Collection, Curation, and Quantitative Structure-Use Relationship (QSUR) Modeling of Flame Retardants and Organohalogenated Flame Retardants for Class-based Assessments

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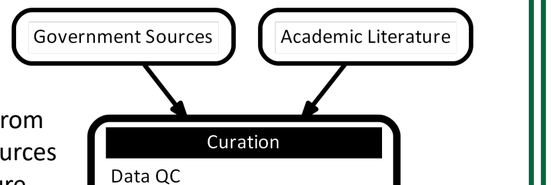
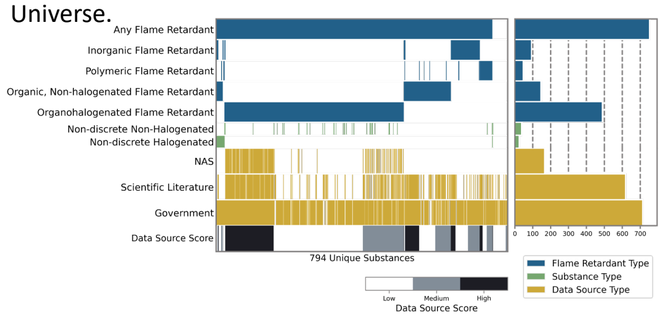
Key Points

- We have compiled a repository of possible flame-retardant substances, including legacy and current substances, from freely available sources.
- We have performed manual curation to organize these substances into types of flame retardants (organohalogenated, polymeric, non-halogenated, inorganic).
- We have constructed built-for-purpose quantitative structure-use relationship (QSUR) models to predict if new compounds could be flame retardants and organohalogenated flame retardants.
- QSUR models afford quicker screening of compounds when information on use is not publicly available.

Data Collection

Lists of chemical flame retardants were collected from worldwide, government sources as well as academic literature sources (using both keyword and forward search strategies). After curation and addition to EPA's Distributed Structure-Searchable Toxicity Database (DSSTox), substances were manually reviewed by a panel of curators for flame-retardant annotations including: organohalogenated, polymeric, inorganic, non-halogenated, and/or ionic. We refer to this curated dataset as the FR Universe.

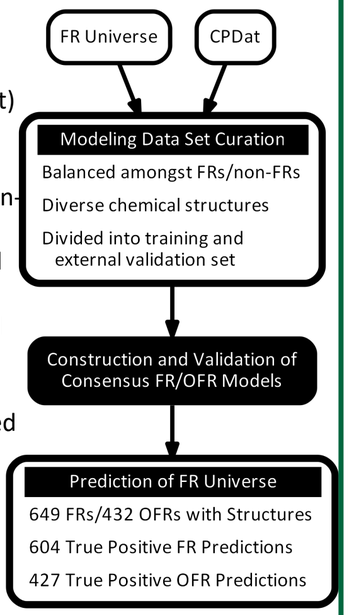




Landscape of FR annotations and distribution across various data sources. Non-discrete substance types indicate anion/cations or chemical mixures.

