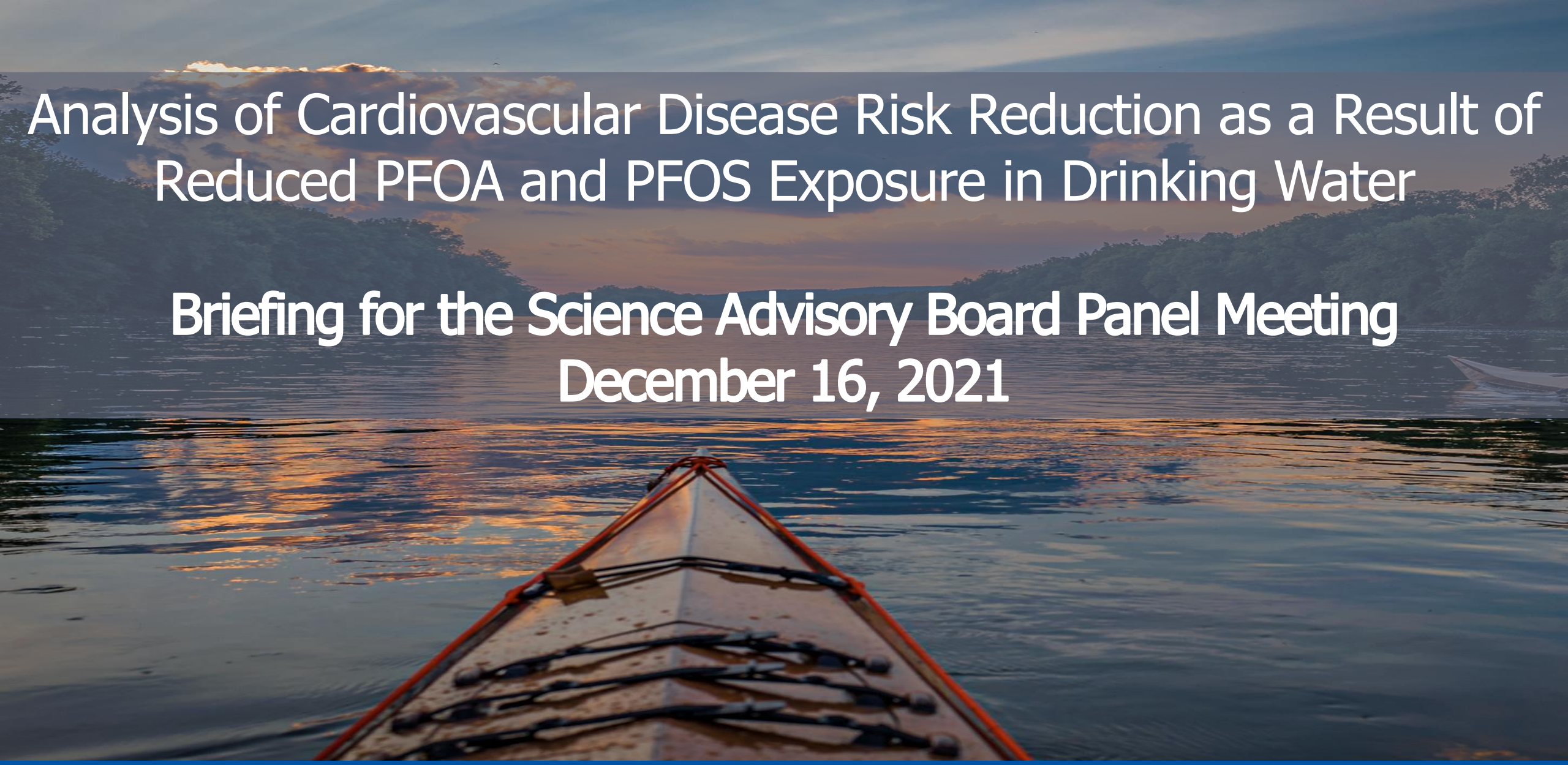


Analysis of Cardiovascular Disease Risk Reduction as a Result of Reduced PFOA and PFOS Exposure in Drinking Water

Briefing for the Science Advisory Board Panel Meeting
December 16, 2021

United States Environmental Protection Agency

Office of Water

Presentation Overview

- Background and Purpose
- Overview of the Cardiovascular Disease (CVD) Risk Reduction Analysis
- Baseline and Treatment Scenarios
- Estimation of Cholesterol Changes
- Estimation of Cardiovascular Disease (CVD) Risk Reductions
- Results
- Limitations and Uncertainty

