



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

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Foreword

The U.S. Environmental Protection Agency (EPA) has initiated the process to develop a Maximum Contaminant Level Goal (MCLG) and National Primary Drinking Water Regulation (NPDWR) for PFAS under the Safe Drinking Water Act (SDWA). The Agency is seeking comment from the EPA Science Advisory Board (SAB) on key scientific issues related to the development of the NPDWR. As part of this proposed rulemaking, EPA has prepared this document, “*Analysis of Cardiovascular Disease Risk as a Result of Reduced PFOA and PFOS Exposure in Drinking Water*” that illustrates the Agency’s approach toward informing EPA’s assessment on human health risk reduction. This paper is being submitted for scientific review by the EPA SAB along with three other documents:

- EPA’s Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for PFOA in Drinking Water (U.S. EPA, 2021d);
- EPA’s Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for PFOS in Drinking Water (U.S. EPA, 2021e); and
- EPA’s Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of Per- and Polyfluoroalkyl Substances (PFAS) (U.S. EPA, 2021b).

Each of the four documents on which EPA is seeking review will inform development of the MCLGs and NPDWR. EPA is moving expeditiously to develop the proposed MCLGs and NPDWR, therefore this draft document was developed concurrently with three other draft documents for the SAB’s review. While qualitative statements on health effects are consistent with the conclusions in the draft MCLG white papers, this document does not fully incorporate the updated information described in the companion MCLG documents. Following the SAB’s review, EPA will consider the input on this and other documents to prepare final documents that will inform the promulgation of MCLGs and NPDWRs.

1 Background and Purpose

1.1 National Primary Drinking Water Regulation (NPDWR) Development Process

The Safe Drinking Water Act (SDWA), as amended in 1996, requires the U.S. Environmental Protection Agency (EPA) to publish a list of contaminants every 5 years, referred to as the Contaminant Candidate List (CCL). The CCL is a list of contaminants that are currently not subject to any proposed or promulgated NPDWRs but are known or anticipated to occur in public water systems (PWSs) and may require regulation under SDWA. The SDWA directs EPA to determine whether to regulate at least five contaminants from the CCL every 5 years; this process is known as the Regulatory Determination process. The Agency must promulgate a NPDWR for a contaminant if the Administrator determines that the following three statutory criteria are met: (1) the contaminant may have an adverse effect on the health of persons, (2) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in PWSs with a frequency and at levels of public health concern, and (3) regulation of

such contaminant presents a meaningful opportunity for health risk reduction for persons served by PWSs.

On March 3, 2021, EPA published the Regulatory Determinations for the fourth CCL in the Federal Register (86 FR 12272–12291). This included a determination to regulate perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) in drinking water. Following publication of the Regulatory Determination, the Administrator shall propose a maximum contaminant level goal (MCLG) and a NPDWR no later than 24 months after determination or withdraw the regulatory determination. The underlying analysis presented in this document is one of many in development to support EPA’s proposed regulation. For more information about the NPDWR process or the regulatory determination for PFOA and PFOS, please see U.S. EPA (2021a).

1.2 Health Risk Reduction and Cost Analysis

SDWA section 1412(b)(3)(C) establishes requirements for EPA 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 is currently developing the HRRCA to support the proposed NPDWR for PFAS. For this analysis, EPA is primarily utilizing EPA’s *Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for PFOA and PFOS in Drinking Water* (U.S. EPA, 2021d; U.S. EPA, 2021e) to identify the adverse health effects of PFOA and PFOS that have the potential to inform a quantified health risk reduction assessment. EPA’s *Proposed Approaches for to the Derivation of a Draft Maximum Contaminant Level Goal for PFOA and PFOS in Drinking Water* identify health effects including immune, hepatic, serum lipids, developmental, and cancer effects. EPA is considering several adverse health effects for quantified health risk reduction assessment. Among the adverse health effects that have sufficient weight of evidence and available data to inform estimates of avoided adverse health outcomes were the effects of PFOA and PFOS on serum lipids, specifically total cholesterol (TC), a well-established risk factor for cardiovascular disease. In terms of weight of evidence, studies have found significant relationships between exposure to PFOA and PFOS and cholesterol levels (Château-Degat et al., 2010; Nelson et al., 2010; Eriksen et al., 2013; U.S. EPA, 2016a, 2016b; ATSDR, 2018; U.S. EPA, 2021a). Notably, increases in TC levels are linked to increases in cardiovascular disease (CVD) risk, especially among individuals over age 40 (D’Agostino et al., 2008; Goff et al., 2014; Lloyd-Jones et al., 2017). Data and modeling approaches are available to estimate the increases in CVD risk as a function of cholesterol changes and to quantify the avoided health outcomes.

In light of the well documented impacts of PFOA and PFOS on cholesterol, EPA is developing national level risk reduction estimates for avoided cardiovascular disease as a result of PFOA and PFOS exposure reduction via drinking water. This document presents the methodology used to determine the avoided cases of CVD events (e.g., first heart attack, first stroke, death from coronary heart disease) for one hypothetical PWS. To support the HRRCA for the proposed NPDWR, EPA intends to use the methodology outlined in this document to quantify cardiovascular risk reduction for the population served by all the PWSs expected to take action to comply with a proposed PFAS NPDWR.

As discussed in EPA's *Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for PFOA and PFOS in Drinking Water*, PFOA and PFOS have significant adverse human health effects on a wide variety of health endpoints. In particular, current epidemiologic literature supports positive associations between PFOA and PFOS exposure on TC (U.S. EPA, 2021d; U.S. EPA, 2021e). As such, EPA will be using this methodology in part to inform the HRRCA and the Agency's consideration of regulatory alternatives by quantifying cardiovascular risk reductions for populations served by PWSs expected to take action to comply with a PFAS drinking water regulation. EPA notes that other adverse health effects discussed in EPA's *Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for PFOA and PFOS in Drinking Water* (U.S. EPA, 2021d; U.S. EPA, 2021e) are being evaluated for inclusion in the HRRCA.

2 Overview of the CVD Risk Reduction Analysis

CVD is one of the leading causes of premature mortality in the United States (D'Agostino et al., 2008; Goff et al., 2014; Lloyd-Jones et al., 2017). As discussed in EPA's *Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for PFOA and PFOS in Drinking Water*, exposure to PFOA and PFOS through drinking water contributes to increased serum PFOA and PFOS concentrations, and thus elevated levels of TC (U.S. EPA, 2021d; U.S. EPA, 2021e). Elevated TC is associated with increased incidence of hard CVD events, which are defined as fatal and non-fatal myocardial infarction (MI; i.e., heart attack), fatal and non-fatal ischemic stroke (IS), or other coronary heart disease (CHD) death occurring in populations without prior CVD event experience (D'Agostino et al., 2008; Goff et al., 2014; Lloyd-Jones et al., 2017). Therefore, individuals exposed to elevated PFOA and PFOS concentrations via drinking water are expected to experience increased risk of CVD and premature mortality.

Figure 1 provides an overview of the approach used to estimate the reductions in CVD risk associated with reductions in exposure to PFOA and PFOS via drinking water. Evaluation of the expected reductions in CVD risk resulting from PFOA and PFOS exposure reduction in drinking water involves three main steps:

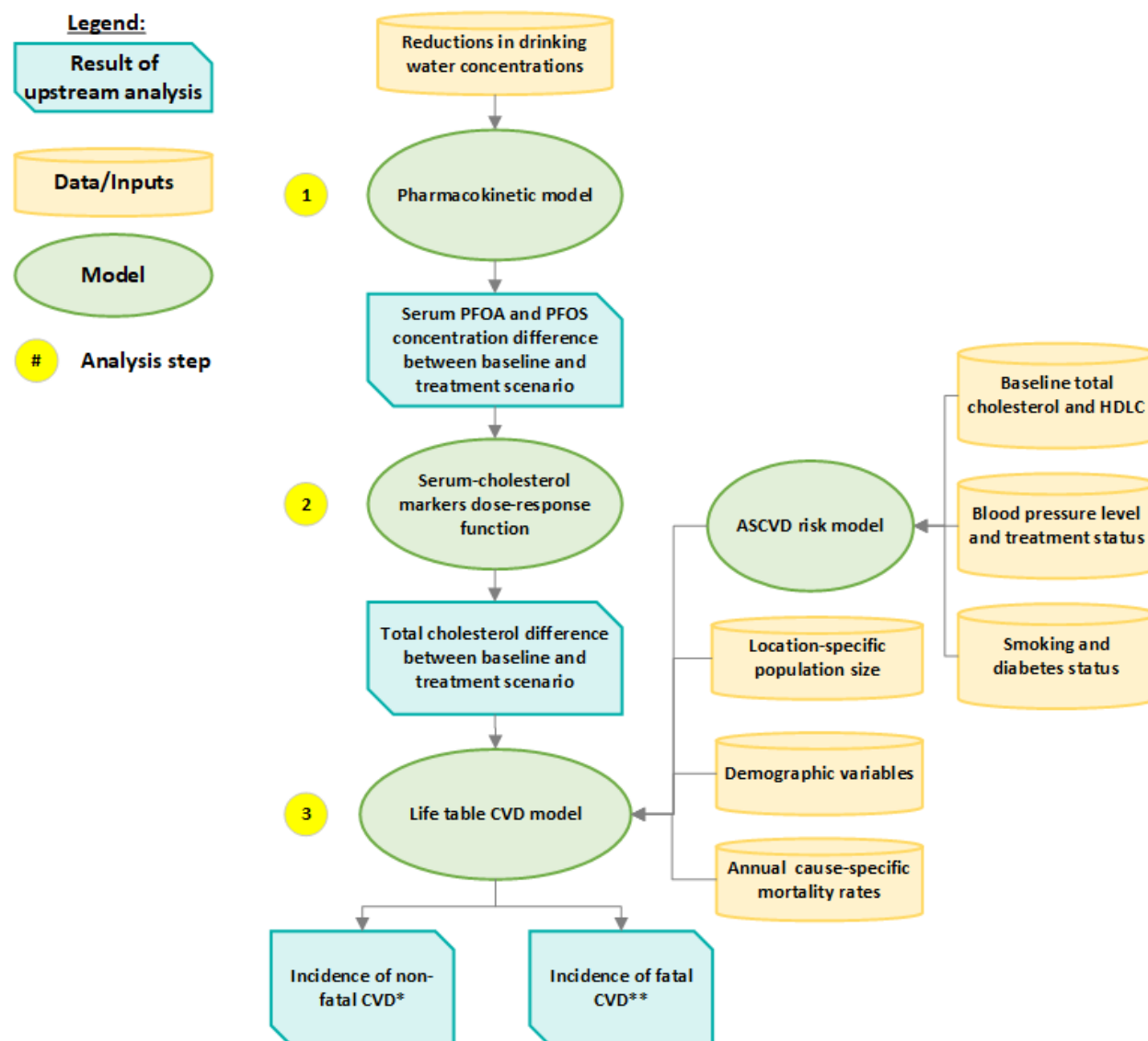
1. Estimation of the changes in serum PFOA and serum PFOS from reduction in drinking water exposure using a Pharmacokinetic (PK) model;
2. Estimation of annual changes in TC¹ levels using exposure-response functions for the effect of serum PFOA/PFOS on TC; and
3. Estimation of the annual incidence of fatal and non-fatal first hard CVD events and post-acute CVD mortality corresponding to baseline and treatment scenario TC levels in all populations alive during or born after the start of the evaluation period.

