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Database of Pharmacokinetic Time-Series Data and Parameters for Environmental Chemicals

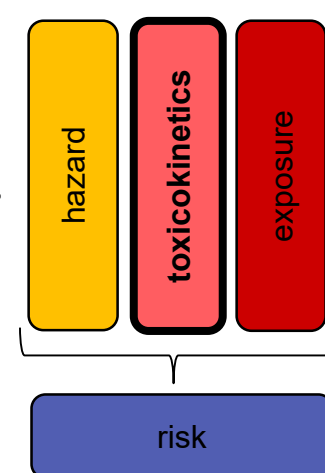
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1. Background

Time courses of compound concentrations in plasma (**CvT data**) can be used to evaluate the relationship between external administered doses and internal tissue exposures. However, CvT data is rarely available for the thousands of chemicals to which people may potentially be exposed. Quantitative uncertainty of pharmacokinetic (PK) models developed using *in vitro* assays and *in silico* models cannot be determined without *in vivo* data for external validation, identified as a key area needed for improvement of chemical safety prioritization in a recent review by authors from governments, academia, and industry (Bell et al. 2018).



To address this need, we present an extensible public database of data points describing changes in amounts of a chemical in a tissue over time after an administered dose, which were extracted from publications and databases, and stored with contextualizing information in a reproducible way for usage in risk characterization or model evaluation.

2. Methods

2.1 Definitions of database terminology

Study: a PK experiment in which a type of *subject* (organism on which the experiment is performed) is exposed to a single *test substance*. May be linked to several *series* if CvT data is available from several individuals or groups of subjects, in several media (tissue, plasma, etc.), or multiple analytes (a test substance and its metabolites, for example).

Series: a set of CvT data measured during a PK experiment, or *study*. A series may represent data from a single subject, or the mean value from a group of subjects (sometimes with a measure of error/variability).

2.2 Data source identification

Data was sourced from the Chemical Effects in Biological Systems (CEBS) database hosted by the National Toxicology Project, and from individual publications. We used machine learning in Python 3.6 to identify candidate document publications from PubMed using Medical Subject Headings (**MeSH**) terms (F1 score: 0.36) and **abstracts** (F1 score: 0.48).

