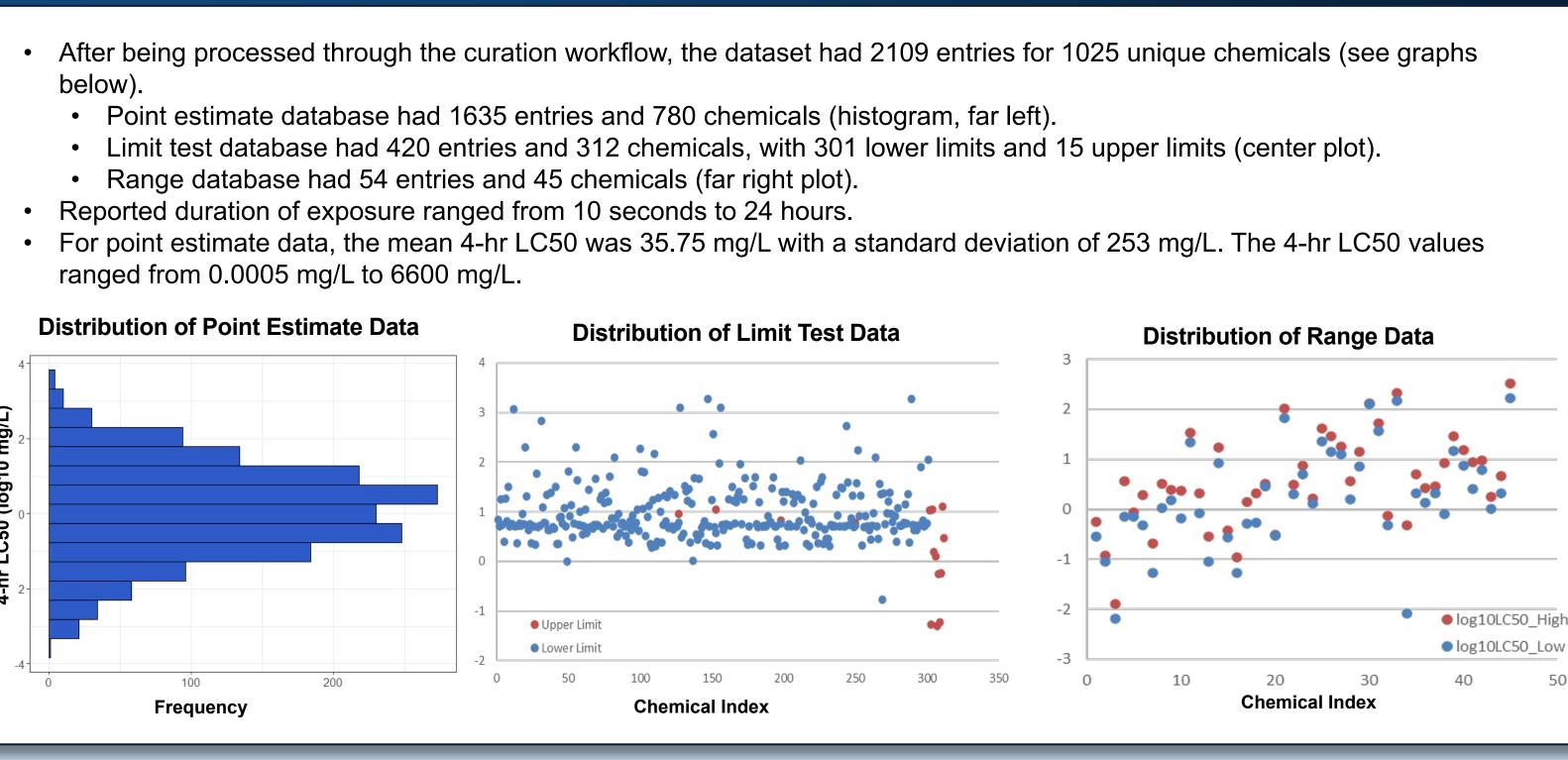
- Where available, data were collected on:
 - Chemical names and identifiers (CASRNs, DTXSIDs, SMILES, InChiKeys)
 - Study information, including duration of exposure, LC50, and units of LC50 (mg/L, ppm, or mg/m³)
 - Study metadata such as species, sex, strain of species, route/phase of exposure (aerosol, gas, vapor), the exposure type (nose-only or whole-body), and vehicle
 - Any additional clarifying data, such as additional details on study design or interpretation of results