Section 3 details the baseline and treatment scenarios, including the estimated drinking water concentrations under each scenario. Section 4 discusses the estimated changes in TC, including the application of the pharmacokinetic and dose-response models. Section 5 details the estimated CVD risk reductions using the Pooled Cohort Atherosclerotic Cardiovascular

¹ EPA discusses the relationship between PFOA/PFOS exposure and other forms of cholesterol in Appendix A.

Disease (ASCVD) risk model and life table approach. Section 6 presents the results of the analysis. Section 7 discusses limitations and uncertainties.

Figure 1: Overview of the CVD Risk Model.



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.

Abbreviations:

UCMR 3 – Third Unregulated Contaminant Monitoring, PFOA – perfluorooctanoic acid, PFOS – perfluorooctanesulfonic acid, CVD – cardiovascular disease, ASCVD – atherosclerotic cardiovascular disease, MI – myocardial infarction, IS – ischemic stroke, CHD – coronary heart disease, HDLC – high-density lipoprotein cholesterol

3 Baseline and Treatment Scenarios

3.1 Baseline Scenario

The CVD risk reduction analysis models PFOA and PFOS occurrence in drinking water at baseline and post-treatment implementation. 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 document for review by the SAB, EPA developed a hypothetical PWS to illustrate the methodology to be used in the national level analysis. The characteristics of the hypothetical PWS are summarized below in Table 1. To model demographic characteristics at the hypothetical PWS, EPA uses national demographic information to estimate age, sex, and race/ethnicity distributions.

During the Agency's collection of nationally representative occurrence data for PFOA and PFOS through the Unregulated Contaminant Monitoring Rule 3 (UCMR 3), the 90th percentile combined concentration for PFOA and PFOS was reported as 0.20 µg/L (U.S. EPA, 2021c). As such, for the purposes of the hypothetical PWS, EPA uses 0.10 µg/L as average baseline concentrations for both PFOA and PFOS (Table 1). For further information on occurrence data for PFOA and PFOS in finished drinking water, please see the Final Regulatory Determination 4 Support Document (U.S. EPA, 2021c).

Table 1: Characteristics of the Hypothetical PWS	
Description	Value
PWS size category	Large
PWS primary source water type	Surface water
Population served	100,000
Number of entry points	1
Average baseline PFOA concentration (µg/L)	0.10
Average baseline PFOS concentration (µg/L)	0.10

3.2 Treatment Scenario

In 2016, EPA established drinking water health advisories for PFOA and PFOS based on the Agency's assessment of the best available peer-reviewed science at that time (U.S. EPA, 2016a, 2016b). EPA issued a drinking water health advisory for PFOA and PFOS of 0.07 µg/L based on developmental toxicity studies in animals and informed by epidemiological studies of human populations exposed to PFOA and PFOS. EPA has since conducted a systematic literature review and analysis of peer-reviewed scientific literature for PFOA and PFOS published since 2013 with the goal of identifying new studies relevant to the derivation of MCLGs (U.S. EPA, 2021d; U.S. EPA, 2021e).² EPA is currently developing the proposed NPDWR and is evaluating several regulatory options. As EPA actively develops the MCLGs and regulatory options for the proposed NPDWR, EPA is using a treatment threshold of 0.07 µg/L for combined PFOA and PFOS as an illustrative example in this document. The example treatment scenario will

² MCLGs represent the level of a contaminant in drinking water below which there is no known or expected risk to health. MCLGs allow for a margin of safety and are non-enforceable public health goals.

demonstrate the methodology that EPA intends to employ in the national CVD risk reduction analysis.

This analysis evaluates reduced cardiovascular disease risk stemming from reductions in PFOA and PFOS at the entry point to the distribution system of a PWS with PFAS concentrations (defined as the sum of PFOS and PFOA concentrations) greater than 0.07 µg/L. The hypothetical PWS has one entry point; therefore, EPA assumes that 100% of the total population served by the hypothetical PWS would experience reduced PFOA and PFOS exposure.

EPA anticipates that PWSs will consider both treatment and non-treatment options to comply with the future NPDWR. In this analysis, EPA models a treatment scenario where a system installs a treatment technology to achieve PFOA and PFOS occurrence below the treatment threshold. The treatment target concentration is considered to be 80% of the illustrative treatment threshold (e.g., for a PFOA and PFOS threshold of 0.07 µg/L, the treatment 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 (U.S. EPA, 2005). For this analysis, EPA assumed the same removal efficiency for both PFOA and PFOS.

At the hypothetical PWS, the reductions required to meet the treatment target concentration are 0.072 µg/L for PFOA and 0.072 µg/L for PFOS. Given the assumed treatment target of 80% of the illustrative treatment threshold, EPA estimates that the population served by the hypothetical PWS would be exposed to 0.028 µg/L of PFOA and 0.028 µg/L of PFOS following treatment installation.

3.3 Additional Scenario Evaluation Details

For this analysis, EPA assumes that the NPDWR will be promulgated by 2023. Many NPDWRs take effect three years after the date on which the regulation is promulgated. EPA assumes that actions to comply with the rule, including installation of treatment technologies, will begin by 2026. The overall time horizon of the baseline and treatment scenario evaluation is from 2023 to 2104, with the impacts evaluated for all adults who turn 40 during the 80-year time horizon.³ EPA notes that the actual timeline for rule finalization may be prior to 2023 and that mandated system compliance may occur prior to 2026.

4 Estimation of Cholesterol Changes

4.1 Pharmacokinetic Model

Baseline and treatment scenario PFOA/PFOS drinking water concentrations were used as inputs to EPA's PK model for adult males and females to estimate serum PFOA/PFOS concentrations. See EPA's *Proposed Approaches to the Derivation of a Draft Maximum*

³ While the period of reduced PFOA/PFOS drinking water levels is from 2023 to 2104, the changes in baseline serum PFOA/PFOS concentrations have considerable latency and the CVD risk model applies to ages 40–89 (see section 5). To appropriately capture the lagging CVD impacts, all populations alive during or born after 2023 are tracked until they attain age 94. This age marks the end of the 6-year follow-up period during which post-acute CVD mortality is evaluated for those who survive a first hard CVD event at age 89.

Contaminant Level Goal for PFOA and PFOS in Drinking Water for further information on the model (U.S. EPA, 2021d; U.S. EPA, 2021e).

The PK model requires total PFOA/PFOS dose in mg/kg of body weight per day to be provided as an input. EPA multiplied PFOA/PFOS drinking water concentrations by a water intake of 0.013 L/kg of body weight per day (U.S. Environmental Protection Agency, 2011b) in order to compute the PFOA/PFOS dose from drinking water sources. To estimate the total daily dose, consistent with the 2016 PFOA and PFOS health advisories and EPA's *Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for PFOA and PFOS in Drinking Water* (U.S. EPA, 2021d; U.S. EPA, 2021e) being concurrently reviewed by the SAB, EPA assumed that the dose from drinking water sources comprises 20% of the total daily PFOA/PFOS dose under the baseline scenario.⁴ EPA additionally assumed that non-drinking water exposure is independent of the drinking water PFOA/PFOS concentration and estimated the total treatment scenario dose as the sum of the baseline non-drinking water dose and the treatment scenario drinking water dose.⁵

EPA used the PK model to evaluate the following exposure scenarios in male and female subpopulations:

- **Lifetime baseline exposure scenario:** Lifetime exposure to baseline PFOA/PFOS dose for cohorts of all ages alive at the start of the evaluation period in 2023 and cohorts born after 2023;
- **Lifetime treatment exposure 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 scenario:** Exposure to baseline PFOA/PFOS dose until age A–1 years and treatment scenario PFOA/PFOS dose thereafter for cohorts aged A > 0 years in 2026.

The PK-modeled serum PFOA/PFOS concentration time series were averaged to the annual time scale. EPA estimated treatment scenario changes in annual average serum PFOA/PFOS concentrations by subtracting baseline annual cohort-specific serum PFOA/PFOS concentrations from either full or partial lifetime treatment scenario annual cohort-specific serum PFOA/PFOS concentrations (as appropriate).

4.2 Dose-Response Analysis

Statistical analyses that combine the results of multiple studies, such as meta-analyses, are widely applied to investigate the dose-specific relationship between contaminant levels and associated health effects. Such analyses are suitable for economic assessments because they

⁴ EPA explored the impact of this assumption on the magnitude of estimated treatment scenario-related *changes* in serum PFOA/PFOS concentrations by alternatively assuming an 80% contribution from drinking water sources. EPA confirmed that, due to the linearities of the PK model, the assumption about drinking water source contribution does not affect the estimated changes in serum PFOA/PFOS, which is the key quantity of interest.

⁵ This implies that the *percentage* of exposure due to drinking water under the treatment scenario is lower compared to the baseline scenario. In reality, some portion of the non-drinking water exposure will be related to drinking water concentration. This portion is difficult to estimate, and, depending on the relationship, there may be a time lag between the decrease in drinking water concentration and the decrease in the non-drinking water exposure.

can improve precision and statistical power (Engels et al., 2000; Deeks, 2002; Rücker et al., 2009). The ASCVD model includes both TC and high-density lipoprotein cholesterol (HDL) as predictors of first hard CVD events. EPA, however, did not identify any readily available meta-analyses for PFOA or PFOS and TC or HDL that were specifically relevant to the age group of interest (40-89 years, the years for which the ASCVD model estimates the probability of a first hard CVD event). Therefore, the Agency developed a meta-analysis of studies reporting associations between serum PFOA or PFOS and TC or HDL in general populations (e.g., populations that are not a subset to workers or pregnant women). Appendix A provides details on the studies selection criteria, meta-data development, meta-analysis results, and discussion of the uncertainty and limitations inherent in EPA's dose-response analysis.