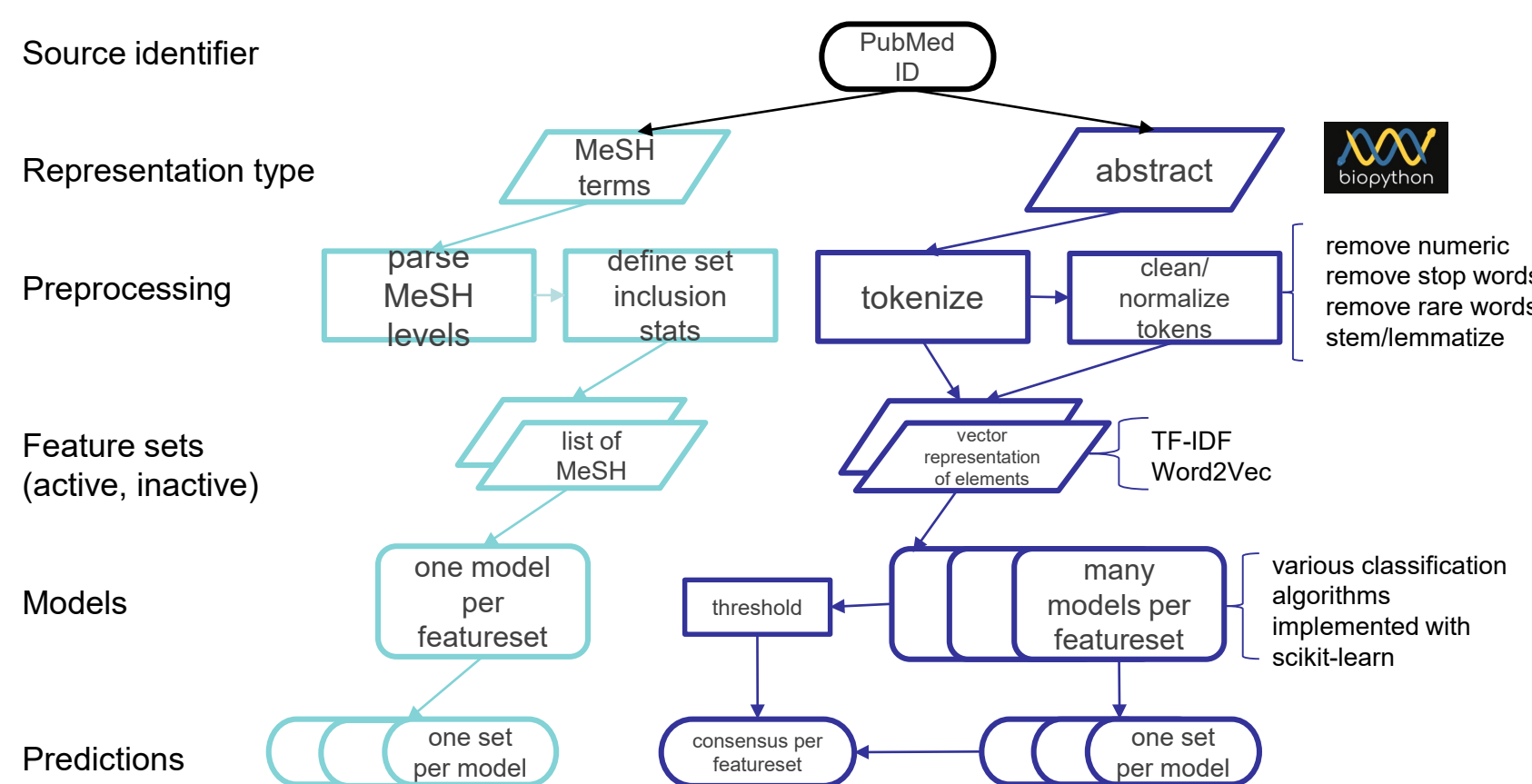


Figure 1. Overview of workflows for machine learning to identify publications containing CvT data from PubMed records (*manuscript in preparation*).

