ORGANOHALOGEN FLAME RETARDANTS AND CHEMICAL CLASSES: NATIONAL ACADEMY OF SCIENCES REPORT

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This presentation reflects my opinion and perspective as a committee member.

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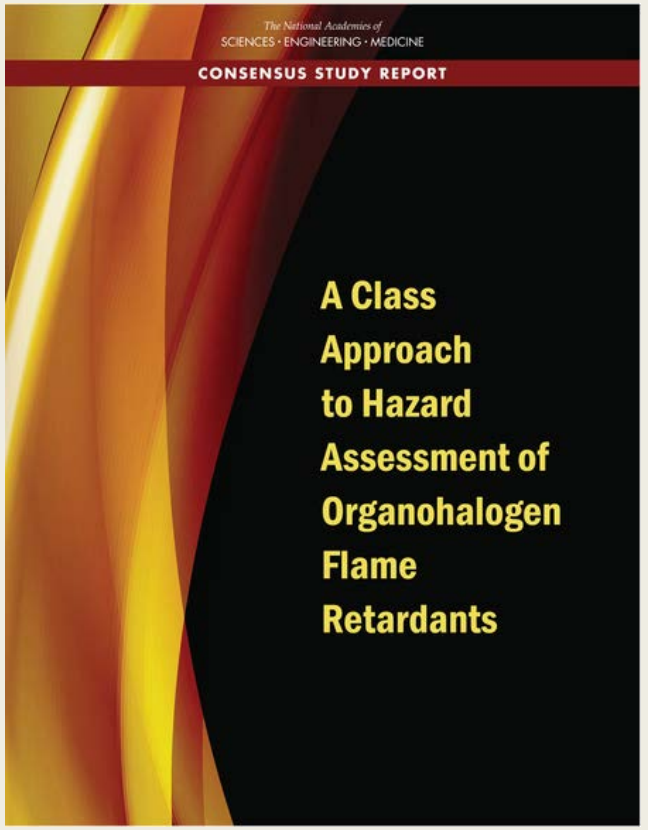
A Class Approach to Hazard Assessment of Organohalogen Flame Retardants

- Released in June 2019
- Committee formed at the request of the Consumer Product Safety Commission (CPSC)
- Triggered by an NGO petition from the Green Science Policy Institute, American Academy of Pediatrics, International Association of Fire Fighters, Learning Disabilities Association, Consumers Union, Worksafe, and others.



Statement of Task

- Survey available data for organohalogen flame retardants (OFRs) and identify data needs.
- Identify at least one approach for scientifically assessing OFRs as a class for hazard assessment.
- Provide a plan on how to most efficiently and effectively conduct research needed to evaluate OFRs.

"CPSC needs the hazard assessment plan…when executed, to be readily integrated with a separate quantitative exposure assessment to complete a human health risk assessment."

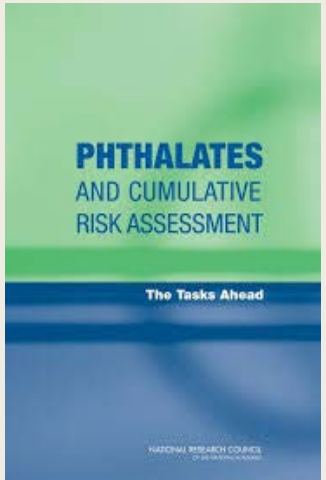
Committee Findings

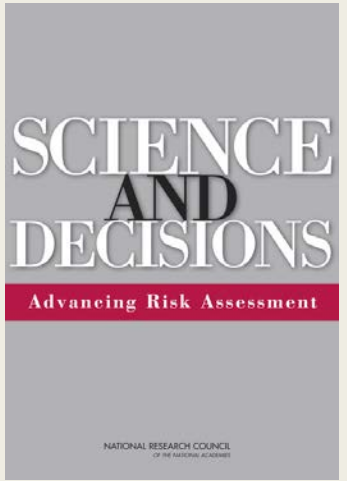
Chemical-by-chemical risk assessment has three main problems:

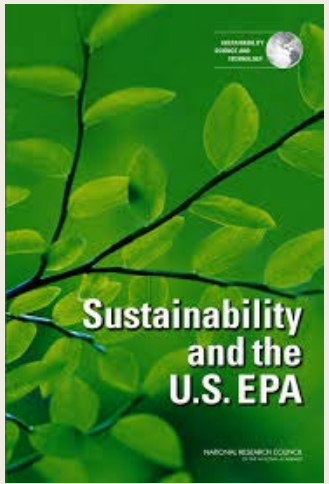
1. Chemicals on which data are insufficient are often deemed not hazardous.
2. Untested chemicals are often substituted for known hazardous chemicals.
3. Cumulative exposure and risk are often ignored.

