

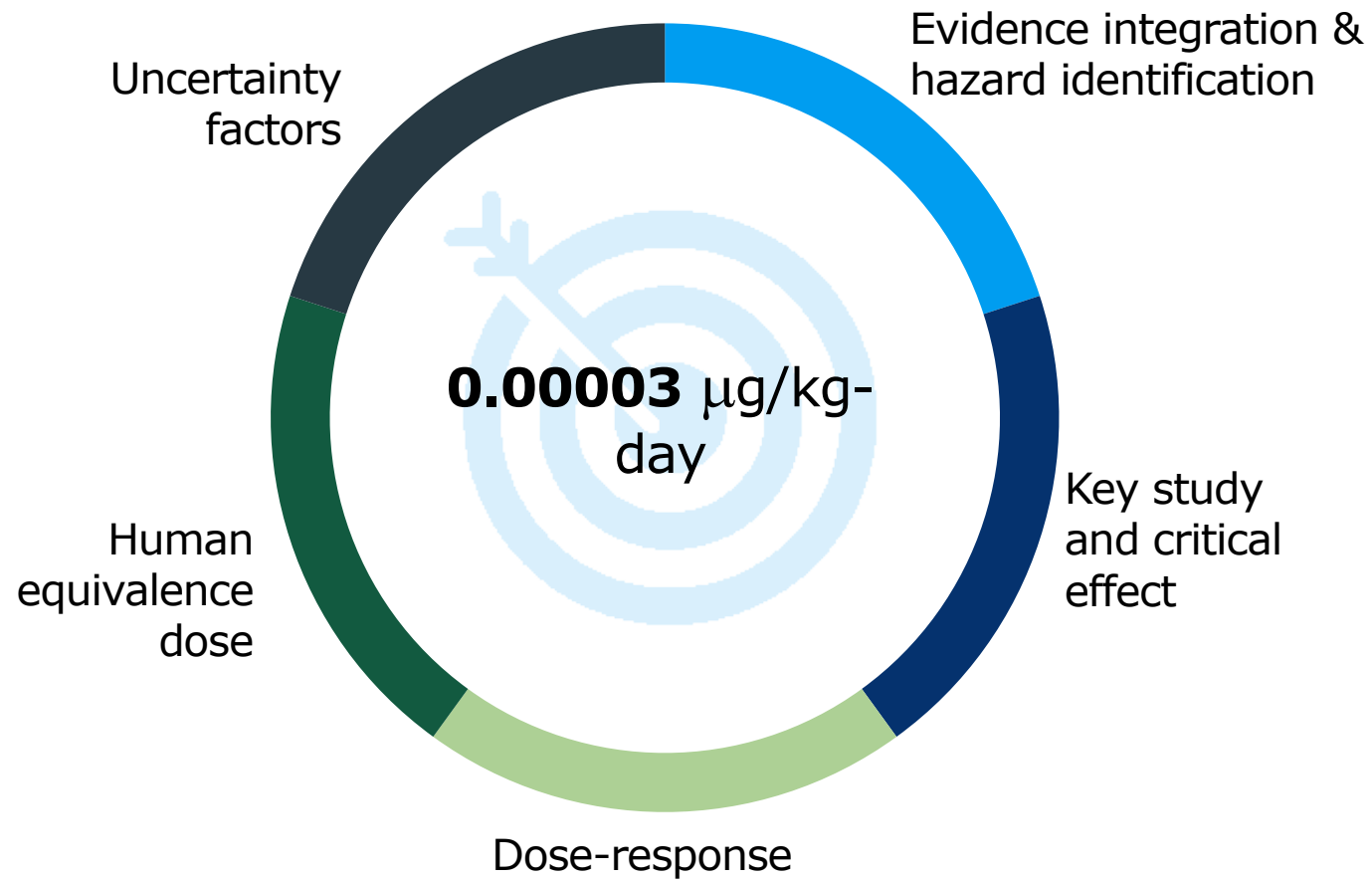
Integrating Evidence for Dose-Response Assessment in PFAS Regulatory Risk Assessment

Linda Dell and Harvey Clewell

Session E8. PFAS Human Health
and Ecological Risk Assessment
and Toxicity

June 6, 2024

Decision points for deriving toxicity values



Associations reported in epidemiologic studies of PFOA and PFOS

Clinical effects

- Increases in total cholesterol
- Decreases in birth weight
- Decreases in antibody titers (IgG) (decreases in antibody response to vaccines)
- Increases in liver enzymes

Expected adverse effects

- Cardiovascular disease (*negative or null associations*)
- Risk of low birth weight (<2500 g) (*null associations*)
- Increased frequency or duration of infectious diseases (*mix of positive and no associations*)
- Liver disease (*few studies, inconsistent associations*)

