Overview of Review Conducted by SAB PFAS Review Panel

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SAB PFAS Review Panel Chair

Presentation for Chartered SAB Meeting
July 20, 2022

PFAS Review Panel

Weihsueh Chiu*, Chair	College Station	TX	Texas A&M University
Sandeep Burman	St. Paul	MN	Minnesota Department of Health
Aimin Chen*	Philadelphia	PA	University of Pennsylvania
Deborah Cory-Slechta	Rochester	NY	University of Rochester
Jamie C. DeWitt	Greenville	NC	East Carolina University
Jeffrey Fisher	Durham	NC	ScitoVation
James K. Hammitt	Boston	MA	Harvard University
Lisa Kamendulis	Bloomington	IN	Indiana University
David Keiser*	Amherst	MA	University of Massachusetts Amherst
Loren Lipworth	Nashville	TN	Vanderbilt University Medical Center
Lala Ma*	Lexington	KY	University of Kentucky
Sheila Olmstead*	Austin,	TX	The University of Texas at Austin
Gloria Post*	Trenton	NJ	New Jersey Department of Environmental Protection
Kristi Pullen-Fedinick*	Washingon	DC	Natural Resources Defense Council
David A. Savitz	Providence	RI	Brown University
Angela L. Slitt	Kingston	RI	University of Rhode Island

*Chartered SAB Members

PFAS Review Panel Public Meetings

- December 16, 2021 – Introduction and discussion of charge questions
- January 4, 6, 7, 2022 – Deliberation on charge questions
- May 3, 2022 – Discuss and finalize draft report

- Oral and written public comments considered throughout

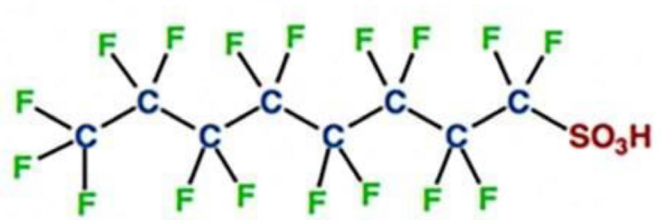
Documents Reviewed

Four documents prepared as part of proposed rulemaking process for per- and polyfluoroalkyl substances:

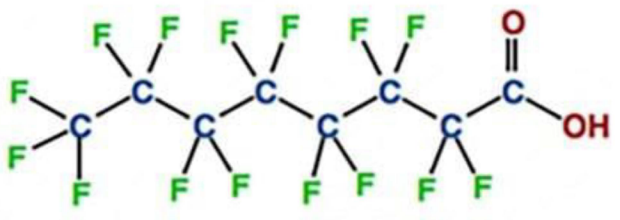
- **Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal (MCLG) for Perfluorooctanoic Acid (PFOA) in Drinking Water**
- **Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal (MCLG) for Perfluorooctanesulfonic Acid (PFOS) in Drinking Water**
- Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of per- and polyfluoroalkyl substances (PFAS)
- Analysis of Cardiovascular Disease Risk Reduction as a Result of Reduced PFOA and PFOS Exposure in Drinking Water

Purpose and Scope of the Proposed Approaches Drafts

- Purpose: Support development of the Maximum Contaminant Level Goals for the PFAS National Primary Drinking Water Regulation (NPDWR)
- Scope:
  - Synthesis of the available toxicological and epidemiological health effects information after exposure to PFOA and PFOS
  - Derive inputs – toxicity values and relative source contribution - needed to support maximum contaminant level goal (MCLG) development
  - These documents do not include derivation of the MCLGs.



PFOS - perfluorooctanesulfonic acid



PFOA - perfluorooctanoic acid

Selected Key Recommendations for MCLG documents for PFOA and PFOS

1. Study Identification and Inclusion
   - More transparency and completeness
   - Studies included in 2016 should be included more completely

2. Non-cancer Hazard Identification
   - Separate hazard and dose-response assessment processes, using a consistent framework for evidence synthesis and integration
   - Focus on endpoints with strongest evidence: liver, immune, serum lipids, fetal growth
   - ALT should be used as an endpoint given clinical and epidemiologic literature as a marker for adverse liver effects

Selected Key Recommendations for MCLG documents for PFOA and PFOS

3. Cancer Hazard Identification and Slope Factor
   - While agreeing with “likely” designation for PFOA, more structured and transparent “weight of evidence” discussion needed for both PFOA and PFOS
   - Multiple candidate cancer slope factors should be developed
   - Additional details and transparency needed for all quantitative modeling

4. Toxicokinetic Modeling
   - More details as to model code, parameters, etc. needed.
   - Reconsider choice of Verner et al. model, and consider whether Goeden et al. model is more appropriate for supporting MCLG development

Selected Key Recommendations for MCLG documents for PFOA and PFOS

5. RfD Derivation
   - Consider multiple human and animal studies for a variety of endpoints/populations in deriving RfD
   - Consider expressing RfD in water concentration equivalents to better account for life-stage-specific differences in ingestion rates and toxicokinetics
   - Stronger and more transparent justification of benchmark responses needed
   - Consider adoption of a probabilistic framework to calculate risk-specific doses
   - Clearly state RfDs apply to both short-term and chronic exposure