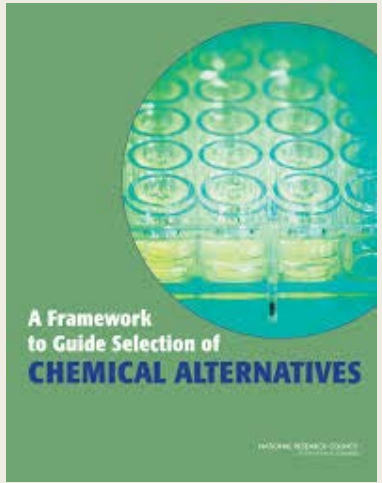
“Ultimately, the sheer number of chemicals in use today demands a new approach to risk assessment.”

The report emphasizes that these findings are consistent with multiple prior NAS reports:









A Class Approach

*"The committee concluded that a science-based class approach does not necessarily require one to evaluate a large chemical group as a single entity for hazard assessment…**an approach that divides a large group into smaller units (or subclasses) to conduct the hazard assessment is still a class approach for purposes of hazard or risk assessment."***

Report p. 8

Recognition of Biomonitoring California

“California’s Environmental Contaminant Biomonitoring Program developed a process for defining chemical classes that combined structure and functional use (Krowech et al. 2016). That approach was adopted by the California Safer Consumer Products Program (DTSC 2013)….

The biomonitoring hazard identification resulted in the adoption of both classes as candidate chemicals for potential regulation in consumer products. The two class identifications, however, have not been used to conduct risk assessments.”

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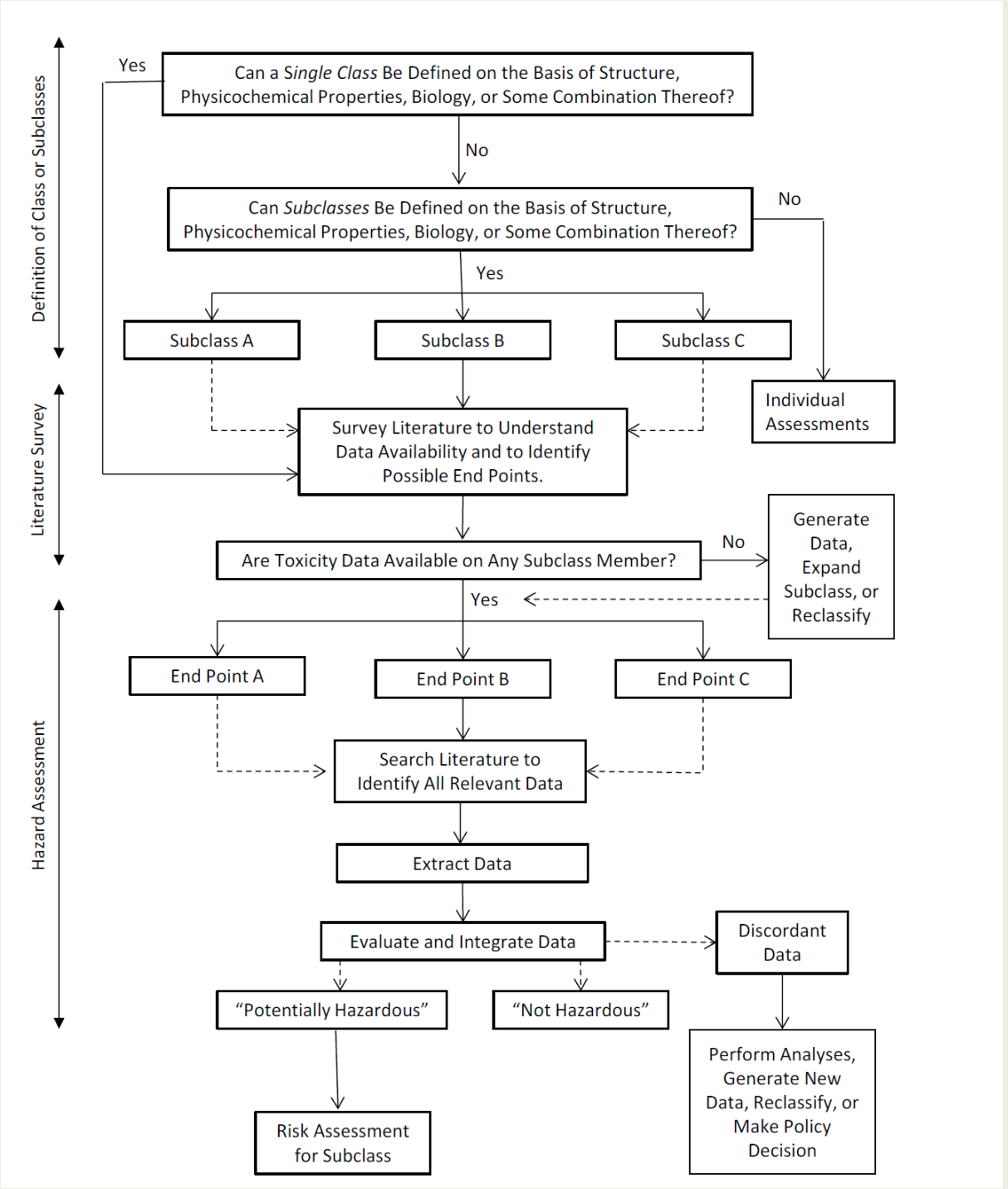
Approach to Defining a Chemical Class