Background and Purpose

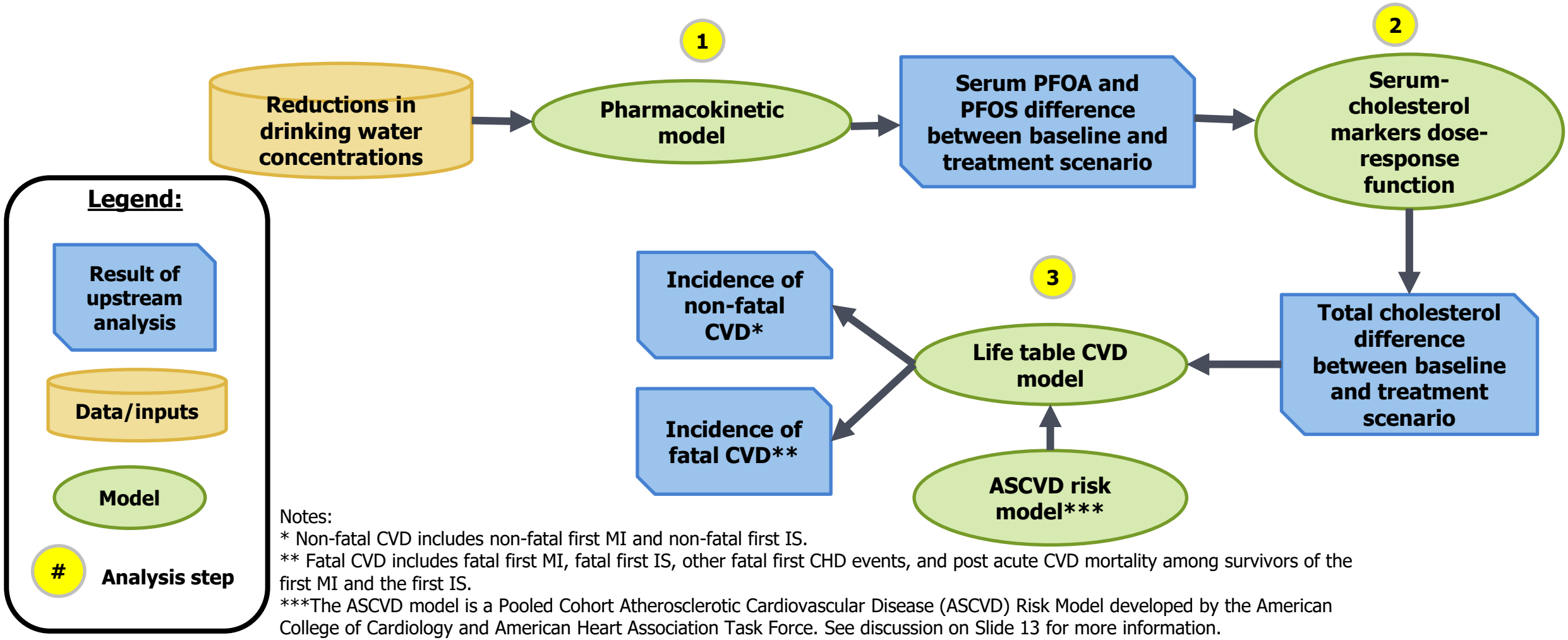
- Safe Drinking Water Act (SDWA) Section 1412(b)(3)(C) establishes requirements to develop a health risk reduction and cost analysis (HRRCA) that presents quantifiable and non-quantifiable benefits and costs likely to occur as a result of compliance with the NPDWR.

- EPA intends to use the methodology outlined in this document to quantify cardiovascular risk reduction benefits for the population served by all PWSs expected to take action to comply with a proposed PFAS NPDWR.
- Utilizing information from *Proposed Approaches to the Derivation of Draft Maximum Contaminant Level Goals for PFOA and PFOS in Drinking Water* and other sources, EPA expects to quantify additional adverse health effects associated with PFOA and PFOS.
- We are seeking SAB input on the CVD risk reduction analysis because of the complexity and novelty of this approach.

Background and Purpose

- In EPA's *Proposed Approaches to the Derivation of Draft Maximum Contaminant Level Goals for PFOA and PFOS in Drinking Water,* one of the adverse health effects identified was the effects of PFOA and PFOS on serum lipids, specifically total cholesterol (TC).
- This health effect has sufficient weight of evidence and available data to inform estimates of avoided adverse health outcomes.
    - Studies have found significant relationships between exposure to PFOA and PFOS and TC levels.
    - Increases in TC levels are linked to increases in CVD risk, especially for individuals over age 40.
- This document presents the avoided cases of CVD events (e.g. heart attack, stroke, death from coronary heart disease) for one hypothetical public water system (PWS) to illustrate the methodology EPA has developed.