Methods: Data Curation Process



- **Data quality flags** included missing or incorrect units for LC50 values, missing study duration, species measured other than rat, and study type indicated as a read-across study.
- Data were flagged as duplicates if two data points met all the following criteria: LC50 values differed by 0.1 mg/L or less; duration of both studies was equal or unreported; sex was the same or unreported; and the route of administration matched.

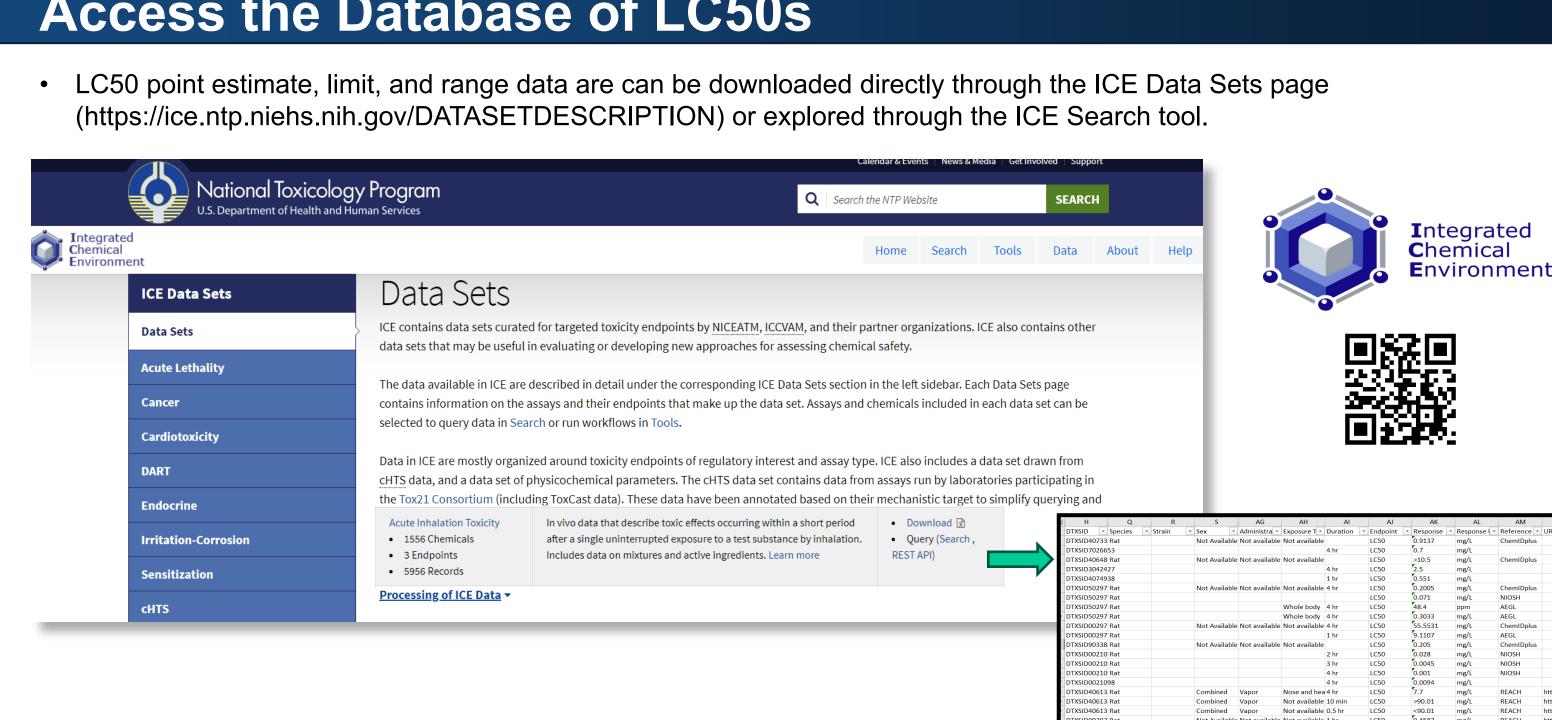
Data Distribution



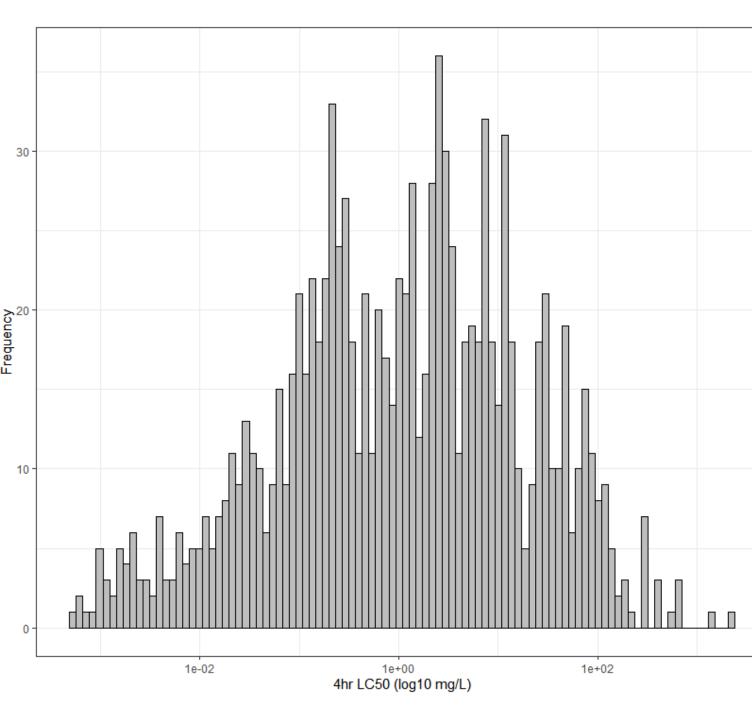
Variability Analysis of Point Estimate LC50s

- below right).

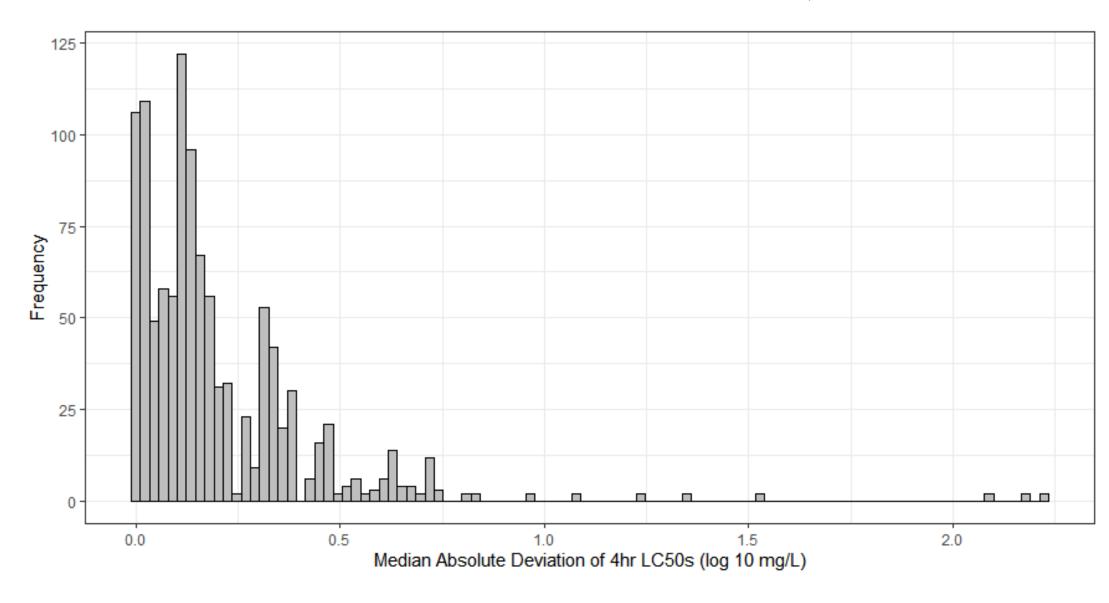
Number of LC50s	Number of Chemicals	Number of LC50s	Number of Chemicals
2	75	12	2
3	49	13	1
4	31	14	1
5	15	15	2
6	19	16	2
7	7	17	1
8	10	19	2
9	5	20	1
10	3	22	1
11	3	29	1