Determine Viability of Class Approach

1. Identify and characterize a “seed” set of chemicals as a working inventory of the class.
2. Generate an “expanded” set of chemical analogues of the seed set based on structural similarities.
3. Evaluate the similarity of the seed set to the analogues to evaluate whether the OFRs are distinguishable as a single class.
4. If needed, define subclasses for hazard evaluation.

What Chemicals are OFRs?

- Developed “seed” set chemical list.
- Searched 7 data sources and identified 161 OFRs.
- Several duplicates and four mixtures were not included in the curated inventory of 148 unique chemical structures.
- List is published at www.nap.edu/25412

Data Sources: Eastmond (2015), the Environmental Protection Agency of Denmark (Danish EPA 2016), the Environment Agency of the United Kingdom (2003), the International Programme on Chemical Safety (IPCS 1997), the European Food Safety Authority (EFSA 2010, 2011a,b,c, 2012a,b), the Consumer Product Safety Commission (TERA 2016), and the US Environmental Protection Agency (EPA 2015).

Trying to Define a Class

1. Using Tanimoto Similarity Index, identified 1,073 similar analogues.
2. Evaluated the similarity of the seed set to the analogues using a principal components analysis (PCA) of physicochemical properties and ToxPrint Chemotype Enrichment.

"The analyses show that many existing organohalogen chemicals… share properties with the known OFRs and might have the potential of being used for the same purpose. Thus, the seed list of OFR chemicals can be separated only on the basis of use category and cannot be considered to be a scientifically defined class by itself on the basis of the structural features or on chemical properties."