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.

PFOA and PFOS Baseline Scenario

- EPA is actively developing estimates of PFOA and PFOS national occurrence that will be used to support the HRRCA for the proposed NPDWR. For purposes of this analysis for review by the SAB, EPA developed a hypothetical PWS to illustrate the methodology to be used in the national level analysis.
- Under the Unregulated Contaminant Monitoring Rule 3 (UCMR 3) among detections (1.37% of samples) the 90th percentile combined concentration for PFOA and PFOS was reported as 0.20 µg/L. [11]

Table 1: Characteristics of the Hypothetical PWS

Description	Value
PWS size category	Large
PWS primary source water type	Surface water
Population served	100,000
Average baseline PFOA concentration (µg/L)	0.10
Average baseline PFOS concentration (µg/L)	0.10

PFOA and PFOS Treatment Scenario

- As EPA actively develops the MCLGs and regulatory options for the proposed NPDWR, EPA is using a threshold of 0.07 µg/L for combined PFOA and PFOS as an illustrative example in this document. The example scenario will demonstrate the methodology that EPA intends to employ in the national CVD risk reduction analysis.
- EPA models a scenario where a system takes active steps to achieve PFOA and PFOS concentrations below the threshold.
- The target concentration is 80% of the illustrative threshold (e.g., **for a PFOA and PFOS threshold of 0.07 µg/L, the target is 0.056 µg/L**).
    - This assumption reflects a 20% operational safety margin, which systems have previously taken to ensure consistent compliance with new drinking water standards.

PFOA and PFOS Treatment Scenario

- At the hypothetical PWS, the reductions required to meet the target concentration are 0.072 µg/L for PFOA and 0.072 µg/L for PFOS.
- Given the assumed target of 80% of the illustrative threshold, EPA estimates that the concentrations at the hypothetical PWS are reduced from 0.1 µg/L of PFOA and 0.1 µg/L of PFOS to 0.028 µg/L of PFOA and 0.028 µg/L of PFOS.

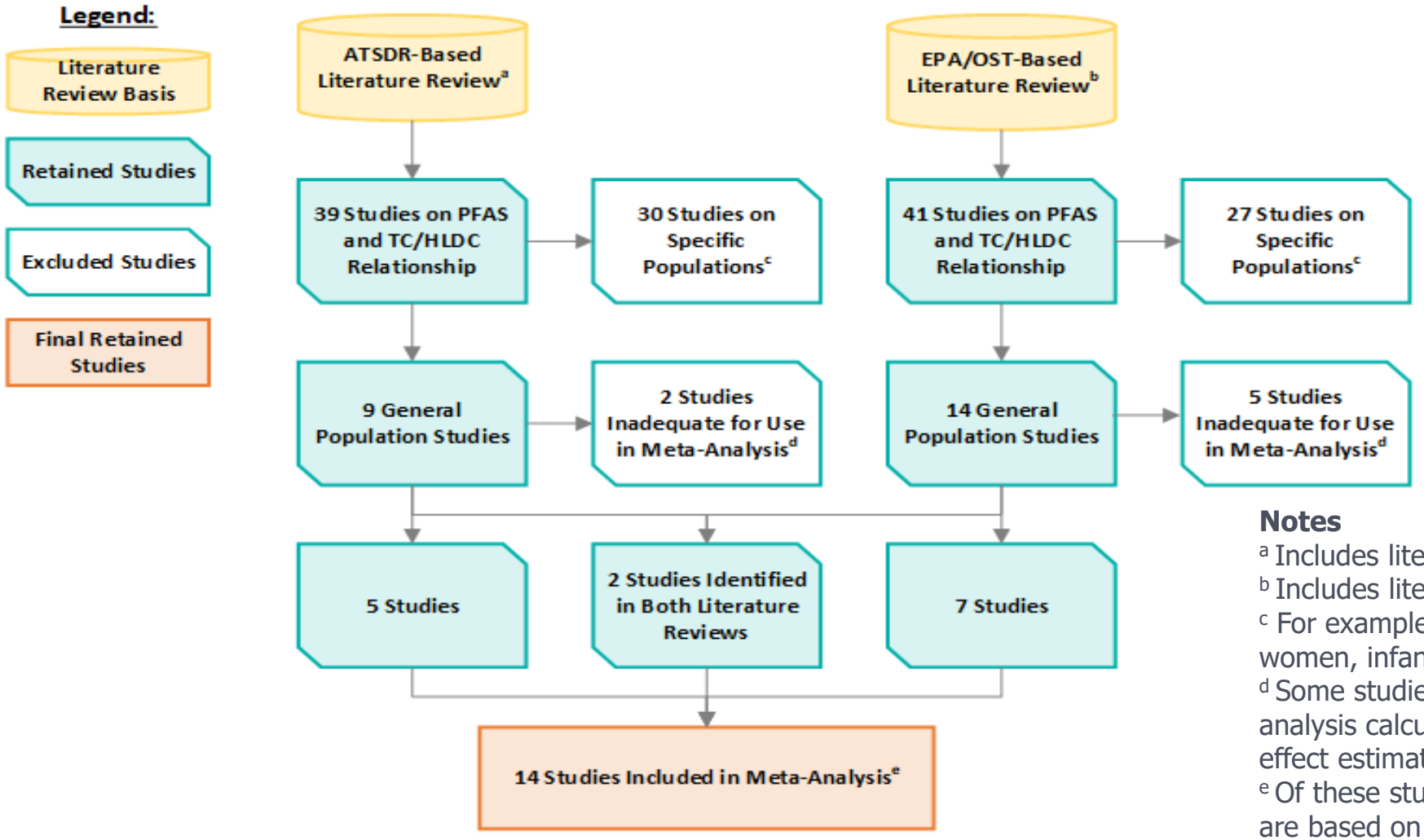
Estimation of Cholesterol Changes: Pharmacokinetic Model