EPA identified studies for inclusion in the meta-analysis using data from literature review efforts, including those performed by the Agency for Toxic Substances and Disease Registry (ATSDR) in the development of their Toxicological Review Public Comment Draft (ATSDR, 2018), which included literature through mid-2017, and those performed for developing EPA's *Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for PFOA and PFOS in Drinking Water* (U.S. EPA, 2021d; U.S. EPA, 2021e) concurrently being reviewed by the SAB, which included studies published from 2016 through September 2020. Studies were included in the meta-analysis if they reported quantitative estimates (e.g., regression coefficients) and measures of uncertainty (e.g., standard errors, confidence intervals) of associations between serum PFOA or PFOS and TC or HDL in general population adults aged 20 years and older. Of these, 11 studies were used to develop exposure-response relationships for serum PFOA or PFOS and TC (i.e., not all relevant studies report the effects for both PFOA and PFOS) and 13 studies were used to develop exposure-response relationships for serum PFOA/PFOS and HDL. The unit in the meta-analysis was change in TC or HDL in mg/dL per ng/mL increases in serum PFOA or PFOS. EPA conducted four separate meta-analyses for each chemical (PFOA or PFOS) and health outcome (TC or HDL). EPA included a total of 14 studies in the meta-analysis.

Table 2 summarizes the 14 studies that EPA identified from literature review efforts and used to derive slope estimates for PFOA and PFOS associations with serum TC and HDL levels.⁶ Six of the studies that EPA retained for use in the meta-analysis were based on serum PFAS and serum lipid measurements from the U.S. general population (National Health and Nutrition Examination Survey [NHANES]) (Dong et al., 2019; Fan et al., 2020; He et al., 2018; Jain et al., 2019; Liu et al., 2018; Nelson et al., 2010); there were also general population studies from Canada (Fisher et al., 2013), Sweden (Y. Li et al., 2020), Taiwan (Yang et al., 2018; C. Y. Lin et al., 2020), and Henan Province, China (Fu et al., 2014). Château-Degat et al. (2010) reported on the relationship between PFOS and serum lipids in a Canadian Inuit population. EPA also retained the results from a study of a highly exposed population in the United States (the C8 cohort) (Steenland et al., 2009) and from a study using participants in a U.S. diabetes prevention program (P.-I. D. Lin et al., 2019).

⁶ For this effort, EPA focused on PFOA and PFOS, since these are by far the most well-studied perfluorinated compounds.

Table 2: Studies Selected for Inclusion in the Meta-Analyses

Author and Year	Title	Cholesterol and Serum PFAS Relationship Evaluated in Study			
		TC		HDL	
		PFOA	PFOS	PFOA	PFOS
Steenland et al., 2009 ^{a,d}	Association of Perfluorooctanoic Acid and Perfluorooctane Sulfonate With Serum Lipids Among Adults Living Near a Chemical Plant	X	X	X	X
Château-Degat et al., 2010 ^{a,d}	Effects of Perfluorooctanesulfonate Exposure on Plasma Lipid Levels in the Inuit Population of Nunavik (Northern Quebec)		X		X
Nelson et al., 2010 ^{a,d}	Exposure to Polyfluoroalkyl Chemicals and Cholesterol, Body Weight, and Insulin Resistance in the General U.S. Population	X	X	X	X
Fisher et al., 2013 ^{a,d}	Do Perfluoroalkyl Substances Affect Metabolic Function and Plasma Lipids?—Analysis of the 2007–2009, Canadian Health Measures Survey (CHMS) Cycle 1	X	X	X	X
Fu et al., 2014 ^{a,d}	Associations Between Serum Concentrations of Perfluoroalkyl Acids and Serum Lipid Levels in a Chinese Population	X	X	X	X
He et al., 2018 ^c	PFOA is Associated with Diabetes and Metabolic Alteration in US Men: National Health and Nutrition Examination Survey 2003–2012	X	X	X	X
Liu et al., 2018 ^c	Association Among Total Serum Isomers of Perfluorinated Chemicals, Glucose Homeostasis, Lipid Profiles, Serum Protein and Metabolic Syndrome in Adults: NHANES, 2013–2014	X	X	X	X
Yang et al., 2018 ^b	Association of Serum Levels of Perfluoroalkyl Substances (PFASs) With the Metabolic Syndrome (MetS) in Chinese Male Adults: A Cross-Sectional Study			X	X
Dong et al., 2019 ^b	Using 2003–2014 U.S. NHANES Data to Determine the Associations Between Per- and Polyfluoroalkyl Substances and Cholesterol: Trend and Implications	X	X	X	
Jain et al., 2019 ^b	Roles of Gender and Obesity in Defining Correlations Between Perfluoroalkyl Substances and Lipid/Lipoproteins	X	X	X	X
P.-I. D. Lin et al., 2019 ^b	Per- and Polyfluoroalkyl Substances and Blood Lipid Levels in Pre-Diabetic Adults—Longitudinal Analysis of the Diabetes Prevention Program Outcomes Study	X	X	X	X
Fan et al., 2020 ^b	Serum Albumin Mediates the Effect of Multiple Per- and Polyfluoroalkyl Substances on Serum Lipid Levels	X	X	X	X
Y. Li et al., 2020 ^b	Associations Between Perfluoroalkyl Substances and Serum Lipids in a Swedish Adult Population With Contaminated Drinking Water	X	X	X	X

Table 2: Studies Selected for Inclusion in the Meta-Analyses

Author and Year	Title	Cholesterol and Serum PFAS Relationship Evaluated in Study			
		TC		HDLc	
		PFOA	PFOS	PFOA	PFOS
C. Y. Lin et al., 2020 ^b	The Association Between Total Serum Isomers of Per- and Polyfluoroalkyl Substances, Lipid Profiles, and the DNA Oxidative/Nitrative Stress Biomarkers in Middle-Aged Taiwanese Adults			X	X

Notes:

^a Studies identified based on ATSDR literature review.

^b Studies identified based on EPA/OST literature review.

^c Studies available in both assessments.

^d Studies available in PFOA and/or PFOS health effects support documents (U.S. EPA, 2016a, 2016b).

EPA developed dose-response relationships between serum PFOA/PFOS and TC and HDLC for use in the CVD analysis using the meta-analyses restricted to studies of adults in the general population reporting similar models. EPA used untransformed serum PFOA/PFOS to reduce bias due to back-transformations of effect estimates. For studies that provided results only for log-transformed serum PFOA/PFOS (five studies) or log-transformed outcomes (two studies), or both log-transformed serum PFOA/PFOS and outcomes (two studies), EPA approximated the results for an untransformed analysis using the approach outlined by Rodríguez-Barranco et al. (2017) and Dzierlenga et al. (2020). When using studies reporting linear associations between TC and serum PFOA or PFOS, EPA estimated a positive increase in TC of 1.57 (95% CI: 0.02, 3.13) mg/dL per ng/mL serum PFOA (p-value=0.048), and of 0.08 (95% CI: -0.01, 0.16) mg/dL per ng/mL serum PFOS (p-value=0.064). EPA selected the pooled slope based on the studies using linear models to ease interpretability and to reduce bias due to back-transformations of effect estimates with log-transformed outcomes or exposures (see Appendix A for details). 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 ($p = .064$). Furthermore, the literature provides sufficient support of a positive association (e.g., Château-Degat et al., 2010; Dong et al., 2019; U.S. EPA, 2021d; U.S. EPA, 2021e). The studies are large with more than 700 and 8,900 participants, respectively (Château-Degat et al., 2010; Château-Degat et al., 2010; Dong et al., 2019) and have low risk of bias. In addition, the estimated values are supported by sensitivity analyses and by the estimates from potential candidate studies from dose-response modeling for ongoing Agency efforts (Dong et al., 2019). Based on the systematic review conducted by EPA of 39 epidemiologic studies published between 2016 and September 2020 for developing EPA's *Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for PFOA and PFOS in Drinking Water*, the available evidence supports a positive association between PFOS and TC in the general population (U.S. EPA, 2021d; U.S. EPA, 2021e). For more information on the systematic review and results, see EPA's *Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for PFOA and PFOS in Drinking Water* (U.S. EPA, 2021d; U.S. EPA, 2021e). The associations observed in the meta-analysis for HDLC and serum PFOA or PFOS were positive

but not statistically significant. EPA's systematic review of HDLC associations found inconsistent and weak evidence to support PFOA or PFOS effects on HDLC. The systematic review concluded that the available evidence does not support an inverse association with HDLC in any population. Therefore, EPA is not including effect estimates for the serum PFOA-HDLC and serum PFOS-HDLC associations in the CVD analysis.

5 Estimation of CVD Risk Reductions

EPA relies on 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, age at the beginning of the PFOA/PFOS evaluation period (i.e., 2023), and age- and sex-specific TC level time series (section 5.1). 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. Baseline and treatment scenarios are evaluated separately, with treatment scenario TC levels estimated using baseline TC information from external statistical data sources and modeled changes in TC due to treatment scenario conditions (section 4.2).

The incidence of first hard CVD events based on TC serum levels is estimated using the ASCVD model (Goff et al., 2014), which predicts the probability of a hard CVD event to be experienced by a person without a prior CVD history (see section 5.2).⁷ Therefore, EPA adjusts the modeled population cohort to exclude individuals with pre-existing conditions, as the ASCVD risk model does not apply to individuals with pre-existing conditions. Modeled first hard CVD events include fatal and non-fatal MI, fatal and non-fatal IS, and other CHD mortality. EPA also has estimated the incidence of post-acute CVD mortality among survivors of the first MI or IS within 6 years of the initial event (section 5.3).

The estimated risk reduction from reducing exposure to PFOA and PFOS in drinking water is the difference in annual incidence of CVD events (i.e., mortality and morbidity associated with first-time CVD events and post-acute CVD mortality) under the baseline and treatment scenarios. Appendix B provides detailed information on all CVD model components and computations, Appendix C describes estimation and projection of the affected population, and Appendix D describes all sources of the data used in modeling.