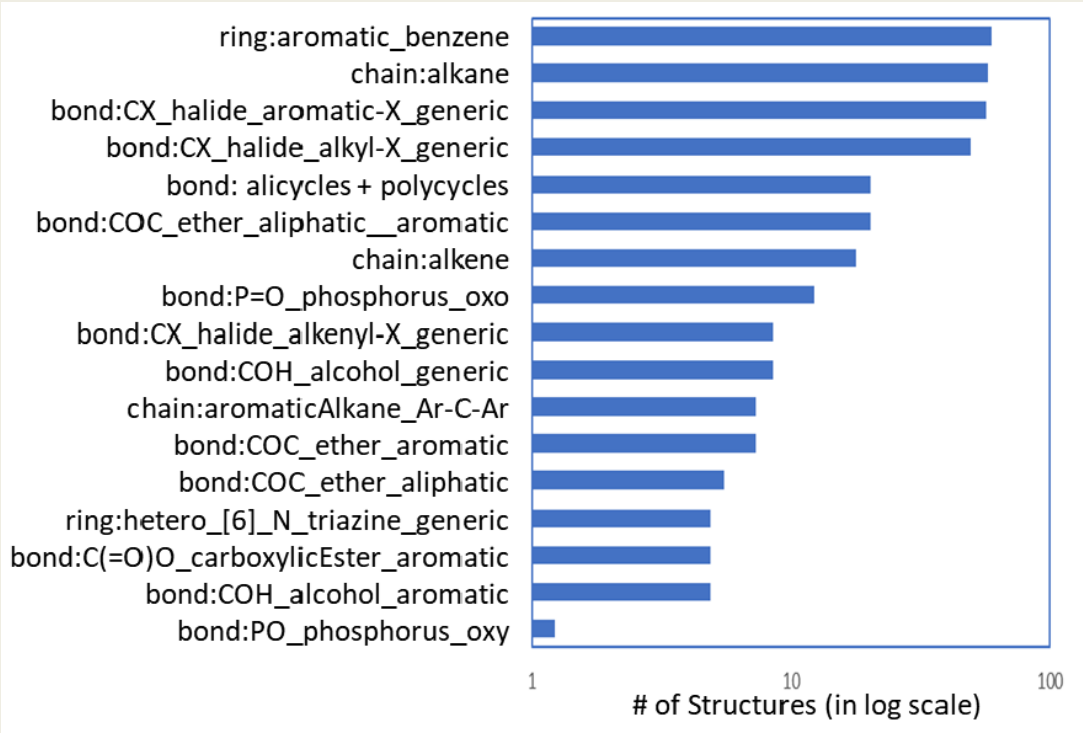
Strategy for Defining Sub-Classes

"The Committee….concluded that the best approach is to define subclasses as broadly as is feasible for the analysis; ***defining subclasses too narrowly could defeat the purpose of a class approach to hazard assessment****."*

Report p. 2

Define Sub-Classes

- Grouped the OFR inventory on the basis of predicted biologic activity (such as GABA receptors, aromatase activity, and ER/AR modulators); 8 biology-informed categories identified.
- Merged structural and biological information.
- 14 biological/structural subclasses, containing 4-22 members.
- Some chemicals in more than one class.