3. Data records

3.1 Data record storage

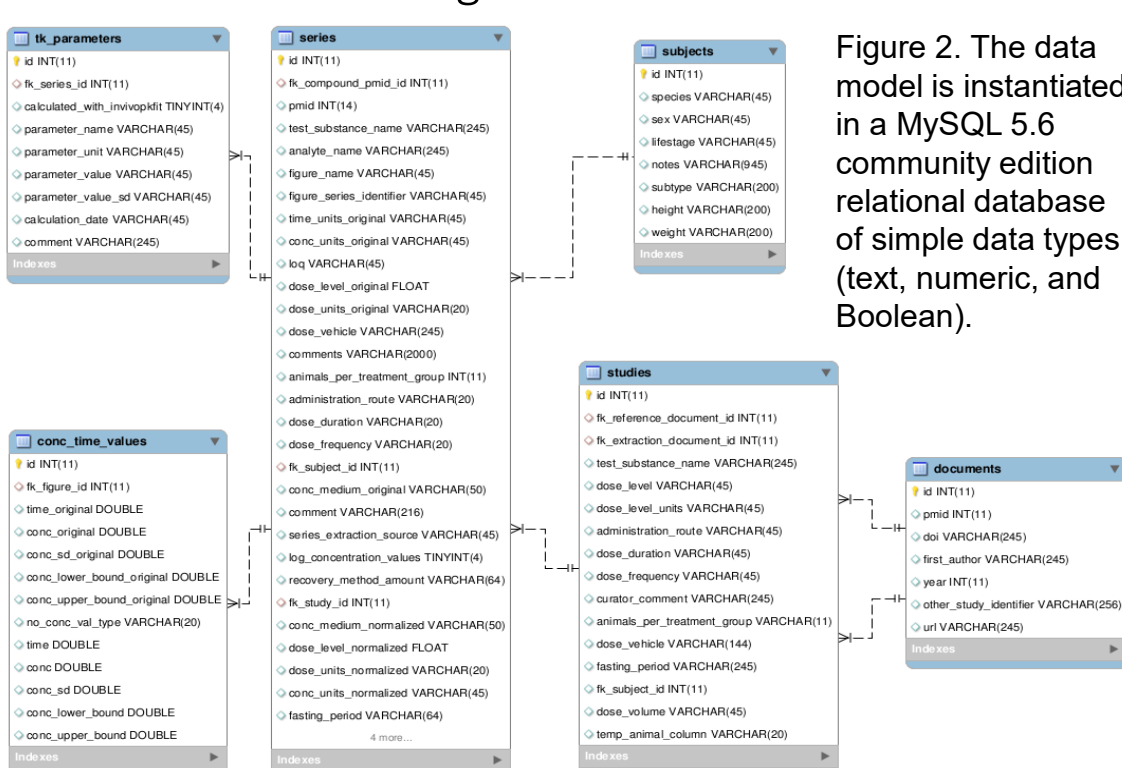


Figure 2. The data model is instantiated in a MySQL 5.6 community edition relational database of simple data types (text, numeric, and Boolean).

3.2 Data collection

CvT data: Efforts at automated data extraction from images were not found to be sufficiently accurate or precise, so we used manual capture.

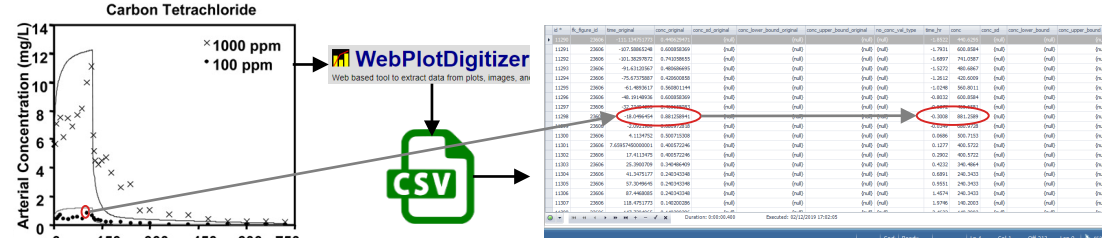


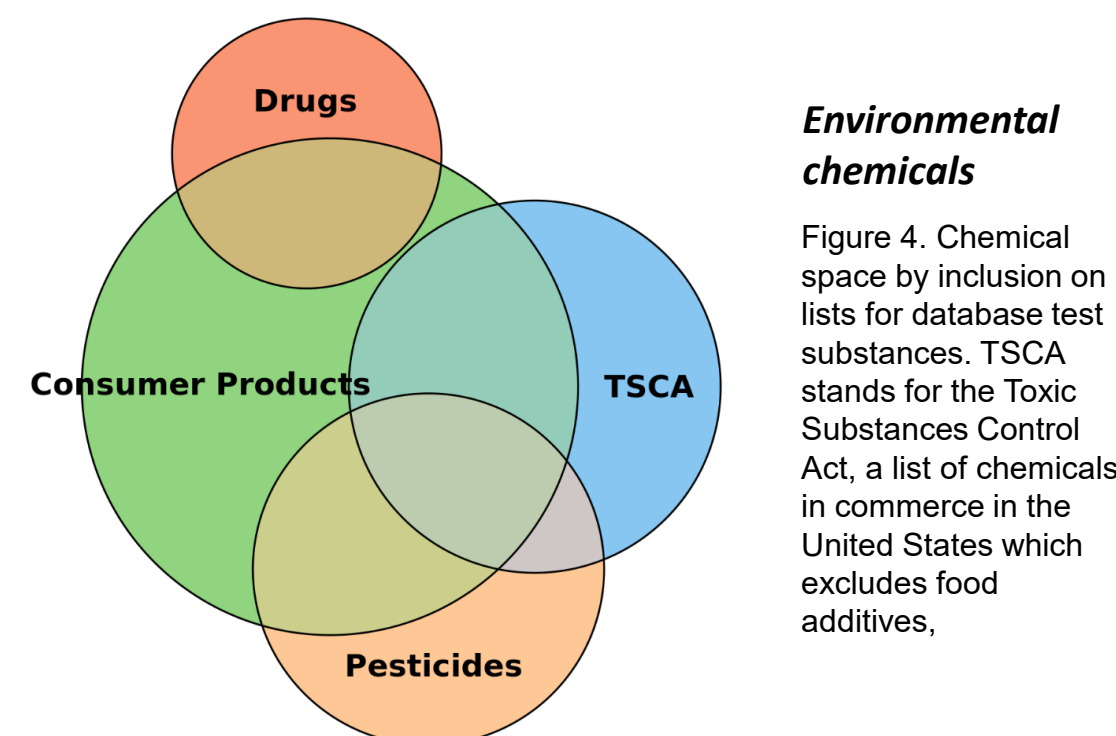
Figure 3. Image files (in this case, from Ng 2007) were uploaded to the webtool *WebPlotDigitizer*. The tool was calibrated to the plot axes, then each data point was clicked (left red oval). Results were exported into comma-separated value transaction files for database import (central red oval). Time units were normalized to *hour*, and concentrations were normalized to the micro scale; all values were rounded to four decimal places (right red oval).