5.1 Life Table Calculations

The CVD model integrates the ASCVD model predictions and post-acute CVD mortality rates in the series of recurrent calculations that produce a life table estimate for the affected population cohort (e.g., non-Hispanic White females aged 70 years at the beginning of the evaluation period). The life table is a metric designed to represent the longevity of people from a certain population. The inputs to the life table are the age-specific probability of death and the initial population size (e.g., 100,000 persons). Based on this information, the life table computes the

⁷ EPA did not identify studies that relate TC to CVD events for populations with a prior CVD history. Discussion of the relevant literature is provided in Appendix B.

number of persons surviving to a specific age, the number of deaths occurring at a given age, the number of person-years lived at a given age, the number of person-years lived beyond a given age, and age-specific life expectancy. The details of standard life table calculations can be found in Anderson (1999). EPA has previously used life table approaches in regulatory analyses, including the analysis of lead-associated health effects in the 2015 Benefit and Cost Analysis for the Effluent Limitations Guidelines, Standards for the Steam Electric Power Generating Point Source Category (U.S. EPA, 2015), and PM_{2.5}-related health effects in revisions to the National Ambient Air Quality Standards for ground-level ozone (U.S. EPA, 2008). Other examples of use of a life table approach among federal agencies include EPA's analysis of Benefits and Costs of the Clean Air Act from 1990 to 2020 (U.S. EPA, 2011a) and the Occupational Safety and Health Administration (OSHA) assessment of lifetime excess lung cancer, nonmalignant respiratory disease mortality, and silicosis risks from exposure to respirable crystalline silica (81 FR 16285, March 25, 2016; OSHA, 2010).

For each PWS, EPA evaluates 1,048 population cohorts defined by a combination of birth year and age in or after 2023 (i.e., pairs of (2023,0), (2022,1), (2021,2), ..., (1934,89)⁸ and pairs of (2024,0), (2025,0), ..., (2065,0)⁹), sex (males and females), and race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Other). In addition to the key standard life table components (i.e., the number of persons surviving to a specific age and the number of all-cause deaths occurring at a given age) for ages 40–89, the CVD model estimates the number of surviving persons with and without a history of hard CVD events, the number of persons experiencing hard CVD events at a given age, and the deaths from CVD and non-CVD causes at a given age.

Figure 2 summarizes the CVD model calculations for a population cohort age 0 at the start of the evaluation period.¹⁰ The CVD model calculations are identical across race/ethnicity and sex demographic subgroups but use subgroup-specific coefficients.¹¹ For cohorts born prior to or in 2023, the CVD model is initialized using the PWS-specific number of persons alive at the beginning of 2023. For cohorts born after 2023, the CVD model is initialized using the projected PWS-specific number of persons aged 0 years in the corresponding future year (i.e., 2024–2104). PWS- and sex, race/ethnicity, and age-specific population estimation and projection details are included in Appendix C.

Once the model is initialized, the following types of calculations occur for each year within the 95-year¹² simulation period:

- Recurrent **standard life table calculations** that rely on the all-cause, age-specific annual mortality rates to evaluate the number of deaths among persons of a specific

⁸ While the ASCVD model applies to ages 40–80, it generates 10-year hard CVD event risk predictions. Therefore, it is possible to use the model predictions to carry incidence calculations out to age 89.

⁹ Those born after 2065 will not reach age 40 by the end of the analysis period in 2104. Because the ASCVD model applies to ages 40–89, changes in CVD risk cannot be quantified in the time horizon of this model run for these cohorts.

¹⁰ This initial population cohort age is chosen because it allows for illustration of the full set of calculation types used in the CVD model.

¹¹ There are different ASCVD model coefficients for non-Hispanic White and non-Hispanic Black males and females. The figure shows the generalized approach of the CVD model.

¹² The model calculates incidences through age 89 and models post-acute probabilities for 6 years after the initial event.

integer age and the number of survivors to the beginning of the next integer age.¹³ These calculations are executed whenever the current cohort age is in the 0–39 range. They are represented by the green segment of the timeline shown in Figure 2.

- **Recurrent life table calculations that separately track subpopulations with and without a history of hard CVD events**, including estimation of the number of annual CVD and non-CVD deaths (in either subpopulation), as well as the number of annual post-acute CVD deaths experienced by survivors of the first hard CVD events that occurred, at most, 5 years ago. These calculations are executed whenever the current cohort age is in the 40–89 range. These calculations are represented by the red segment of the timeline in Figure 2. Figure 3 further illustrates the year-specific calculations required for explicit tracking of subpopulations with and without a hard CVD event history. These calculations also are summarized in Table 3.
- **Recurrent life table calculations tracking survivors of the first hard CVD event at ages 85–89 who attain ages 90–94** in order to estimate the number of annual post-acute CVD deaths that occur within 6 years of the initial event. These calculations are represented by the orange segment of the timeline in Figure 2. Table 3 and Figure 3 provide additional details.

Figure 2: Overview of Life Table Calculations in the CVD Model.

Notes: The figure illustrates the model for population cohort age 0 years at the beginning of the evaluation period (i.e., calendar year 2023). The model is initialized using the age 0 PWS-specific population (see Appendix C for PWS population estimation and projection details).

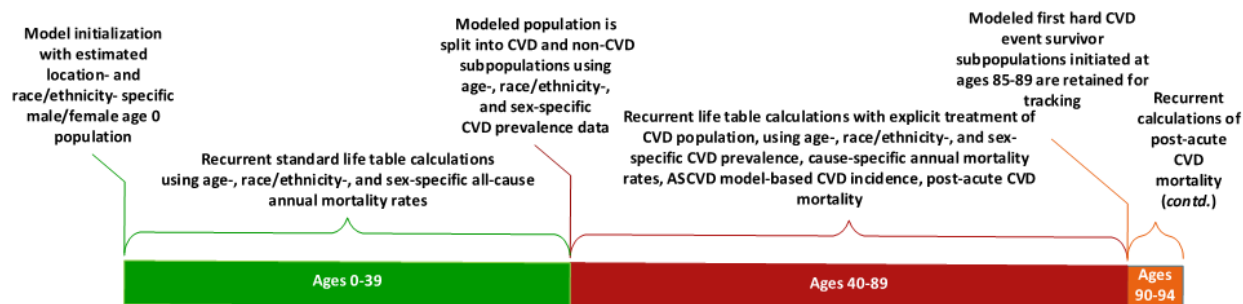


Table 3 offers a more detailed summary of the year-specific calculations required for explicit tracking of subpopulations with and without a hard CVD event history illustrated in Figure 3. Some of the calculation steps differ depending on whether the baseline or the treatment scenario is evaluated. In addition to providing estimates of the quantities of interest (e.g., the number of persons experiencing their first CVD event in a given year), the execution of the baseline scenario allows EPA to obtain age-specific baseline CVD mortality rates for the CVD subpopulation that are calibrated to the relevant baseline data (i.e., cause-specific mortality in the general population, CVD prevalence statistics, and baseline incidence of first hard CVD events). These calibration factors are not affected by differences between baseline and

¹³ Life table calculations are based on the present-day information about life expectancy, disease, environmental exposure, and other factors.

treatment scenario conditions. As shown in Table 3 (Steps 6, 7, 9, and 10), EPA uses these rates to support CVD and non-CVD subpopulation calculations under the treatment scenario.

Figure 3 and the notes to Table 3 provide additional information on the post-acute CVD mortality estimation. Each person included in the surviving current age-specific incident CVD subpopulation¹⁴ (corresponding to the group F result in Figure 3 or Step 9 result in Table 3) is tracked for 5 additional years to estimate the number of CVD deaths occurring in that timeframe. The recurrent estimates rely on age-specific non-CVD mortality rates, estimated based on the Centers for Disease Control and Prevention's (CDC) life table data and annual CVD mortality rates, and on post-acute CVD mortality rates, estimated based on Thom et al. (2001) and S. Li et al. (2019).

¹⁴ For example, persons who experienced their first non-fatal MI or IS at age 70 and survived through the first post-event year.

Figure 3: CVD Model Calculations for Ages 40–89 Tracking CVD and Non-CVD Subpopulations for a Specific Current Age of the Cohort.