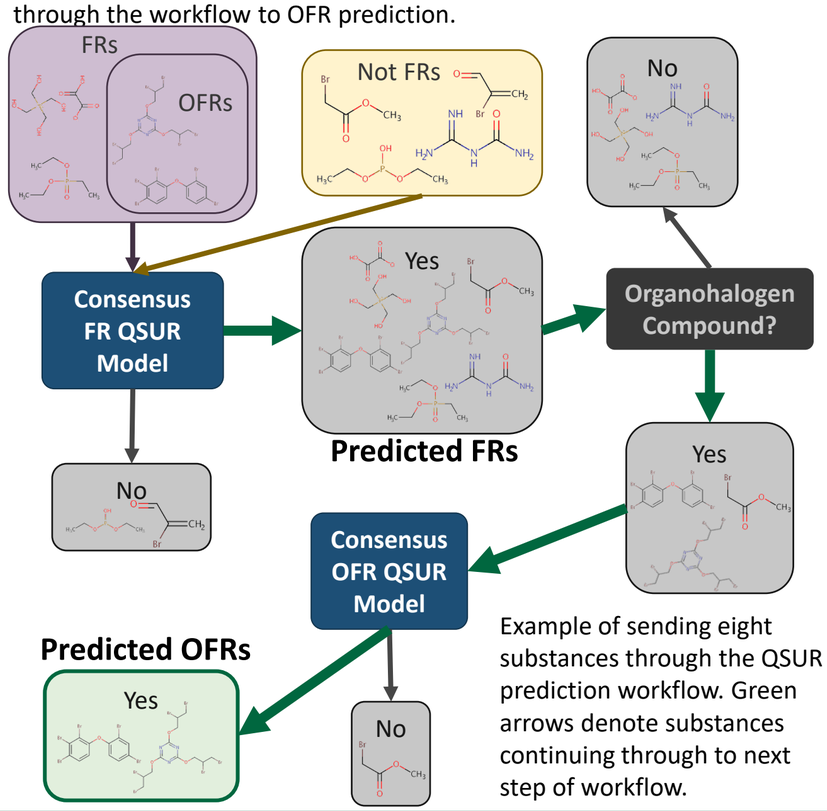
Developing QSUR Models

A subset of chemicals in the FR Universe and EPA's Chemical and Products Database (CPDat) were used to develop a balanced, chemically diverse dataset used to construct QSURs for both flame retardants (FR) and organohalogenated flame retardants (OFR). The Kennard-Stone algorithm was used to ensure chemical diversity, and artificial neural networks, random forest, support vector machines, and logistic regression algorithms were used to construct the consensus QSUR models. The entirety of the FR Universe was then predicted with the validated QSUR models.



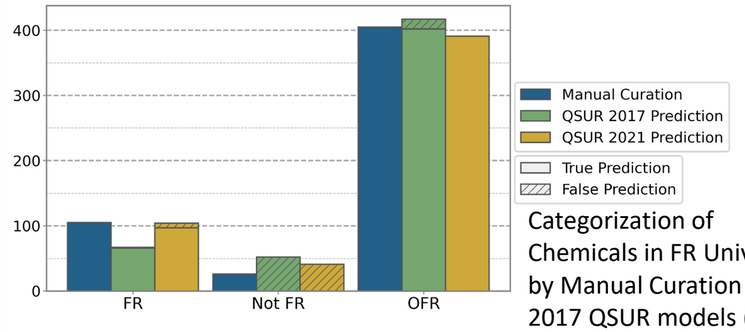
QSUR Prediction Workflow

Chemical compound structures are fed into the workflow and then predicted to be FRs. Substances predicted FRs continue through the workflow to OFR prediction.



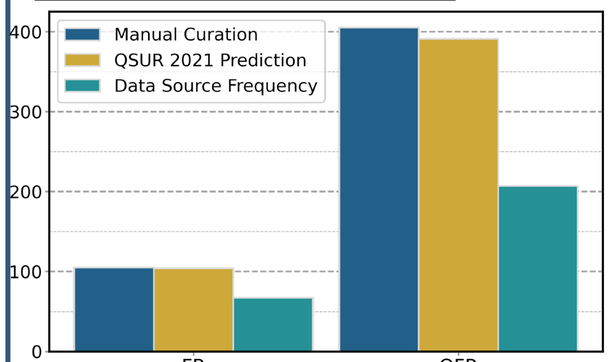
Example of sending eight substances through the QSUR prediction workflow. Green arrows denote substances continuing through to next step of workflow.

Comparison with Previous QSURs



Categorization of Chemicals in FR Universe by Manual Curation (blue), 2017 QSUR models (green) and refined QSUR models (yellow). Solid colors show correct predictions, while hatched colors show false predictions. Addition of the OFR QSUR model improved the number of correct predictions and reduced number of incorrect predictions of organohalogen flame retardants over previous models.

Prediction of FR Universe



Often the only tool readily available to assessors to determine if a chemical should have a given use is to look at the frequency of a use's occurrence in literature sources. Here, the frequency of a chemical occurrence in sources as a flame retardant are compared to its probability of being a flame retardant. Low occurrence (occurrence in only 1 data source) were removed; presence of a carbon-halogen bond was used distinguish between FRs and OFRs for substances with medium and high occurrence. Use of QSURs would identify more of the actual FRs than just choosing substances with a high data source score.

Conclusions

While present and historical use of flame retardants in commerce have presented a challenge for chemical assessors to catalogue, we have developed a dataset of substances that represents publicly available chemicals that can be linked to flame retardancy and have been curated by a panel of experts.

We have further developed QSUR models that predict this property for compounds that are not in the FR Universe to determine those substances that potentially could serve a functional role as a flame retardant.

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