We had at least two LC50 point estimates for 231 chemicals (table below left). The remaining 549 chemicals in the database with LC50 point estimates had only a single LC50 value available. The distribution of the chemicals with two or more point estimate 4-hr LC50s (log10 mg/L) was approximately normal (histogram



The mean absolute deviation of repeat 4-hr LC50s ranged from 0.0 to 2.2 (histogram below). There was more variation between chemicals than within chemicals (ANOVA, $F_{230,855}$ = 61.52, p < 0.001).



Access the Database of LC50s

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Variability of EPA OPP Categories

- Of the 1019 chemicals with an EPA OPP category, 339 chemicals had at least two reported LC50s.
- Conditional probabilities (the probability of a chemical being within a category given that it was previously categorized in that same category) were calculated for those chemicals with $n \ge 2$.
- Recategorization to the same category was always the most likely outcome.
- A Category IV categorization is the most consistent, with an 85.9% probability of being recategorized as Category IV.
- A Category III categorization is the least consistent, with a 46.9% probability of being recategorized as Category III.

EPA OPP Category	I	II	III	IV
I	70.3%	24.6%		5.2%
II	10.7%	68.0%	13.8%	7.5%
III		25.8%	46.9%	27.2%
IV	0.6%	3.9%	9.7%	85.9%

Summary and Discussion

- NICEATM compiled and curated a database of rat acute inhalation study data to support predictive modeling and regulatory decision-making. • LC50s, duration of exposure, and associated metadata within the
- database are publicly accessible through ICE. High-level variability analyses show that 4-hr LC50 point estimate data are fairly consistent, and there is more variability between chemicals than within chemicals
- Efforts are still ongoing to assign 4-hr LC50s to different hazard schema and assess variability within those categories.
- There are many complexities that need to be considered before these data are made publicly available and full variability analyses can be conducted.
- Conditional probabilities for EPA OPP categories show that Category IV categorization is most consistent and Category III categorization is least consistent
- Assessment of effects of animal sex or exposure (head-only or whole-body) could not be conducted due to a paucity of adequate repeat study data.

Future Development and Applications

- A future version of the database will include both reported and predicted phase of exposure so that hazard categories can be assigned. • Exposure phase will be modelled based on melting point, boiling point,
- and vapor pressure utilizing EPA Pollution Prevention Framework (2012) rules
- We will continue to evaluate reproducibility and variability of the acute inhalation toxicity database.
- We are scoping the feasibility of using the database to support a multistakeholder modeling project, similar to models developed to predict estrogen activity (CERAPP, Mansouri et al. 2016), androgen activity (CoMPARA, Mansouri et al. 2020), and acute oral toxicity (CATMoS, Mansouri et al. 2021).

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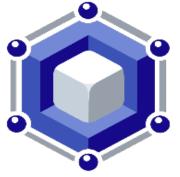
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