- Baseline and treatment scenario PFOA and PFOS drinking water concentrations were used as inputs to EPA's Pharmacokinetic (PK) model for adult males and females to estimate serum concentrations.
- The PK model is detailed in the *Proposed Approaches for Deriving Maximum Contaminant Level Goals for PFOA and PFOS in Drinking Water* also under SAB review.
- In this analysis, EPA uses the PK model to evaluate the following exposure scenarios:
    - Baseline exposure: lifetime exposure to baseline PFOA/PFOS dose for cohorts of all ages at the start of the evaluation period in 2023 and cohorts born after 2023
    - Lifetime treatment exposure reduction scenario: lifetime exposure to treatment scenario PFOA/PFOS dose for cohorts born during or after 2026 (i.e., the year of full treatment scenario implementation)
    - Partial lifetime treatment exposure reduction scenario: exposure to baseline PFOA/PFOS dose until age A-1 year and treatment scenario PFOA/PFOS dose thereafter for cohorts ages A > 0 years in 2026

Estimation of Cholesterol Changes

- TC and high-density lipoprotein cholesterol (HDLC), among other factors, are predictors of CVD risk.
- EPA relied on two literature review efforts to identify potential sources of exposure-response information for the effect of PFAS on serum cholesterol, lipids, and lipoproteins:
    - A literature review built on the one conducted by the Agency for Toxic Substances and Disease Registry (ATSDR) in the development of their Toxicological Review Public Comment Draft, which included literature through mid-2017.
    - The most recent systematic review of the newly published epidemiological literature for PFAS performed by EPA's Office of Science and Technology (EPA/OST), which included literature from 2016 to 2020.

Estimation of Cholesterol Changes (2)



ATSDR= Agency for Toxic Substances and Disease Registry
OST= Office of Science and Technology

Notes

[a] Includes literature published through mid-2017.
[b] Includes literature published from 2016-2020.
[c] For example, studies based on occupational data, pregnant women, infants or children.
[d] Some studies did not include estimates required for meta-analysis calculations. For example, studies did not report effect estimates or interquartile ranges.
[e] Of these studies, 8 are based on data from the US and 6 are based on data from outside the US.