Major top-level chemotypes present in the OFR seed set

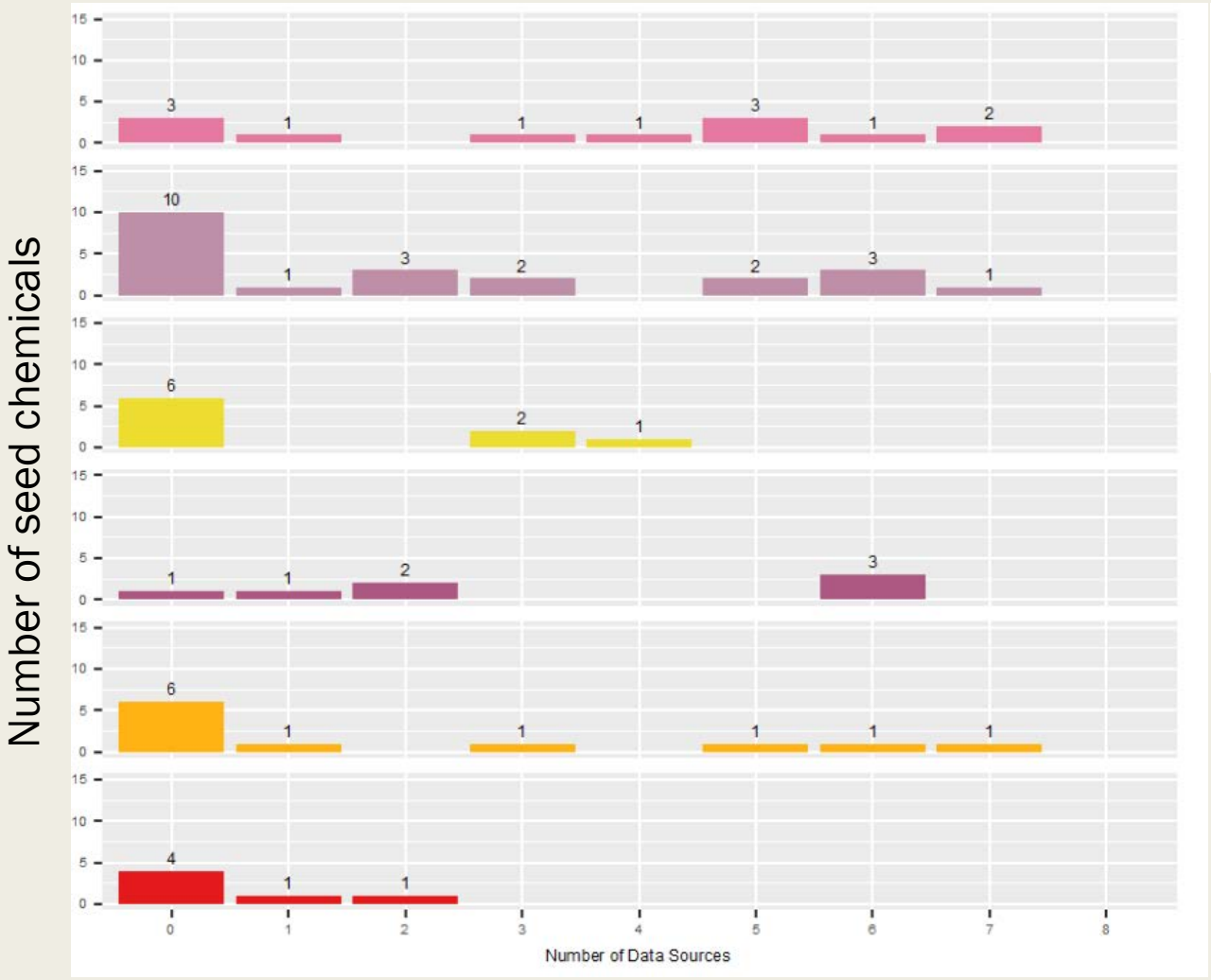
14 Organohalogen Flame Retardant Sub-Classes

TABLE 3-2 OFR Subclasses Formulated by Using Chemotypes and Predicted Biologic Activity

OFR Subclass	No. Chemicals in Subclass[a]
Polyhalogenated alicycles	17
Polyhalogenated aliphatic carboxylate	4
Polyhalogenated aliphatic chains	12
Polyhalogenated benzene alicycles	4
Polyhalogenated benzene aliphatics and functionalized	19
Polyhalogenated benzenes	19
Polyhalogenated bisphenol aliphatics and functionalized	11
Polyhalogenated carbocycles	15
Polyhalogenated diphenyl ethers	12
Polyhalogenated organophosphates (OPs)	22
Polyhalogenated phenol derivatives	7
Polyhalogenated phenol–aliphatic ether	9
Polyhalogenated phthalates/benzoates/imides	11
Polyhalogenated triazines	6

[a]Seven chemicals were categorized by using two chemotypes and included in two subclasses. This analysis was performed by using the chemicals in the OFR inventory.