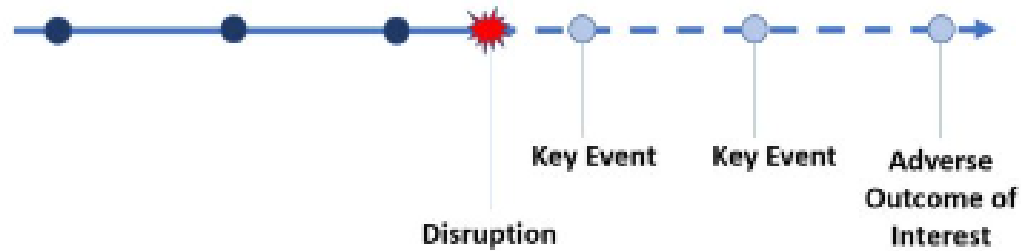
The most sensitive effects are related to biomarkers or birth weight when groups with higher blood concentrations are compared to groups with lower blood concentrations

General issues with epidemiological studies of PFOA and PFOS

- Most studies are cross-sectional studies
 - Measure biomarkers of exposure at the same time as biomarkers of effect
 - Report statistical associations between differences in levels of a clinical measure in those with higher blood concentrations compared to lower blood concentrations
- Most studies are of the general population
 - Exposure to unidentified (or ill-defined) sources of PFAS
- Potential for pharmacokinetic bias
 - i.e., physiological process (sometimes disease status) affects the PFOA/PFOS serum concentrations

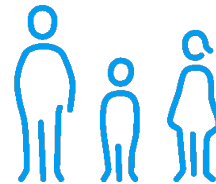
Some of the limitations of the existing epidemiological studies are overlooked

Biological Pathway



Mode of action analysis

- What is the relevance of experimental animal studies to humans?
- Are the observed associations in epidemiological studies causal?
- Are the associations biologically plausible?



Source of Biological Pathways figure: USEPA. <https://www.epa.gov/chemical-research/adverse-outcome-pathways>

Mode of action considerations are different for animal studies and human studies

Challenge: Mode of action

- PFOA (and PFOS) is mistaken by the body for a medium-length essential fatty acid, but it is resistant to metabolism.
- Active uptake of PFOA from the GI tract results in high oral bioavailability, and active resorption of PFOA excreted in the bile and urine limits clearance.
- PFOA disrupts lipid homeostasis at sufficiently high concentrations in animal studies
- Due to the complexity of the active control of PFOA pharmacokinetics associated with lipid homeostasis, it may be that human interindividual differences in lipid homeostasis at low human exposures is significant (Andersen et al. 2021)

(Adapted from Harvey Clewell, 2022. Society of Toxicology Annual meeting)

What makes
PFOA different?