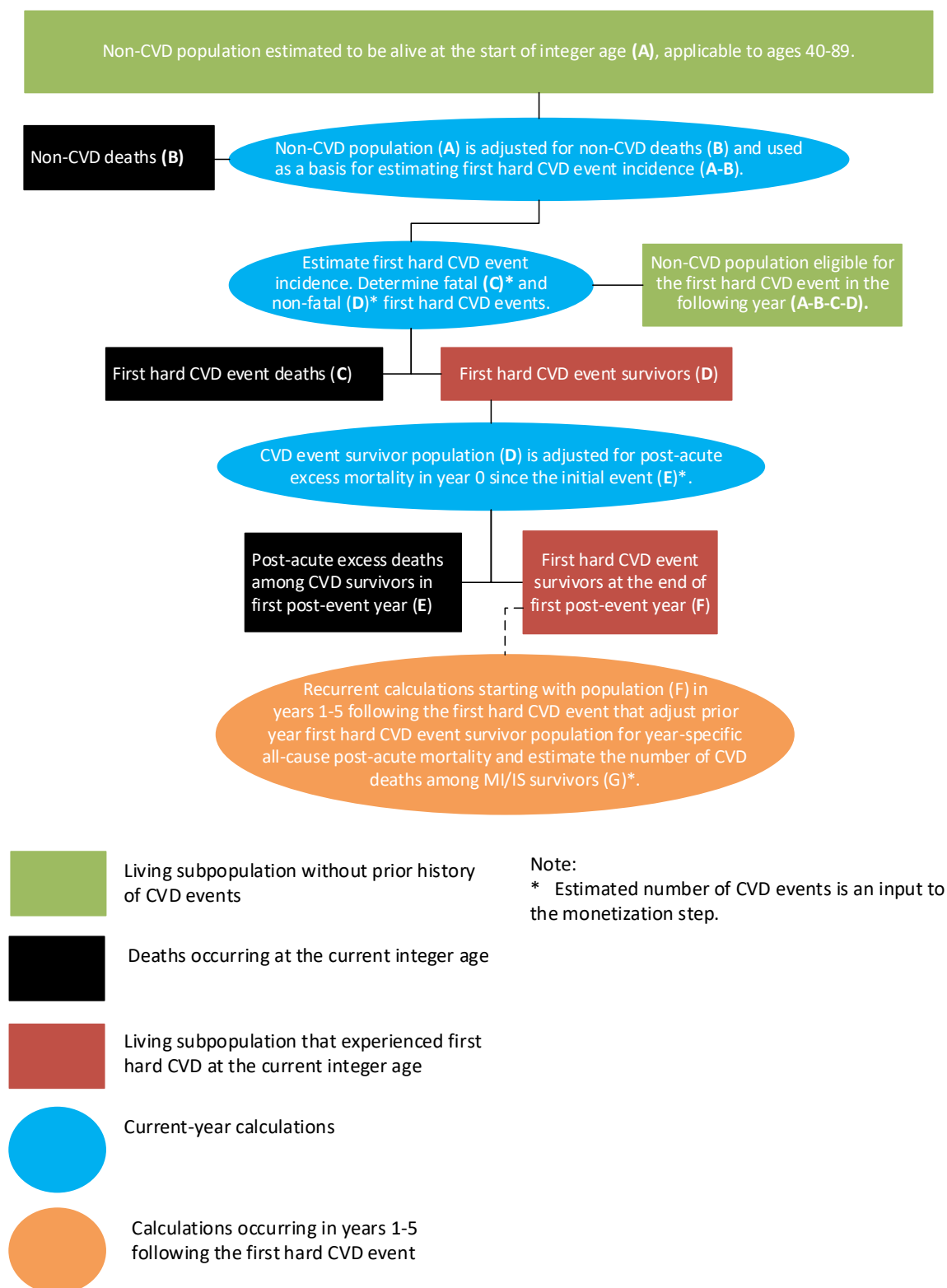


Table 3: Year-Specific Calculations Required for Explicit Tracking of Subpopulations With and Without a Hard CVD Event History, Ages 40–89

Calculation Step	Baseline Calculations	Treatment Scenario Calculations
1. Estimate the sizes of subpopulations with and without a hard CVD event history alive at the start of the year.	National-level CVD prevalence statistics are used to allocate the overall population alive at the start of the year.	The sizes of these subpopulations are estimated using within-year computations, based on internal quantities estimated in the previous year (see Step 13).
2. Estimate the number of non-CVD deaths in subpopulations with and without a hard CVD event history.	Sex-, race/ethnicity, and age-specific mortality rates for causes other than CVD are applied to the surviving subpopulation size (Step 1) to estimate the number of non-CVD deaths in the CVD subpopulation and non-CVD subpopulation.	
3. Estimate the <i>uncalibrated</i>* initial number of persons experiencing their first hard CVD events .	The non-CVD subpopulation (Step 1) adjusted for non-CVD deaths (Step 2) is multiplied with the probability of the first hard CVD event generated by the ASCVD model.	
4. Estimate the <i>uncalibrated</i>* number of CVD deaths among persons experiencing their first hard CVD events .	The national-level statistics (see section 5.2) and results in Thom et al. (2001) and S. Li et al. (2019) are used to estimate acute and post-acute CVD mortality** among persons experiencing their first hard CVD events in the current year (Step 3).	
5. Estimate the <i>uncalibrated</i>* end-of-year number of persons who experienced their first hard CVD event in the current year .	The initial number of persons experiencing their first hard CVD event (Step 3) is reduced by the number of CVD deaths in this population occurring within the same year (Step 4).	
6. Estimate the number of CVD deaths in the overall population.	Sex-, race/ethnicity, and age-specific CVD mortality rates are applied to the overall surviving population size (Step 1) net of the total number of non-CVD deaths (Step 2).	The number of deaths among persons experiencing their first CVD event this year (Step 10) is added to the number of deaths in the start-of-the year CVD subpopulation (Step 1) multiplied by the corresponding baseline CVD death rate in the CVD subpopulation (Step 12 baseline).
7. Estimate the CVD event incidence consistent with the change in published baseline CVD prevalence .	Current year CVD incidence is calculated as the difference in next year's CVD prevalence (Step 1 applied to the next year's population) and this year's CVD prevalence (Step 1) plus CVD deaths (Step 6) and non-CVD deaths in the CVD population (Step 2).	Current year CVD incidence is calculated as the product of the raw ASCVD model-based incidence adjusted for post-acute mortality (Step 4 + Step 5) and the CVD event incidence calibration factor (Step 8 baseline).
8. Estimate the CVD event incidence calibration factor .	Divide the reported prevalence and CVD mortality rate-based CVD event incidence (Step 7) by the raw ASCVD model-based incidence adjusted for post-acute mortality (Step 4 + Step 5).	Not applicable

Table 3: Year-Specific Calculations Required for Explicit Tracking of Subpopulations With and Without a Hard CVD Event History, Ages 40–89

Calculation Step	Baseline Calculations	Treatment Scenario Calculations
9. Estimate the end-of-year number of persons who experienced their first hard CVD event in the current year.	Multiply the uncalibrated estimate of first hard CVD event survivors (Step 5) by the minimum of the calibration factor value (Step 8 baseline) and 1 (i.e., min (factor value,1)) to ensure that the ASCVD model-based CVD incidence does not exceed the reported statistics-based CVD incidence.	
10. Estimate the number of CVD deaths among persons experiencing a first hard CVD event.	Multiply the uncalibrated estimate of the number of deaths among persons experiencing their first hard CVD event this year (Step 4) by the minimum of the calibration factor value (Step 8) and 1 (i.e., min (factor value,1)) to ensure that the ASCVD model-based CVD incidence does not exceed the reported statistics-based CVD incidence.	
11. Estimate the number of post-acute CVD deaths that occur within 6 years of the initial non-fatal MI or IS.	The post-acute, all-cause mortality in years 1–5 of the initial non-fatal MI/IS**, U.S. life table data, and U.S. general population CVD mortality data are combined with the number of first hard CVD event survivors (Step 9) to recurrently estimate CVD mortality. See Appendix B for further details.	
12. Estimate the baseline CVD mortality rate in the CVD subpopulation.	<p>Compute the baseline CVD mortality rate for subpopulations with a CVD event history, which is an important input for the treatment scenario life table calculations but is not reported in published statistics.</p> <p>This rate is estimated by subtracting the number of deaths among persons experiencing their first hard CVD event (Step 10) from the overall number of CVD deaths (Step 6) and dividing the result by the initial size of the CVD subpopulation (Step 1).</p>	Not applicable
13. Estimate next year’s CVD subpopulation and non-CVD subpopulation for the treatment scenario.	Not applicable	<p>The size of the next year’s subpopulation with a CVD event history is estimated by adding CVD incidence (Step 7) to the CVD population at the start of the year (Step 1) and subtracting the number of non-CVD deaths in the CVD subpopulation (Step 2) and the number of CVD deaths (Step 6).</p> <p>The size of the next year’s subpopulation without a CVD</p>

Table 3: Year-Specific Calculations Required for Explicit Tracking of Subpopulations With and Without a Hard CVD Event History, Ages 40–89

Calculation Step	Baseline Calculations	Treatment Scenario Calculations
		history is estimated by subtracting the CVD incidence (Step 7) and the number of non-CVD deaths in the non-CVD subpopulation (Step 2) from the non-CVD subpopulation in the beginning of the year (Step 1).

Notes:

* ASCVD-based estimates may be inconsistent with the recent CVD prevalence statistics. This is because (1) ASCVD events are a subset of all CVD events that may occur in the CVD population and (2) the ASCVD model is not a perfect fit to the recent prevalence data. Therefore, EPA calibrates raw ASCVD model-based predictions to the baseline CVD prevalence and mortality statistics at baseline.

** The recurrent estimates rely on non-CVD mortality and post-acute CVD mortality specific to the year since the initial event based on Thom et al. (2001) and Li et al. (2019).

Abbreviations: ASCVD – atherosclerotic cardiovascular disease, CVD – cardiovascular disease

Further details of the life table calculations are provided in Appendix B. The outputs of the life table calculations and application of the ASCVD model are the PWS-specific estimates of the annual number of persons experiencing their first non-fatal MI or IS event and the number of deaths among those who have experienced their first hard CVD event, at most, 6 years ago. Note that the ASCVD model does not predict risks separately by type of first hard CVD event (i.e., non-fatal MI, non-fatal IS, and fatal CVD). The distribution of these events by type is estimated as described in section 5.2 and integrated into the overall CVD impacts modeling.

5.2 Risk and Distribution of First Hard CVD Events

The first hard CVD event incidence estimates are generated by the Pooled Cohort ASCVD model (Goff et al., 2014). The ASCVD model is commonly used in clinical practice to estimate CVD risk for those between ages 40 and 80, as well as for overall population risk management (Lloyd-Jones et al., 2017). 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 MI, IS, congestive heart failure, percutaneous coronary intervention, coronary bypass surgery, or atrial fibrillation. The ASCVD model is a survival model that links predictor levels at the start of the 10-year follow-up period to the first hard CVD event incidence during the follow-up period; the modeling does not account for changes in CVD risk predictors over time.

Four large longitudinal community-based epidemiologic cohort studies were combined to develop a geographically and racially diverse dataset used for the ASCVD model estimation.¹⁵ The predictors of the ASCVD model include age, TC and HDLC concentrations, systolic blood pressure, current smoking, diagnosed diabetes, and whether the participant is undergoing

¹⁵ These studies include the Atherosclerosis Risk in Communities (ARIC) study (ARIC Investigators, 1989) and the Cardiovascular Health Study (Fried et al., 1991), along with applicable data from the Coronary Artery Risk Development in Young Adults (CARDIA) study (Friedman et al., 1988) and the Framingham Original and Offspring cohort data (D’Agostino et al., 2008).

treatment for high blood pressure. The model was fit separately to four population subgroups: non-Hispanic White females, non-Hispanic Black females, non-Hispanic White males, and non-Hispanic Black males. Although models for other race/ethnicity groups have not yet been developed, Goff et al. (2014) recommend that the model for non-Hispanic Whites be used for other race/ethnicity groups. EPA does not follow this recommendation in the development and parameterization of the CVD model for Hispanic, Asian American, and American Indian/Alaska Native people, and instead applies the model for non-Hispanic Blacks based on the ASCVD model validation relative to reported CVD prevalence and mortality statistics (EPA analysis based on Medical Expenditure Panel Surveys from 2010–2017), as described in Appendix B. The results of this validation exercise showed that the ASCVD model coefficients for the non-Hispanic Black model are more consistent with data on CVD prevalence and mortality for Hispanic and non-Hispanic other race subpopulations than the ASCVD model coefficients for the non-Hispanic White model. The all-cause and CVD mortality was obtained from CDC's National Vital Statistics System, whereas CVD prevalence was estimated using Agency for Healthcare Research and Quality survey data (see Appendix D for details). As explained in Appendix B, race/ethnicity and sex-specific CVD incidence consistent with these reported statistics was compared with the incidence estimated using the ASCVD model, where the baseline race/ethnicity- and sex-specific values for the ASCVD model predictors were obtained from CDC's public health surveys (see Appendix D for details).