Estimation of Cholesterol Changes (3)

Results:

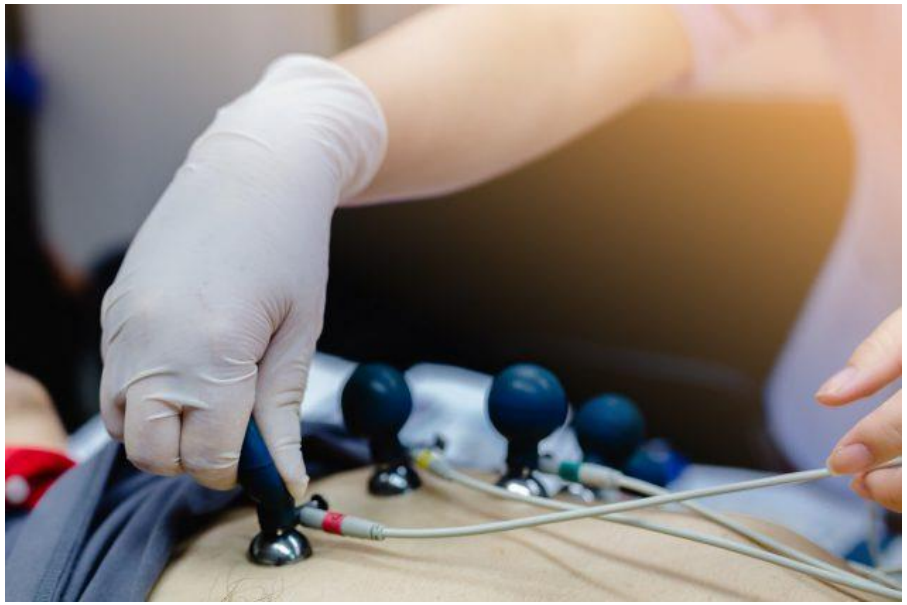
- Positive increase in TC of **1.57 (95% CI: 0.02, 3.13) mg/dL per ng/mL serum PFOA** (p-value=0.048).
- Positive increase in TC of **0.08 (95% CI: -0.01, 0.16) mg/dL per ng/mL serum PFOS** (p-value=0.064).
- While the association for PFOS and TC is not significant at the 0.05 confidence level, it is significant at the 0.10 confidence level. Furthermore, the literature provides sufficient support of a positive association.
- In both analyses EPA conducted that we are presenting to the SAB, EPA found insufficient evidence to consider HDLC in the analyses.
    - The associations observed in the meta-analysis for HDLC and serum PFOA or PFOS were positive but not statistically significant at the 0.05 confidence level (PFOA p-value=0.378; PFOS p-value=0.070).
    - EPA's systematic review of HDLC associations found inconsistent and weak evidence to support PFOA or PFOS effects on HDLC.
    - Therefore, EPA is not including effect estimates for the serum PFOA-HDLC and serum PFOS-HDLC associations in the CVD analysis.

Estimation of CVD Risk Reductions: ASCVD Risk Model

- The CVD event incidence estimates are generated by the Pooled Cohort Atherosclerotic Cardiovascular Disease (ASCVD) Risk Model.
  - Developed by an American College of Cardiology/American Heart Association Task Force charged with developing clinical practice guidelines for assessment of cardiovascular risk.
  - Four large longitudinal community-based epidemiologic cohort studies were combined to develop a geographically and racially diverse dataset used for the ASCVD model estimation.
  - The ASCVD risk model is commonly used in clinical practice to estimate CVD risk for those between ages 40 and 80.

Estimation of CVD Risk Reductions: ASCVD Risk Model

- The ASCVD model predicts the 10-year probability of a *hard CVD event*—fatal and non-fatal MI, fatal and non-fatal IS, or CHD death—to be experienced by a person without a prior history of CVD.
    - Predictors include age, TC and HDLC concentrations, systolic blood pressure, current smoking, diagnosed diabetes, and whether the participant is undergoing treatment for high blood pressure. The model was fit separately to four population subgroups: non-Hispanic White females, Black females, non-Hispanic White males, and Black males.