6. Relative Source Contribution
   - Supports selection of RSC of 20%, but rationale needs to be better described

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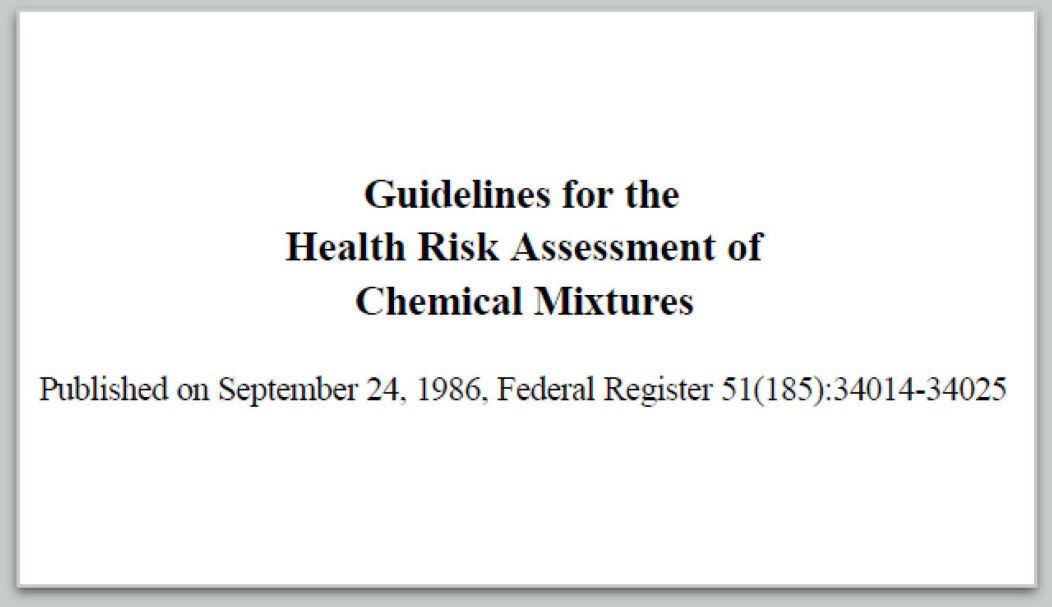
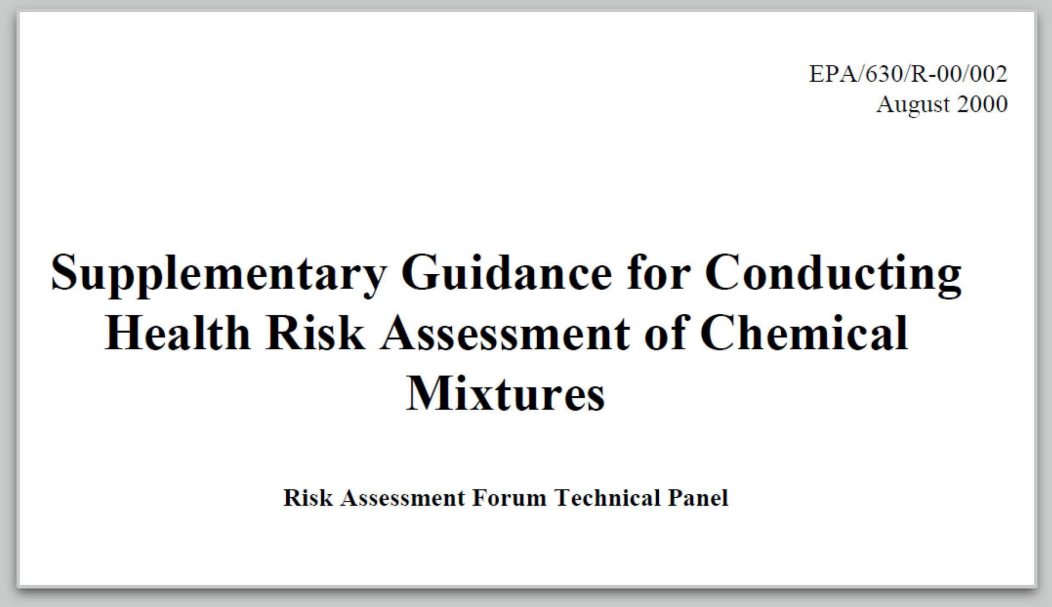
- **Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of per- and polyfluoroalkyl substances (PFAS)**
- Analysis of Cardiovascular Disease Risk Reduction as a Result of Reduced PFOA and PFOS Exposure in Drinking Water

Key Aspects of the Framework

- Purpose: Provide a data-driven framework for estimating human health risks associated with oral exposures to mixtures of PFAS, consistent with existing EPA guidance.
- Based on common health outcomes/endpoints among PFAS.
- Assumes dose additivity for chemicals with common health outcomes.
- Relies on EPA component-based mixture assessment methods:
  - **Hazard Index,**
  - **Relative Potency Factors,** and
  - **Mixture Benchmark Dose** approach.





