# Curation and Characterization of a Reference Rat Acute Inhalation Toxicity Database

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## Background and Purpose

Chemical safety evaluation has traditionally relied on animal models to identify potential acute inhalation toxicants and define safety standards that protect human health. New approach methodologies (NAMs) that include in vitro and computational approaches have been proposed as complementary resources that can be integrated to identify and/or mechanistically evaluate such toxicants and also yield human-relevant insight into inhalation toxicity. Developing and evaluating such approaches requires robust, well-curated, and chemically diverse reference data. Accordingly, the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) has curated a database with in vivo rat acute inhalation data for approximately 1200 unique substances. The database was evaluated for coverage of chemical properties and functional use and variability of quantitative and categorical results to assess the usefulness and limitations of the database for developing and evaluating NAMs for inhalation toxicity.

## Methods

Rat acute inhalation toxicity data were compiled from six open-access sources: the National Institute for Occupational Safety and Health Pocket Guide; European Chemicals Agency Registration, Evaluation, Authorisation and Restriction of Chemicals Database; U.S. Environmental Protection Agency (EPA) Acute Exposure Guideline Levels; U.S. Department of Defense; and PubChem/ChemIDPlus. In addition to LC50 values (exposure concentration of a toxic substance lethal to half of the test animals), metadata collected for each entry included exposure type, exposure route, species, sex, and number of animals tested when available. Automated and manual curation steps standardized the data, removed duplicate entries, retrieved quantitative structure-activity relationship (QSAR)-ready structures, and imputed exposure phase information (i.e., gas, vapor, and/or aerosol).

The diversity of chemical space represented in the database was characterized using predicted chemical properties and functional use categories obtained from the EPA Chemical and Products Database (CPDat). Hazard categories (e.g., nontoxic, toxic, highly toxic) were assigned based on LC50 values and exposure phase data following various agency-specific classification schemes. To evaluate categorical variability, conditional probabilities were calculated for the phase-independent classifications from the EPA Office of Pesticide Programs (OPP) scheme. The conditional probabilities define the probability that a chemical would be assigned a specific hazard category, given that it was previously assigned the same or another category.

## Results

The final curated database contains 2565 entries for 1209 unique substances. Of these, 1020 unique chemicals (2076 entries) have a QSAR-ready structure. These chemicals showed robust coverage across physicochemical properties and functional use categories.

In the database, 780 chemicals (1635 entries) had point-estimate LC50 data (log10 mg/L; range = -3.3 to 3.8; mean = 0.07; standard deviation = 1.2). For the 231 chemicals that have at least two point-estimate LC50 values, the per-chemical median absolute deviations ranged from 0.0 to 2.2 (log10 mg/L).

The EPA OPP hazard classification scheme categorized 1019 chemicals. Of these, 339 chemicals had at least two independent study results which were used to calculate conditional probabilities for each hazard category. The conditional probabilities for recategorizing a chemical to the same hazard category were 70% for Category I (most potent), 68% for Category II, 47% for Category III, and 86% for Category IV (least potent).

**Conclusions**

NICEATM has curated a database of rat acute inhalation study data to support the development and evaluation of NAMs for inhalation toxicity. Preliminary variability analysis of the data showed lognormally distributed LC50 point data with broad coverage across multiple chemical descriptors. Ongoing characterization of the database includes variability analysis of phase-dependent hazard classifications. This characterization will be used to contextualize potential modeling endpoints. The database can be downloaded from NICEATM's Integrated Chemical Environment (https://ice.ntp.niehs.nih.gov/DATASETDESCRIPTION). This project was funded in whole or in part with federal funds from the NIEHS, NIH under Contract No. HHSN273201500010C.

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