Toxicokinetic parameters: Calculated values summarizing the absorption, distribution, metabolism, and excretion (ADME) represented by a series are included in this dataset, either as presented in original publications and/or as calculated from the CvT data points using the R package *invivopkfit* as described in Wambaugh et al. 2018. It fits the curve with one-compartment kinetics, then calculates the corresponding parameters (such as total clearance and concentration at steady-state) and their uncertainty.

Metadata: Manually captured study details (based on the 1998 test guideline for metabolism and pharmacokinetics released by the U.S. EPA Office of Prevention, Pesticides, and Toxic Substances) may apply to an entire study, while some are specific to a series. Inclusion in this set does not imply that studies meet OPPTS testing requirements.

3.3 Data record content

The total set consists of 16542 series from 567 **studies** for 144 **test substances** and 187 analytes.



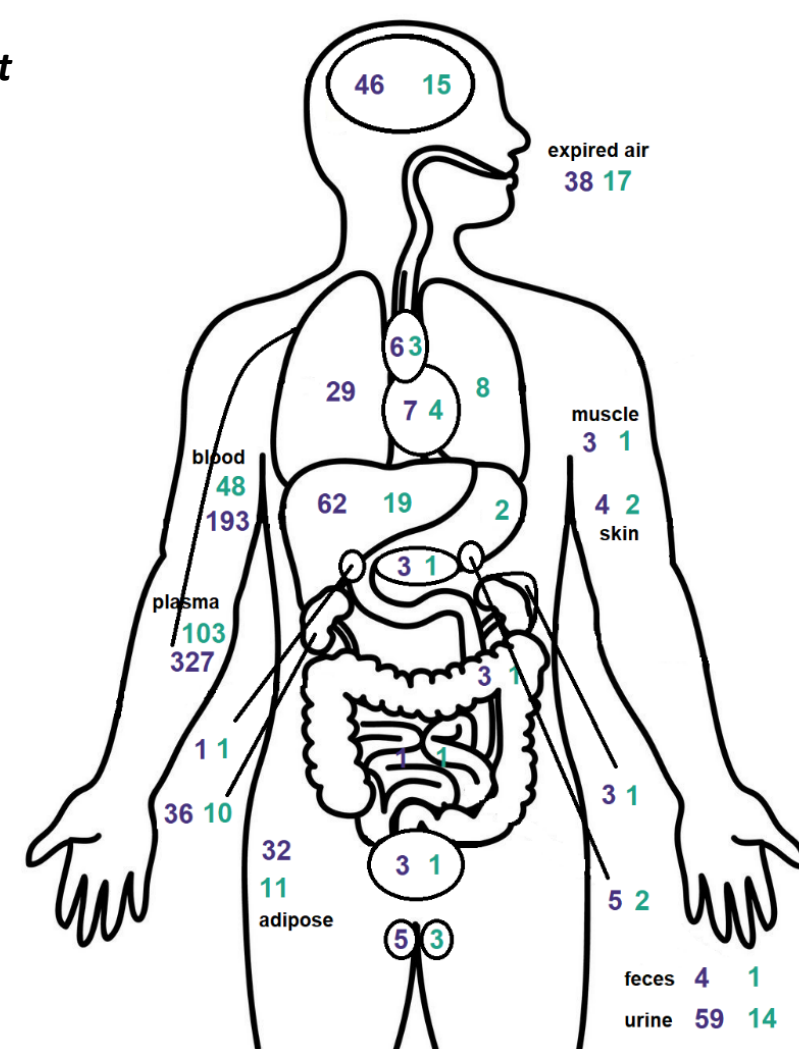
Environmental chemicals

Figure 4. Chemical space by inclusion on lists for database test substances. TSCA stands for the Toxic Substances Control Act, a list of chemicals in commerce in the United States which excludes food additives,

Results per test substance:

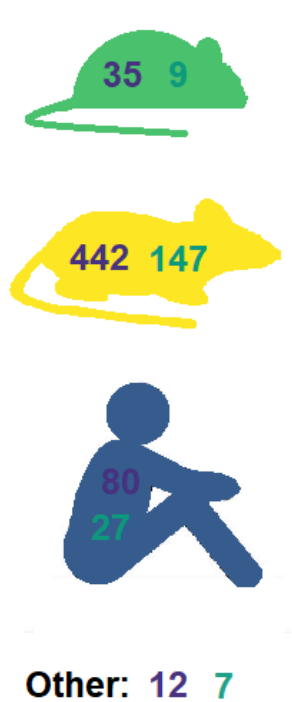
By detection medium

Figure 5 (right). Count of studies and test substances with CvT results in different media (for any species, but represented on a human body).



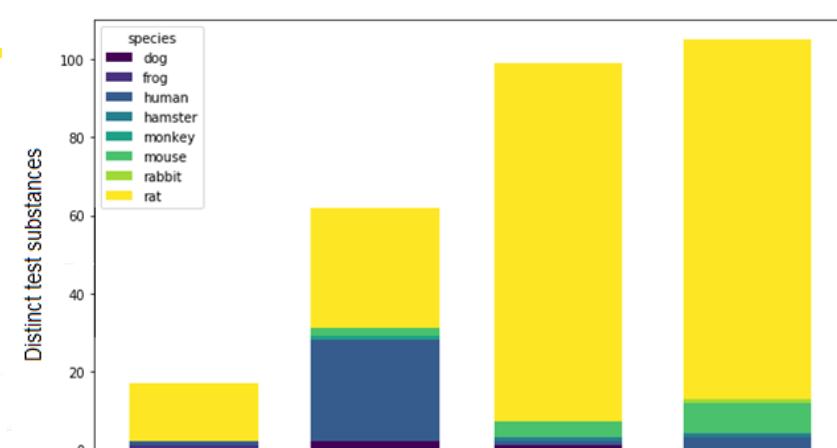
By species

Figure 6 (below). Count of studies and test substances by species type.



By route

Figure 7 (below). Count of distinct test substances per route, color-coded by species type



4. Data quality

Measurement error in chemical quantification: Recovery amounts vary based on method and method execution

Capture error due to graphical presentation: Some figures were blurry. Some concentration points were below the datum, which implies a printing error

Chemical identification validity: Chemicals in unstructured data were usually only identified by their name in the source documents. This leaves some room for ambiguity (Richard & Williams, 2002). Published names were mapped to unique substances (designated by DSSTox substance ID) through expert curation

Intra- and inter-curator extraction variability: Variability was measured using the fractional difference ($\frac{AUC_{1,curator} - AUC_{2,curator}}{AUC_{1,curator}}$) between results collected at different times by the same curator, and between results from different curators. The fractional difference in AUCs from 13 tested documents was 0.06% for intra-curator, and 0.44% for inter-curator.

Random error due to uncontrollable experimental factors: One document described several trials of the same experiment to serve as controls for different treatment groups. The fractional difference across these trials was 5%.