Selected Key Recommendations for Mixtures Document

1. Dose Additivity Assumption
   - Supports dose additivity based on common outcome, but need clearer presentation of uncertainties and information supporting this approach

2. – 4. Hazard Index Approach, Relative Potency Factor, Mixture BMD
   - Consider replacing the “tiered approach” with a “menu-based” framework that better supports fit-for-purpose selection of approaches
   - Clarification is needed as to similarities and differences among the different approaches, such as when they converge mathematically
   - Consider having the RPF and mixture BMD approaches being based on Human Equivalent Doses

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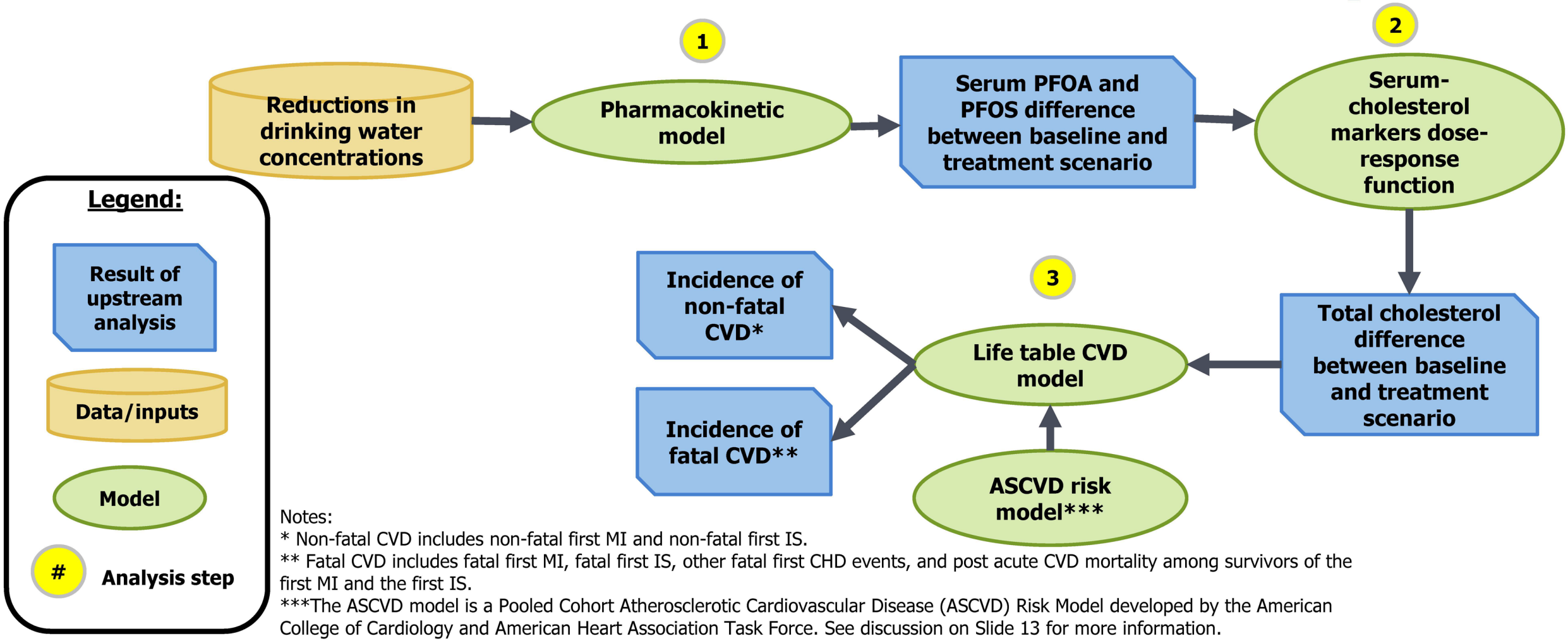
Overview of the CVD Risk Reduction Analysis



Notes:
* Non-fatal CVD includes non-fatal first MI and non-fatal first IS.
** Fatal CVD includes fatal first MI, fatal first IS, other fatal first CHD events, and post acute CVD mortality among survivors of the first MI and the first IS.
***The ASCVD model is a Pooled Cohort Atherosclerotic Cardiovascular Disease (ASCVD) Risk Model developed by the American College of Cardiology and American Heart Association Task Force. See discussion on Slide 13 for more information.

Selected Key Recommendations for Benefits from CVD Reduction

1. – 3. EPA's Meta-Analysis, Life Table Approach, and ASCVD model

- Recommendations from MCLG documents should be applied where applicable
- Supports overall approach, but concerned with apparent discrepancy with MCLG document's conclusion on CVD.
- More discussion needed as to rationale for this endpoint and consideration of other endpoints for risk reduction analysis

4. Uncertainties and Limitations

- Additional clarity needed as to application of EPA's analyses, including sensitivity analyses
- Additional discussion needed as to exclusion of HDLC, and evaluation as to whether its inclusion would influence results

Questions?