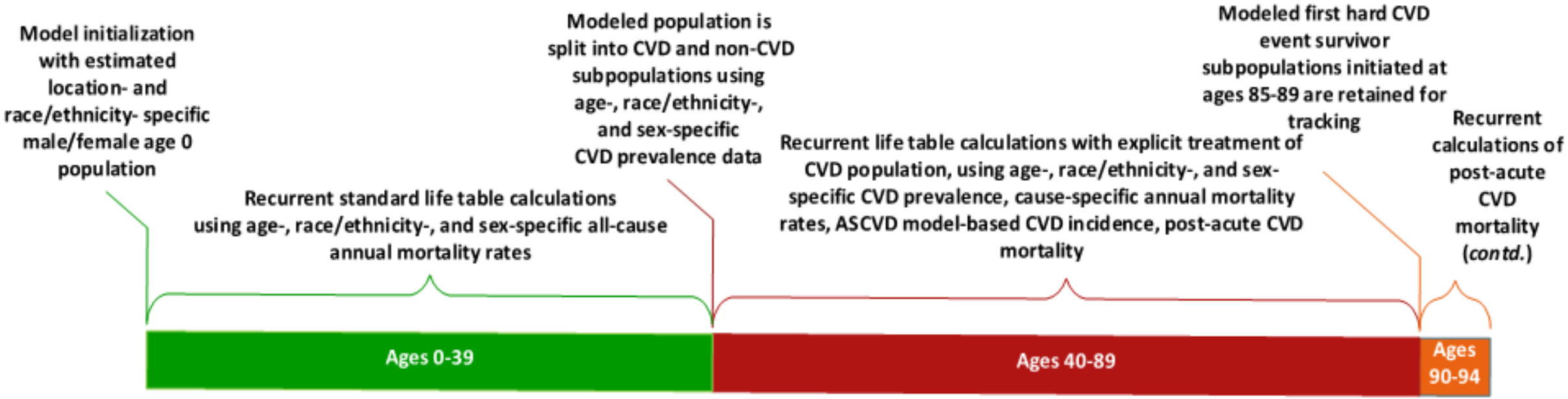
Estimation of CVD Risk Reductions: Life Table Calculations

- EPA uses a life-table approach to estimate CVD risk reductions. Life tables are a statistical tool used to analyze the mortality experience of a population over time. This modeling step uses recurrent life table calculations to estimate a PWS-specific time series of hard CVD event incidence for a population cohort characterized by sex, race/ethnicity, birth year, and age at the beginning of the PFOA/PFOS evaluation period (i.e., 2023), and age- and sex-specific TC level time series.
- To account for population survival over time, EPA uses a life table approach because
  - (1) changes in serum PFOA/PFOS in response to changes in drinking water PFOA/PFOS occur over multiple years,
  - (2) CVD risk, relying on the ASCVD model, can be modeled only for those older than age 40, and
  - (3) non-fatal CVD events have elevated mortality implications.

Estimation of CVD Risk Reductions: Life Table Calculations (2)

- The CVD model tracks PWS populations from 2023 to 2104
- EPA uses age-, sex-, race/ethnicity-, and county-specific population growth rates obtained from the extrapolated Woods & Poole, 2021 dataset to estimate population growth over the evaluation period.

Estimation of CVD Risk Reductions: Life Table Calculations (3)



Estimation of CVD Risk Reductions: Risk of Post-Acute CVD Mortality

- The CVD model evaluates post-acute CVD mortality among survivors of the initial MI/IS event under baseline and treatment scenarios using the baseline post-acute mortality rates that do not depend on TC levels.
- For survivors of the first hard CVD event at ages 40-65, EPA uses estimates of sex- and race/ethnicity-specific all-cause post-acute mortality for MI survivors at 1- and 5-year follow-up from Thom et al. (2001).
- For survivors of the first hard CVD event ages 66-89, EPA uses the results in S. Li et al. (2019) to estimate the number of post-acute deaths for survivors of the first MI and IS events age 66 or older within 6 years of the initial event.

Results

Treatment Scenario-Related Reductions in Serum PFOA/PFOS, Total Cholesterol at Hypothetical PWS serving 100,000 persons			
Decade	Average Reduction in Serum Concentration*		
	PFOA (ng/mL)	PFOS (ng/mL)	TC (mg/dL)
2023–2034	2.56	2.08	4.19
2035–2044	7.47	6.64	12.28
2045–2054	7.08	6.49	11.66
2055–2064	7.09	6.53	11.68
2065–2074	7.35	6.78	12.10
2075–2084	7.62	7.08	12.55
2085–2094	7.77	7.26	12.80
2095–2104	7.04	6.60	11.60
Total Evaluation Period	**6.64**	**6.08**	**10.94**

Note:
*Average reductions in concentration and cases are weighted by population within the cohort. Cohorts near the end of the evaluation period have smaller eligible (e.g., without prior CVD history) populations. Thus, the reported total evaluation period average values are not the average of the decade-specific values but are population-weighted averages for the entire cohort.
Abbreviations: CVD – cardiovascular disease, IS – ischemic stroke, MI – myocardial infarction, TC – total cholesterol

Results (2)

Treatment Scenario-Related Reductions in CVD Morbidity and Mortality at Hypothetical PWS serving 100,000 persons