The ASCVD model generates predictions of the 10-year probability of the first hard CVD event without differentiation across CVD event types. The specifics of annual first hard CVD event probability derivation, which is needed for the life table calculations in section 5.1, are provided in Appendix D. As is also detailed in Appendix D, EPA combined the Medical Expenditure Panel Survey (MEPS) 2010–2017 data and the Healthcare Cost and Utilization Project (HCUP) 2017 data to derive the ASCVD event distribution over the following event types: non-fatal MI, non-fatal IS, and fatal CVD events. The fatal CVD events include fatal MI, fatal IS, and other fatal CHD events. EPA used the MEPS data to identify the subpopulation of persons without a prior CVD event history and estimate the rate of new CVD events by type (i.e., MI, IS, and other CHD) in this subpopulation. The probabilities of in-hospital death for MI, IS, and other CHD were obtained from HCUP.

Table 4 shows the derived race/ethnicity-, sex-, and age group-specific distributions of first hard CVD events over the following event types: non-fatal MI, fatal MI, non-fatal IS, fatal IS, other non-fatal CHD, and other fatal CHD. For males, looking across race/ethnicity and age categories, the share of non-fatal MI events is 4.9% to 28%, the share of non-fatal IS events is 9.4% to 38%, and the share of other non-fatal CHD events is 44% to 78%. For females, across race/ethnicity and age categories, the share of non-fatal MI events is 6.4% to 19%, the share of non-fatal IS events is 8.7% to 29%, and the share of other non-fatal CHD events is 51% to 76%. For both sexes, shares of all fatal events increase with age. The share of fatal CVD events is largest for Hispanic and non-Hispanic other race subpopulations of both sexes. Table 4 also shows derived race/ethnicity-, sex-, and age group-specific distributions of first hard CVD events over ASCVD event types (i.e., non-fatal MI, non-fatal IS, and fatal CVD). Note that these distributions were re-normalized to sum to 100% after exclusion of other non-fatal CHD not predicted by the ASCVD model. The CVD model relies on the re-normalized distributions to allocate the total number of first hard CVD events predicted by the ASCVD model.

Table 4: Estimated Distribution of Fatal and Non-Fatal First Hard CVD Events Based on MEPS and HCUP Data

Sex	Age (in years)	Race/ Ethnicity	Non-Fatal MI (%)	Non-Fatal IS (%)	Other Non-Fatal CHD (%)	Fatal CVD Event (%)	Fatal IS (%)	Other Fatal CHD (%)
Distribution Over First Hard CVD Events								
Males	18–44	NH White	14	9.4	77	0.19	0.17	0
	45–64	NH White	16	15	69	0.39	0.34	0.44
	65–84	NH White	13	20	64	0.71	0.75	0.76
	85 or older	NH White	13	20	63	1.3	1.4	1.9
	18–44	NH Black	4.9	17	78	0.067	0.31	0
	45–64	NH Black	11	38	50	0.28	0.88	0.32
	65–84	NH Black	8.9	22	67	0.48	0.8	0.79
	85 or older	NH Black	8.5	21	66	0.87	1.5	2
	18–44	Hispanic	23	17	59	0.31	0.31	0
	45–64	Hispanic	19	29	51	0.48	0.67	0.32
	65–84	Hispanic	20	17	60	1.1	0.65	0.71
	85 or older	Hispanic	19	17	59	2	1.2	1.8
	18–44	NH Other	26	30	44	0.35	0.54	0
	45–64	NH Other	28	19	52	0.71	0.43	0.33
	65–84	NH Other	13	25	60	0.71	0.92	0.71
	85 or older	NH Other	12	24	59	1.3	1.7	1.8
Females	18–44	NH White	8.1	19	72	0.13	0.41	0
	45–64	NH White	6.9	20	72	0.2	0.55	0.54
	65–84	NH White	11	28	58	0.68	1.2	0.82
	85 or older	NH White	10	27	57	1.2	2.3	2.1
	18–44	NH Black	15	8.7	76	0.23	0.18	0
	45–64	NH Black	10	27	61	0.29	0.74	0.46
	65–84	NH Black	6.7	29	62	0.42	1.2	0.87
	85 or older	NH Black	6.4	28	61	0.76	2.3	2.2
	18–44	Hispanic	8.8	18	73	0.14	0.38	0
	45–64	Hispanic	13	27	59	0.37	0.73	0.45
	65–84	Hispanic	19	26	52	1.2	1.1	0.73
	85 or older	Hispanic	18	25	51	2.1	2.1	1.9
	18–44	NH Other	11	13	75	0.17	0.27	0
	45–64	NH Other	14	29	55	0.42	0.78	0.42
	65–84	NH Other	12	28	58	0.74	1.2	0.81
	85 or older	NH Other	11	27	56	1.3	2.3	2.1

Table 4: Estimated Distribution of Fatal and Non-Fatal First Hard CVD Events Based on MEPS and HCUP Data

Sex	Age (in years)	Race/ Ethnicity	Non-Fatal MI (%)	Non-Fatal IS (%)	Other Non-Fatal CHD (%)	Fatal CVD Event (%)	Fatal IS (%)	Other Fatal CHD (%)
Distribution Over First Hard CVD Event Categories Predicted by the ASCVD Model*								
Males	18–44	NH White	58	40	–	1.5		
	45–64	NH White	50	47	–	3.7		
	65–84	NH White	37	57	–	6.2		
	85 or older	NH White	34	53	–	13		
	18–44	NH Black	22	77	–	1.7		
	45–64	NH Black	22	75	–	2.9		
	65–84	NH Black	27	66	–	6.4		
	85 or older	NH Black	25	62	–	13		
	18–44	Hispanic	56	42	–	1.5		
	45–64	Hispanic	38	59	–	3.0		
	65–84	Hispanic	50	44	–	6.1		
	85 or older	Hispanic	47	41	–	12		
	18–44	NH Other	46	53	–	1.6		
	45–64	NH Other	58	39	–	3.1		
	65–84	NH Other	33	62	–	5.8		
	85 or older	NH Other	30	58	–	12		
Females	18–44	NH White	29	69	–	1.9		
	45–64	NH White	24	71	–	4.6		
	65–84	NH White	26	67	–	6.5		
	85 or older	NH White	24	63	–	13		
	18–44	NH Black	62	36	–	1.7		
	45–64	NH Black	26	70	–	3.9		
	65–84	NH Black	18	76	–	6.7		
	85 or older	NH Black	16	70	–	14		
	18–44	Hispanic	32	66	–	1.9		
	45–64	Hispanic	31	65	–	3.8		
	65–84	Hispanic	40	54	–	6.4		
	85 or older	Hispanic	37	51	–	12		
	18–44	NH Other	45	53	–	1.8		
	45–64	NH Other	32	64	–	3.6		
	65–84	NH Other	28	66	–	6.5		
	85 or older	NH Other	26	61	–	13		

Notes:

* The distribution is derived by (1) excluding the other non-fatal CHD category; (2) aggregating fatal MI, fatal IS, and other fatal CHD categories into the fatal CVD category; and (3) re-normalizing the data to sum to 100%.

Abbreviations: CHD – coronary heart disease; fatal CVD – includes fatal MI, fatal IS, and fatal other coronary heart disease events; HCUP – Healthcare Cost and Utilization Project; IS – ischemic stroke; MEPS – Medical Expenditure Panel Survey; MI – myocardial infarction; NH – non-Hispanic

5.3 Risk of Post-Acute CVD Mortality

Persons who have experienced non-fatal MI and non-fatal IS have an elevated risk of post-acute CVD mortality and morbidity (Roger et al., 2012). Studies focusing on secondary hard CVD events point to an elevated risk of these events among survivors of the first hard CVD event (e.g., Beatty et al., 2015; S. Li et al., 2019; Thom et al., 2001), but do not support the link between these risks and TC levels (Beatty et al., 2015). (See Appendix B for details.) Therefore, 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. The CVD model does not explicitly evaluate secondary CVD morbidity because available first non-fatal MI/IS valuation measures (e.g., O’Sullivan et al., 2011) incorporate incidence of these secondary events.

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). Because Thom et al. (2001) reports all-cause post-acute mortality rates, EPA adjusted these rates to exclude deaths from non-CVD causes. To this end, EPA used general population integer age- and sex-specific all-cause mortality from U.S. Life Tables, 2017 (Arias et al., 2019), U.S. CVD mortality rates (Centers for Disease Control and Prevention, 2020), and U.S. Life Tables Eliminating Certain Causes of Death, 1999–2000 (Arias et al., 2013). Appendix B provides additional estimation details. Although EPA was unable to identify comparable post-acute mortality statistics for non-fatal IS, an analysis of the Medicare population by S. Li et al. (2019) suggests that post-acute MI mortality is a reasonable approximation for post-acute IS mortality.¹⁶ Table 5 shows estimated post-acute CVD mortality rates for survivors of the first MI or IS at ages 40–65 that are used to parameterize the CVD model.

For survivors of the first hard CVD event at ages 66–89, EPA uses the results in S. Li et al. (2019) to estimate the number of post-acute CVD deaths for survivors of the first MI and IS events aged 66 years or older within 6 years of the initial event. Because S. Li et al. (2019) reports only all-cause post-acute mortality rates, EPA adjusted these rates to exclude deaths from non-CVD causes. Integer age- and sex-specific probability of death from non-CVD causes was derived from U.S. Life Tables, 2017 (Arias et al., 2019), U.S. CVD mortality rates (Centers for Disease Control and Prevention, 2020), and U.S. Life Tables Eliminating Certain Causes of Death, 1999–2000 (Arias et al., 2013). See Appendix B for additional estimation details. Table 5 shows estimated post-acute CVD mortality rates for survivors of the first MI and survivors of the first IS at ages 66–89 that are used to parameterize the CVD model.