Step 5: Survey Available Data

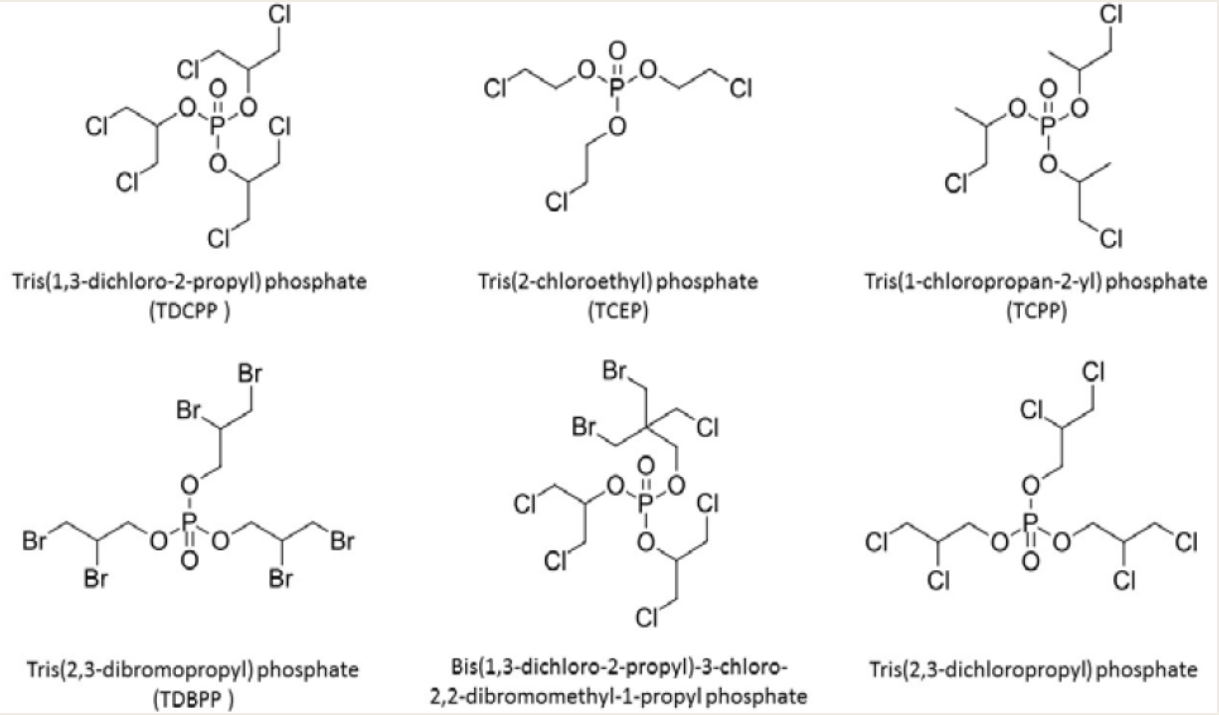


Data Sources:

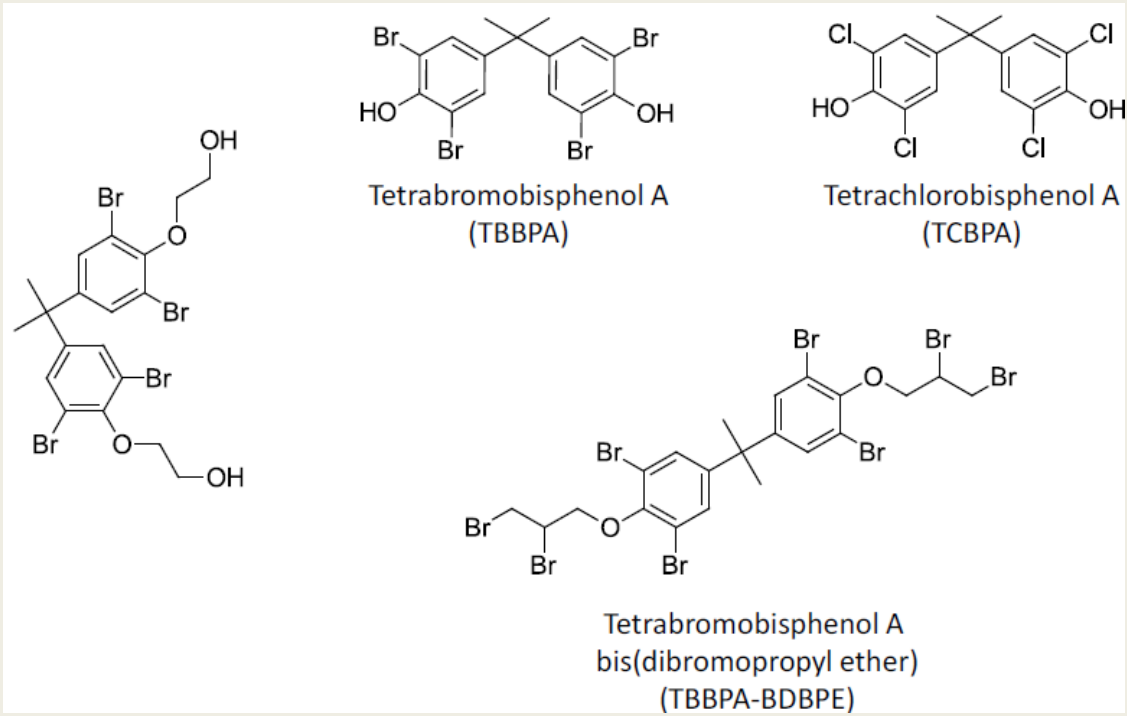
1. Comparative Toxicogenomics Database (CTD)
2. EPA Chemical Dashboard
3. Hazardous Substances Data Bank (HSDB)
4. Integrated Risk Information System (IRIS)
5. ToxCast/Tox21
6. Toxicity Reference Database (ToxRefDB)
7. PubChem
8. ChEMBL