Decade	Total Reduction in Cases				Average Annual Reduction in Cases*			
	Non-Fatal MI	Non-Fatal IS	Acute Premature CVD Deaths	Post-Acute Premature CVD Deaths	Non-Fatal MI	Non-Fatal IS	Acute Premature CVD Deaths	Post-Acute Premature CVD Deaths
2023–2034	16.81	26.10	2.40	6.30	1.40	2.17	0.20	0.53
2035–2044	40.33	62.46	6.05	22.25	4.03	6.25	0.61	2.23
2045–2054	34.97	53.44	5.10	19.08	3.50	5.34	0.51	1.91
2055–2064	31.50	47.81	4.39	15.70	3.15	4.78	0.44	1.57
2065–2074	28.37	42.22	3.59	11.82	2.84	4.22	0.36	1.18
2075–2084	27.32	40.11	3.24	9.93	2.73	4.01	0.32	0.99
2085–2094	27.53	40.59	3.30	10.42	2.75	4.06	0.33	1.04
2095–2104	25.56	38.01	3.11	9.92	2.56	3.80	0.31	0.99
Total Evaluation Period	**232.39**	**350.74**	**31.19**	**105.42**	**2.83**	**4.28**	**0.38**	**1.29**

Note:
*Average reductions in concentration and cases are weighted by population within the cohort. Cohorts near the end of the evaluation period have smaller eligible (e.g., without prior CVD history) populations. Thus, the reported total evaluation period average values are not the average of the decade-specific values but are population-weighted averages for the entire cohort.
Abbreviations: CVD – cardiovascular disease, IS – ischemic stroke, MI – myocardial infarction, TC – total cholesterol

Key Limitations and Uncertainties

- The analysis does not account for evidence linking PFOA/PFOS exposure to other cardiovascular outcomes, such as systolic blood pressure (underestimate).
- The analysis does not account for survivors of first hard CVD events that are neither MI nor IS. The analysis does not account for people aged <40 years or >89 years at the time of their first hard CVD event (underestimate).
- Analysis assumes that prior TC levels do not have an impact on the TC decrease-related reductions in first hard CVD event risk (uncertain).
- Analysis assumes that there is no lag between changes in serum PFOA/PFOS concentrations and changes in TC and that there is no lag between changes in TC and changes in CVD risk (overestimate).