¹⁶ For those age 65 or older, S. Li et al. (2019) have estimated the probability of death within 1 year after non-fatal IS to be 32.07% and the probability of death within 1 year after non-fatal MI to be 32.09%.

Table 5: Estimated Risk of Post-Acute CVD Mortality Following the First Non-Fatal Hard CVD Event

Type of First Non-Fatal Hard CVD Event	Demographic Group	Post-Acute CVD Mortality Rate per 100,000 by Integer Year Since the First Non-Fatal Hard CVD Event					
		0	1	2	3	4	5
Source: Thom et al. (2001)							
MI, IS*	Non-Hispanic White males aged 45–65 years	4,500	910	860	820	760	–
	Non-Hispanic Black** males aged 45–65 years	12,000	1,200	1,100	1,100	1,000	–
	Non-Hispanic White females aged 45–65 years	8,600	1,900	1,900	1,900	1,800	–
	Non-Hispanic Black** males aged 45–65 years	7,700	4,300	4,200	4,100	4,100	–
Source: S. Li et al. (2019)							
MI	Persons aged 66–89 years	27,000	11,000	9,600	9,040	8,600	8,040
IS	Persons aged 66–89 years	28,000	9,900	10,000	9,800	8,900	8,030

Notes:

* Thom et al. (2001) reported data for the first MI survivors only for aged 45–64 years. The CVD model applies these rates to both the first MI and first IS survivors.

** Estimates for non-Hispanic Whites are applied to other ethnic groups.

Abbreviations: IS – ischemic stroke (International Classification of Disease Ninth Revision [ICD9]=433, 434; International Classification of Disease Tenth Revision [ICD10]=I63), MI – myocardial infarction (ICD9=410; ICD10=I21)

6 Results

Table 6 presents reductions in serum PFOA/PFOS, total cholesterol, and CVD morbidity and mortality at the hypothetical PWS corresponding to an illustrative treatment threshold of 0.07 µg/L PFOA/PFOS combined, estimated to occur overall and within each of the eight decades of the evaluation period from 2023 to 2104. The table also shows the total number of person-years lived by individuals without a CVD event history aged 40 years or older at baseline to provide a reference for the affected population size and for the treatment scenario to illustrate the longer term impact of CVD risk reductions.¹⁷ The baseline survival and CVD risk dynamics result in the slightly declining number of person-years lived by the affected population during the evaluation period from 427.70 thousand in the first decade to 392.24 thousand in the last evaluation decade. Under the treatment scenario, CVD risk reductions over time lead to larger non-CVD populations later in the evaluation period compared with the baseline scenario.

¹⁷ EPA uses person-years to represent the size of the affected population (i.e., persons without a CVD event history age 40 years or older) in the CVD analysis. This is because the CVD analysis is a prospective evaluation that follows the affected population over time, as individuals without a CVD history join the population without CVD history eligible for first hard CVD event estimation at age 40 and leave this population at death or by moving to the CVD population. Person-years are commonly used in prospective evaluations. This metric accounts for both the number of people in the evaluation and the amount of time each person spends in the evaluation. For example, a cohort of 100 persons without a CVD history followed for 2 years, with half of the individuals leaving the non-CVD population at the end of the first year, would contain 150 person-years of data.

The average reductions in concentrations of serum PFOA/PFOS and TC increase as the later-born cohorts with longer experiences related to the reduction of PFOA and PFOS in drinking water start to dominate the affected population. In the first evaluation decade, average reductions in serum PFOA, serum PFOS, and TC are 2.56 ng/mL, 2.08 ng/mL, and 4.19 mg/dL, respectively. In the last evaluation decade, average reductions in serum PFOA, serum PFOS, and TC are 7.04 ng/mL, 6.60 ng/mL, and 10.94 mg/dL, respectively.

Table 6 presents two metrics of the overall health effects by evaluation decade and over the entire analysis period for the hypothetical PWS—total and annual average number of cases avoided. These metrics are reported for each health effect type (i.e., first non-fatal MI, first non-fatal IS, acute CVD mortality, and post-acute CVD mortality among MI and IS survivors). EPA estimated that during the evaluation period from 2023 to 2104, the example treatment scenario would prevent 232.39 cases of the first non-fatal MI, 350.74 cases of the first non-fatal IS, 31.19 cases of premature acute mortality associated with first CVD events, and 105.42 cases of premature CVD mortality occurring among survivors of the first MI/IS.

Table 6 and Figure 4 also illustrate the dynamics in the number of avoided adverse health effects at the hypothetical PWS over time and by the health effect type. Both health impact metrics (i.e., total and annual average) show similar patterns over time. The lowest effect magnitude is seen in the first evaluation decade from 2023 to 2034 (when the treatment scenario is being phased in and affected cohorts experience TC reductions for a relatively short time). The peak effect magnitude occurs during the second evaluation decade from 2035 to 2045 and declines thereafter until a steady state is reached in 2065 to 2074. The initial surge in the health effect magnitude with subsequent dampening occurs because the annual number of first CVD events is a product of the first CVD event risk and the size of the population without a prior CVD event history. The first CVD event risk is always lower under the treatment scenario, which over time leads to a larger non-CVD population size. Over a longer time horizon, this leads to dampening of the overall magnitude of CVD health effects avoided by the treatment scenario relative to the baseline scenario.

Table 6: Treatment Scenario-Related Reductions in Serum PFOA/PFOS, Total Cholesterol, and CVD Morbidity and Mortality at Hypothetical PWS

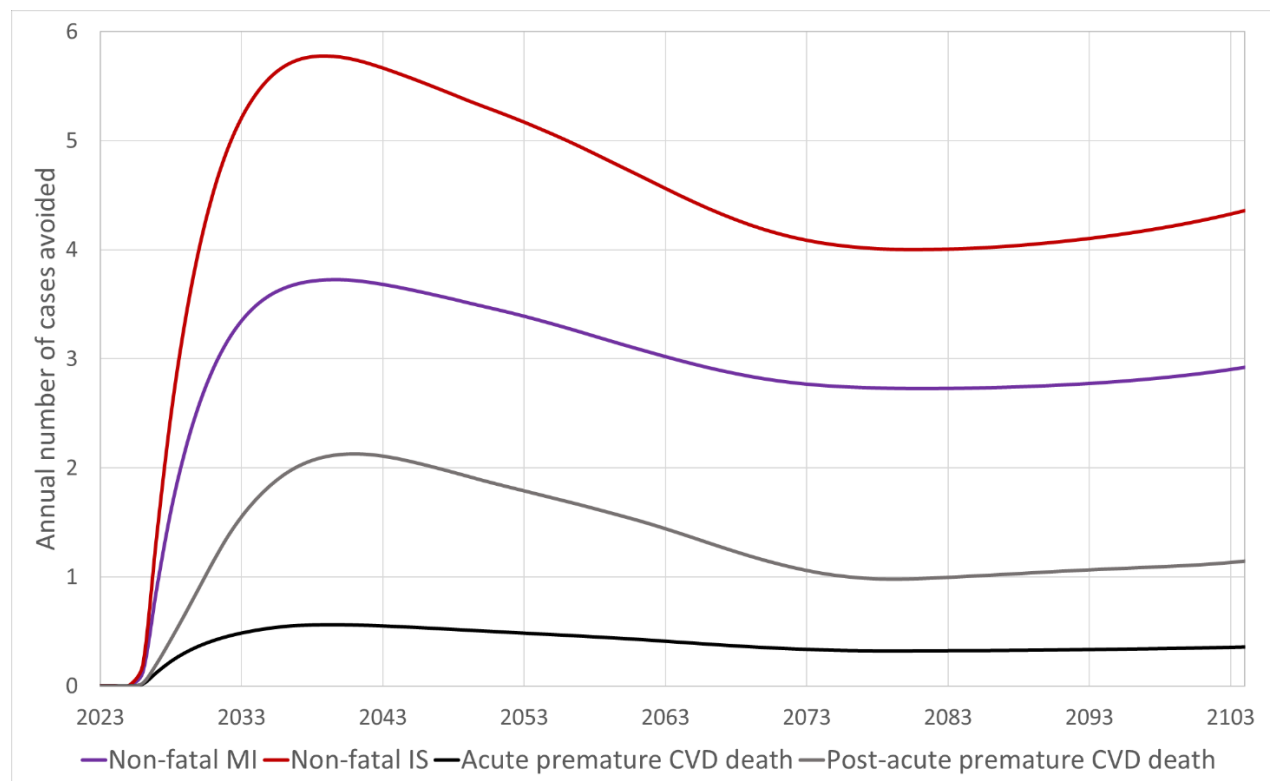
Decade	Person-Years Lived by the Affected Population (in thousands)		Average Reduction in Serum Concentration*			Total Reduction in Cases				Average Annual Reduction in Cases*			
	Baseline	Treatment Scenario	PFOA (ng/mL)	PFOS (ng/mL)	TC (mg/dL)	Non-Fatal MI	Non-Fatal IS	Acute Premature CVD Deaths	Post-Acute Premature CVD Deaths	Non-Fatal MI	Non-Fatal IS	Acute Premature CVD Deaths	Post-Acute Premature CVD Deaths
2023–2034	427.70	427.87	2.56	2.08	4.19	16.81	26.10	2.40	6.30	1.40	2.17	0.20	0.53
2035–2044	443.92	445.42	7.47	6.64	12.28	40.33	62.46	6.05	22.25	4.03	6.25	0.61	2.23
2045–2054	397.64	400.12	7.08	6.49	11.66	34.97	53.44	5.10	19.08	3.50	5.34	0.51	1.91
2055–2064	388.99	392.08	7.09	6.53	11.68	31.50	47.81	4.39	15.70	3.15	4.78	0.44	1.57
2065–2074	377.86	381.12	7.35	6.78	12.10	28.37	42.22	3.59	11.82	2.84	4.22	0.36	1.18
2075–2084	371.74	374.88	7.62	7.08	12.55	27.32	40.11	3.24	9.93	2.73	4.01	0.32	0.99
2085–2094	377.12	380.14	7.77	7.26	12.80	27.53	40.59	3.30	10.42	2.75	4.06	0.33	1.04
2095–2104	392.24	395.22	7.04	6.60	11.60	25.56	38.01	3.11	9.92	2.56	3.80	0.31	0.99
Total Evaluation Period	3,177.21	3,196.84	6.64	6.08	10.94	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

Figure 4: Annual Treatment Scenario-Related Reductions in CVD Incidence and Premature CVD Mortality at Hypothetical PWS.