Two Case Studies

Polyhalogenated organophosphates (OPs)



Polyhalogenated bisphenol aliphatics



Case Studies

- Performed literature search and data extraction, including traditional toxicology, Zebrafish data; ToxCast/Tox21 data.
- Focused on developmental toxicity and thyroid homeostasis.
- Evaluated and integrated data.
- Result: “The available data are too heterogeneous or inconsistent on biologic activity.”
- Conclusion: **Discordant data**.

What to Do if Discordant?

- Option 1: Make a policy decision, for example, to extend the most conservative conclusion regarding hazard to the subclass.
- Option 2: Reclassify members to improve their biologic similarity; generate data to increase confidence that reclassification has resulted in biologically similar members.
- Option 3: Perform analyses to explain the discordance and allow the assessment to move forward.
- Option 4: Generate new data that could increase clarity and the scientific basis for a decision.

Other Possible Scenarios

- No data on any member of the subclass. Three options:
  1. Generate data
  2. Broaden the subclass
  3. Reclassify.
- Data on 1-2 chemicals; no data on the rest. Three options:
  1. Science-based policy decision to treat them all like the ones with data
  2. Extrapolate/interpolate
  3. Generate some data.

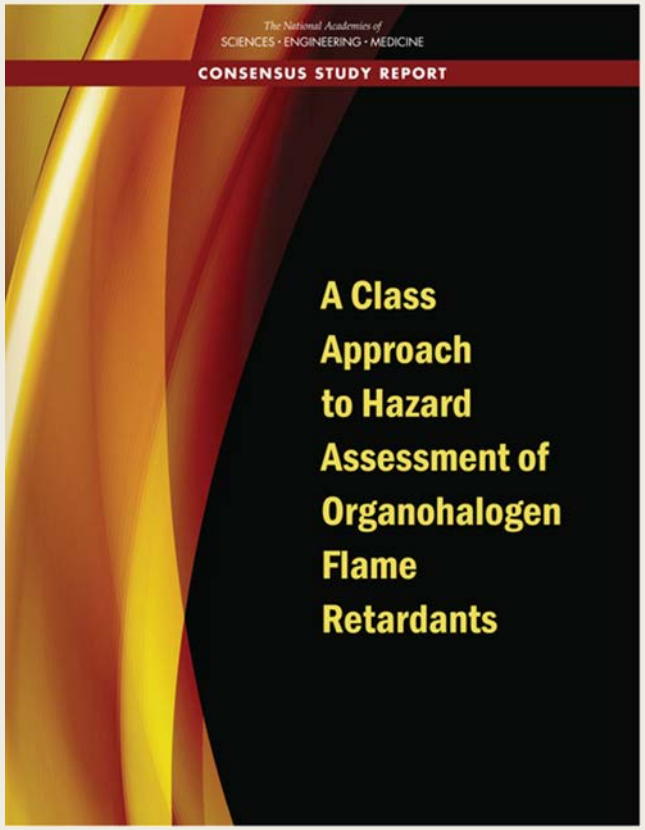
Other Possible Scenarios

- Data-rich subclass; data are concordant (example: PBDEs)
  - *“The present committee concludes that because the data are concordant for the well-studied members of the subclass, a designation of “potentially hazardous” can be applied to the entire subclass.”*

Conclusions

1. A class approach to chemicals is scientifically justifiable in all decision contexts, but the approach to forming classes may differ.
2. In a risk assessment context, classes should be based on a combination of chemistry and predicted biology.
3. If the available data are relatively concordant, it is scientifically justifiable to extrapolate to class members that do not have data.
4. Predictive toxicology can be useful for establishing classes and supporting extrapolations across classes.
5. Discordant data within classes is a challenge that will require additional investigation.

Thank you!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