Contributors and Expert Reviewers

Anna Belova

Elena Besedin

Sorina Eftim

Rachel Gonsenhauser

Austin Heinrich

Alex Lan

Morgan McCabe

Kate Munson

Ryan Albert

Wes Austin

Eric Burneson

Chris Dockins

Ruth Etzel

Erik Helm

Hannah Holsinger

Brittany Jacobs

Elizabeth Radke-Farabaugh

Nathan Wittstruck

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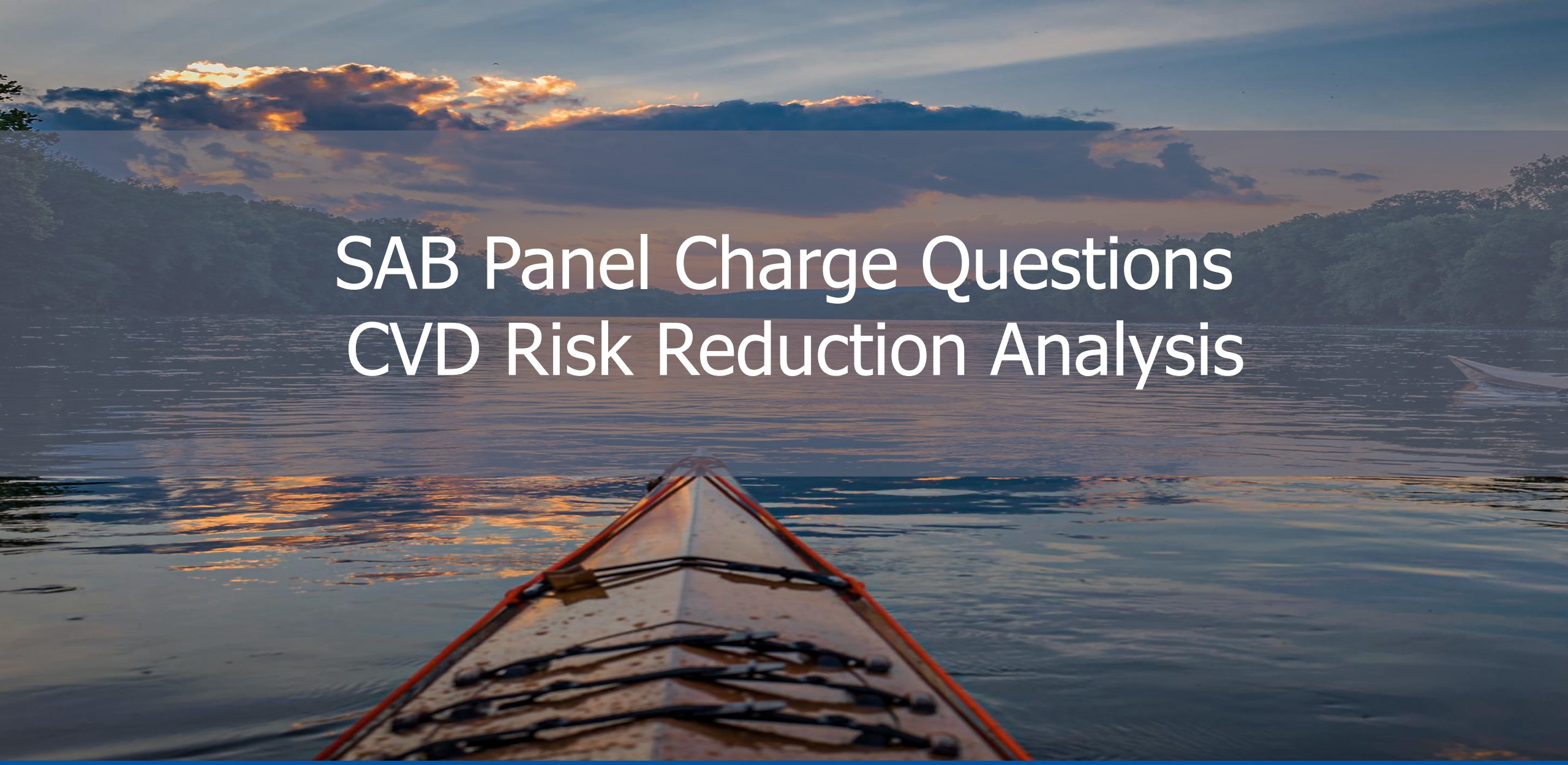

SAB Panel Charge Questions
CVD Risk Reduction Analysis

EPA United States Environmental Protection Agency

Office of Water

SAB Charge: Overall Charge Question

EPA is seeking SAB evaluation on the extent to which the approach to estimating reductions in CVD risk associated with reductions in exposure to PFOA and PFOS in drinking water is scientifically supported and clearly described.

SAB Charge Question #1

Section 4.2 presents EPA's meta-analysis for the total cholesterol dose-response function.

i. Please provide specific feedback on the extent to which the study selection criteria, the identified studies, and the methodological approach of the meta-analysis are complete and capture up to date scientific literature.

ii. To inform the CVD risk reduction analysis for those ages 40-89 using the ASCVD risk model, EPA used a meta-analysis approach for the total cholesterol dose-response function. Please provide specific feedback on the extent to which this approach is reasonable for this application, or whether using a single dose-response study (e.g. Dong et al., 2019) selected in the analysis of cholesterol impacts in the *Proposed Approaches for Deriving Maximum Contaminant Level Goals for PFOA and PFOS in Drinking Water* would add additional strengths for the CVD risk reduction application.

SAB Charge Question #2

Section 5.1 presents EPA's life table approach methodology.

i. Please comment on the extent to which this analysis is scientifically supported and clearly described. To the extent improvements are suggested, please provide specific changes that are implementable in a U.S. national-level benefits analysis with readily available data.

SAB Charge Question #3

Section 5.2 presents EPA's application of the atherosclerotic cardiovascular disease (ASCVD) risk model used to estimate the probability of hard CVD events corresponding to total cholesterol changes.

i. Please comment on the scientific validity of the ASCVD model application for estimating the probability of first time CVD events in various sub-populations and the extent to which it is clearly described.

ii. Please comment on whether EPA's approach and assumption of a uniform first CVD event hazard distribution over the 10-year period is sufficiently robust given current data sources and literature. If additional distributional sources of information are suggested, please provide specific citations/sources for EPA's consideration.

iii. Please comment on the scientific validity of using the ASCVD risk model for estimating reduced CVD risk stemming from changes in total cholesterol in response to reducing exposure to PFOA and PFOS in drinking water.

SAB Charge Question #4

Section 7 and Appendix A describe the limitations and uncertainties of the CVD risk reduction analysis. Has EPA clearly described the individual contributions of the sources of uncertainty?


Thank you.
Questions?