5. Usage examples

Comparison of compound distribution in various species and media at different doses

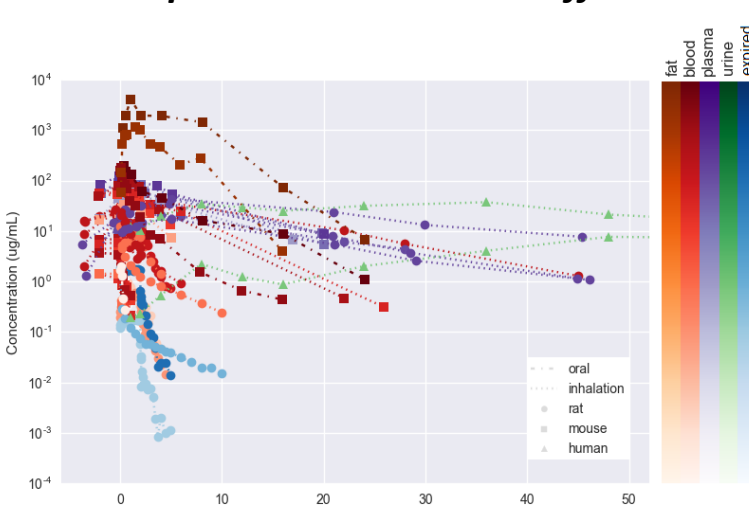


Figure 7. Comparison of all series results for a single test substance from the database.

Evaluation & calibration of pharmacokinetic (PBPK) model results

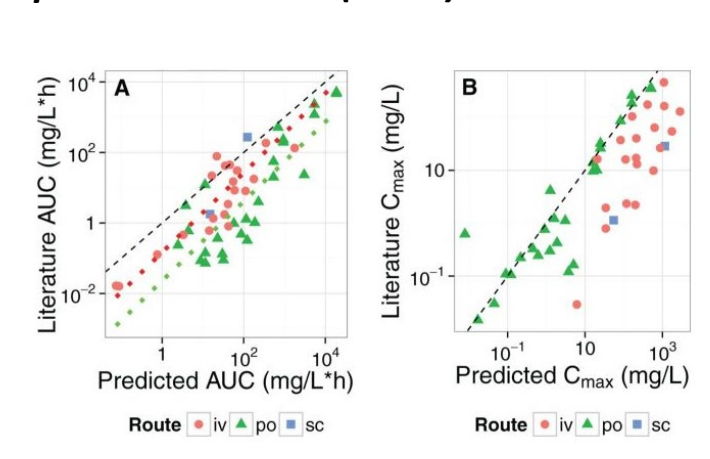


Figure 8 (from Wambaugh et al. 2015). See an example of this usage at "Development of a Generalized Inhalation Model for Use with the High-Throughput Toxicokinetics (*httk*) Package in R", poster P167 in session Computational Toxicology II.

Other ideas:

- Compare ADME of different compounds, and investigate relationship to chemical structure (QSAR)
- Pharmacokinetic study meta-analyses
- Calculation of other pharmacokinetic parameters

6. Acknowledgements

The authors would like to acknowledge the many scientists who generated the original *in vivo* data.

!) Bell, S.M. et al. In vitro to in vivo extrapolation for high throughput prioritization and decision making. *Toxicol In Vitro*. 2018 Mar;47:213-227. 2) Ng, L.J. et al. Incorporation of acute dynamic ventilation changes into a standardized physiologically based pharmacokinetic model. *Inhal Toxicol*. 2007 Mar;19(3):247-63. 3) Richard, A.M. & Williams, C.R. Distributed structure-searchable toxicity (DSSTox) public database network: a proposal. *Mutat Res*. 2002 Jan 29;499(1):27-52. 4) Rohatgi, A. WebPlotDigitizer, Version 4.1 <https://automeris.io/WebPlotDigitizer> 5) Wambaugh, J.F. et al. Evaluating In Vitro-In Vivo Extrapolation of Toxicokinetics. *Toxicol Sci*. 2018 May 1;163(1):152-169. doi: 10.1093/toxsci/kfy020. 6) Wambaugh, J.F. et al. Toxicokinetic Triage for Environmental Chemicals. *Toxicol Sci*. 2015 Sep;147(1):55-67. doi: 10.1093/toxsci/kfv118.

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This poster does not necessarily reflect U.S. EPA policy.