Abbreviations: CVD – cardiovascular disease, IS – ischemic stroke, MI – myocardial infarction

7 Limitations and Uncertainty

Table 7 summarizes the principal limitations and sources of uncertainties associated with the estimation of avoided cases of CVD events from reductions in exposure to PFOA/PFOS in drinking water. There are several sources of CVD model uncertainty that can be analyzed quantitatively; Appendix E contains the proposed uncertainty analysis approach.

Table 7: Limitations and Uncertainties in the CVD Analysis		
Uncertainty/Assumption	Effect on Estimate	Details
The scope of the analysis does not include intra or international migration throughout the evaluation period.	Uncertain	Throughout the analysis period people may migrate from one place to another. If persons migrate to locations with larger decreases in treatment scenario PFOA/PFOS, EPA would be underestimating the impacts. The opposite is true if persons migrate to locations with smaller decreases in treatment scenario PFOA/PFOS.
The analysis assumes the same removal efficiency for both PFOA and PFOS.	Underestimate	The capacity of granular activated carbon and ion exchange treatment media for PFOS is greater than for PFOA (Boodoo, 2018; McNamara et al.,

Table 7: Limitations and Uncertainties in the CVD Analysis

Uncertainty/Assumption	Effect on Estimate	Details
		2018; Zaggia et al., 2016). The capacity of the treatment media determines how frequently the media must be replaced to maintain a given removal efficiency, among other factors such as source water characteristics. A treatment system with a media replacement frequency designed to achieve 90% removal of PFOA should maintain a higher removal efficiency for PFOS. EPA's assumption of equal removal efficiency for both PFOA and PFOS means that PFOS exposure reductions are likely underestimated and thus the risk reduction is also likely underestimated.
The analysis assumes that there is no lag between changes in serum PFOA/PFOS concentrations and changes in TC. Likewise, the analysis assumes that there is no lag between changes in TC and changes in CVD risk.	Overestimate	The studies estimating the link between serum PFOA/PFOS and TC and the ASCVD model are not dynamic, and hence do not provide insights into whether TC may respond gradually to changes in serum PFOA/PFOS and/or if CVD risk may respond gradually to changes in TC. The analysis assumes immediate adjustment, which may overestimate impacts to the exposed population. Note, however, that reductions in TC and CVD risk do not instantaneously follow the reductions in PFOA/PFOS drinking water concentrations, because the reductions in serum PFOA/PFOS are gradual, as predicted by the PK model.
The derivation of PFOA/PFOS exposure-response functions for the relationship between PFOA/PFOS serum and TC levels assumes that the six studies used in meta-analysis capture the majority of PFOA/PFOS effects on serum TC levels.	Uncertain	The exposure-response function was developed based on six general population studies with high-quality data and clearly defined serum PFAS-TC level relationships. These studies may not represent all possible relationships between PFOA/PFOS and serum TC levels.
The derivation of PFOA/PFOS exposure-response functions for the relationship between PFOA/PFOS serum and TC assumes that there are no threshold serum concentrations below which effects do not occur.	Uncertain	The exposure-response function assumes that the effects of PFOA and PFOS on serum TC are independent and that there are no threshold serum concentrations below which effects do not occur.
The derivation of PFOA/PFOS exposure-response functions for the relationship between PFOA/PFOS serum and TC assumes that the effects on serum TC are independent.	Uncertain	The exposure-response function assumes that the effects of PFOA and PFOS on serum TC are independent.

Table 7: Limitations and Uncertainties in the CVD Analysis

Uncertainty/Assumption	Effect on Estimate	Details
The analysis does not account for evidence linking PFOA/PFOS exposure to other cardiovascular outcomes, such as systolic blood pressure.	Underestimate	PFOA/PFOS exposure has been linked to other cardiovascular outcomes, such as systolic blood pressure and hypertension (Liao et al., 2020; U.S. EPA, 2021d; U.S. EPA, 2021e). Systolic blood pressure is another predictor used by the ASCVD model. In this analysis, systolic blood pressure is held at the baseline population average levels. Given that systolic blood pressure is significantly and positively associated with the risk of first hard CVD event in the ASCVD model (see Appendix B), EPA's analysis underestimates the magnitude of PFOA/PFOS exposure impact on CVD risk.
The ASCVD analysis assumes that person's TC level history does not have an impact on the TC decrease-related reductions in first hard CVD event risk.	Uncertain	The ASCVD model links TC levels at the start of the 10-year follow-up period to first hard CVD event incidence during the follow-up period. The modeling does not account for TC changes over time, which could have an impact on the CVD event risk.
The analysis uses the ASCVD model developed for non-Hispanic Blacks to assess potential CVD risks for race/ethnicity groups other than non-Hispanic Blacks and non-Hispanic Whites.	Uncertain	The ASCVD model documentation encourages the use of equations for non-Hispanic Whites for other race/ethnicity categories, specifying that estimated risks may be overestimates, especially for Hispanic and Asian Americans. EPA's model validation analysis detailed in Appendix B shows that the non-Hispanic Black model is a better fit for these race/ethnicity groups. However, the ultimate impact of this assumption is uncertain.
EPA uses the fraction of the population who smokes and has diabetes as inputs into the ASCVD model.	Underestimate	The ASCVD model uses binary values to indicate whether a person is a current smoker or has diabetes. EPA simplifies calculations by using the percentage of the population who smokes and has diabetes as inputs to the ASCVD model. EPA has implemented a targeted evaluation of the effect of this assumption and confirmed that this simplification likely underestimates impacts by approximately 5% to 10%, depending on the age group, due to the non-linearity of the estimated model.
The analysis assumes that the threshold for high blood pressure is a systolic/diastolic measurement of 140/90.	Underestimate	In November 2017, the threshold defined for high blood pressure was reduced to 130/80. The analysis relies on high blood pressure prevalence data that is based on NHANES surveys from 2011 to 2014 and treated, untreated, and normal blood pressure measurements from 2001 to 2008, therefore, EPA adheres to the pre-2017 threshold. The ASCVD model was also developed

Table 7: Limitations and Uncertainties in the CVD Analysis

Uncertainty/Assumption	Effect on Estimate	Details
		prior to the change in high blood pressure definition. Adhering to the pre-2017 threshold may affect the number of people sorted into the high blood pressure population category, potentially underestimating CVD risk.
The analysis assumes independence among the prevalence of high blood pressure, smoking, and diabetes.	Overestimate	Smoking and high blood pressure are often related, and smoking is a risk factor for Type 2 diabetes. Assuming independence among the prevalence of high blood pressure, smoking, and diabetes may result in overestimated CVD risk impacts.
The analysis assumes that deaths from causes other than hard CVD events occur first.	Underestimate	By assuming that deaths from causes other than hard CVD events occur first, EPA underestimates the eligible population (e.g., population without CVD history) evaluated for the first hard CVD event estimation.
The analysis does not account for survivors of first hard CVD events that are neither MI nor IS. The analysis does not account for persons who were younger than 40 years or older than 89 years at the time of their first hard CVD event.	Underestimate	The ASCVD risk captures non-fatal MI, non-fatal IS, and fatal CVD; however, it does not capture other non-fatal CHD. The ASCVD model can be used to predict the annual probability of a first hard CVD event for persons aged 40–89 years. The prevalence of CVD history before age 40 is low (<7% based on estimates from the Medical Expenditure Panel Survey) and likely includes persons whose CVD arises from genetic factors (Zhang et al., 2019). Early life PFAS exposures and TC are inconclusively associated for PFOA and positively associated for PFOS (U.S. EPA, 2021d; U.S. EPA, 2021e). TC later in life is highly positively correlated with early TC as seen in Pletcher et al. (2016) and Zhang et al. (2019). This analysis does not directly capture effects of early life increases in TC due to PFAS exposures. The analysis does capture the effects of early life TC indirectly to the extent that early and later in life TC levels are correlated.
The analysis does not capture post-acute CVD mortality beyond 5 years of the first MI or IS for those ages 40–65 at the time of the initial event nor does it capture post-acute CVD mortality beyond 6 years of the first MI or IS for those ages 66–89 at the time of the initial event.	Underestimate	The risk of post-acute CVD mortality was estimated based on Thom et al. (2001) for those aged 40–65 years and on S. Li et al. (2019) for those older than 65 years. Neither study reported post-acute mortality information for a longer follow-up period. The reported information does not support complete post-acute mortality risk elimination beyond the longest follow-up period.
The analysis assumes that post-acute CVD mortality for survivors of IS at ages 40–65 is the same as	Uncertain	Post-acute mortality estimates for IS and MI were very close in the Medicare population (S. Li et al., 2019). For those aged 65 years or older, S. Li et al.

Table 7: Limitations and Uncertainties in the CVD Analysis

Uncertainty/Assumption	Effect on Estimate	Details
post-acute CVD mortality for survivors of MI at ages 40–65.		(2019) have estimated the probability of death within 1 year after non-fatal IS to be 32.07% and the probability of death within 1 year after non-fatal MI to be 32.09%. Therefore, reliance on the post-acute mortality for MI to approximate the same for stroke is reasonable.
The analysis relies on projected population estimates and historical data to model long-term effects.	Uncertain	Projected population estimates are based on expected trends in migration and job opportunities. These trends may change over time given changes in migration trends, economic trends, and other factors. Using the most recently available population projections may result in an over- or underestimate of future health risk reductions. Furthermore, EPA uses present-day information on life expectancy, disease, environmental exposure, and other factors, which are likely to change in the future.
The analysis does not include the impacts of COVID-19 on future population health and economic growth.	Uncertain	Cardiovascular impacts of the COVID-19 pandemic (Long et al., 2020; Sattar et al., 2020) will likely increase the prevalence of persons with CVD history, thereby reducing the size of the non-CVD population without CVD history evaluated in risk reduction calculations and increasing the size of the population that EPA cannot estimate risks for with the ASCVD model. Individuals affected by COVID-19 may be more vulnerable to a first hard CVD event.

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