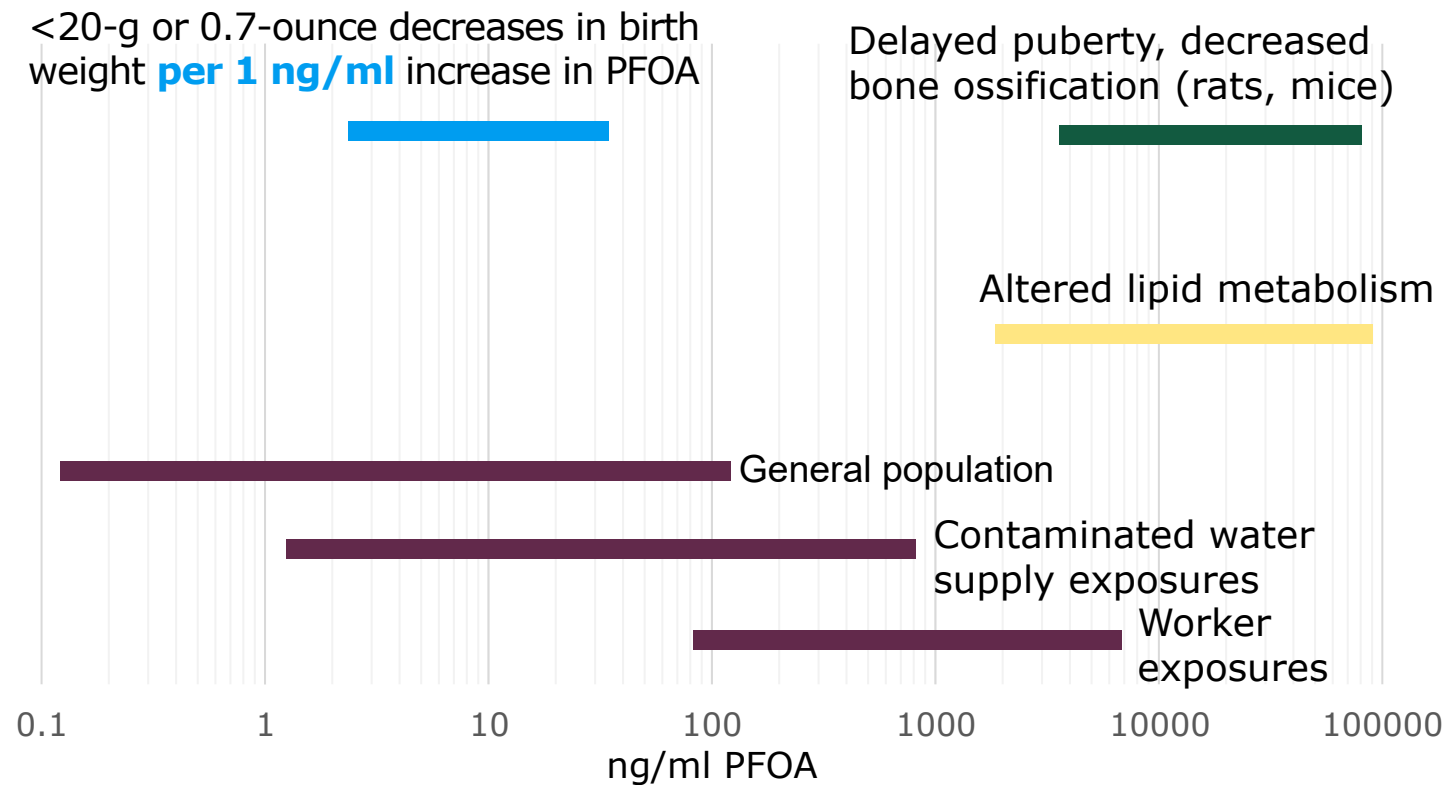
Potential mode(s) of action for PFOA

- Disruption of lipid homeostasis in the liver at sufficiently high concentrations
 - Activation of nuclear receptors including PPAR α , PPAR γ , CAR, PXR, FXR
 - Activation of these receptors occur at concentrations on the order of 10 – 100 $\mu\text{g/mL}$ (ppm)
- Misincorporation of PFOA in lipid membranes resulting in dysfunction
 - In vitro exposure of human peripheral blood mononuclear cells to 1, 10, or 100 μM showed clear effects on immune cells only at the highest concentration (40 $\mu\text{g/mL}$)

Mode(s) of action the observed effects in animals and/or at high exposure concentrations are reasonably understood

The MOA for observed effects at blood concentrations in general population are not understood

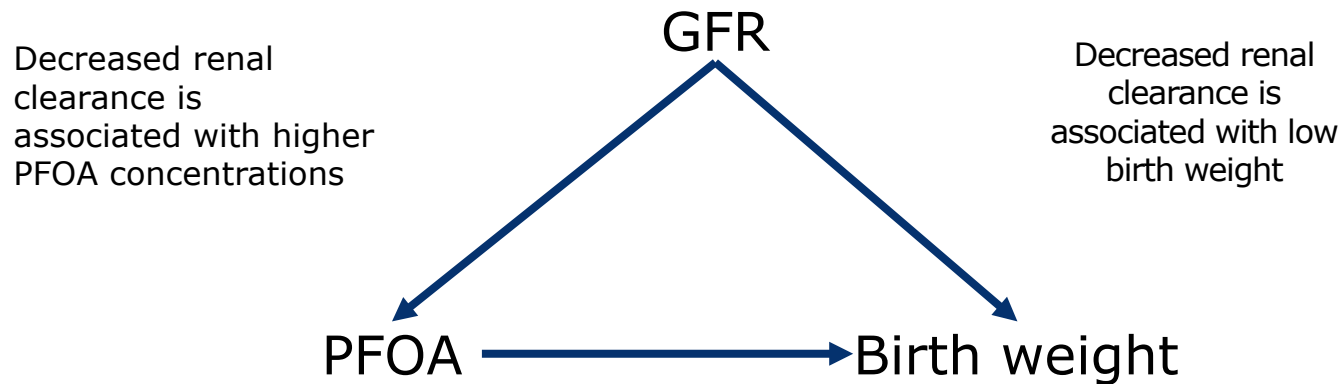
Range of exposures and developmental effects in humans and animals



Adverse effects seen in humans at much lower PFOA concentrations than those reported in animals

Adapted from Fig 3 in: Andersen et al. 2021. Using quantitative modeling tools to assess pharmacokinetic bias in epidemiological studies showing associations between biomarkers and health outcomes at low exposures. *Environ Res.* 197:111183.

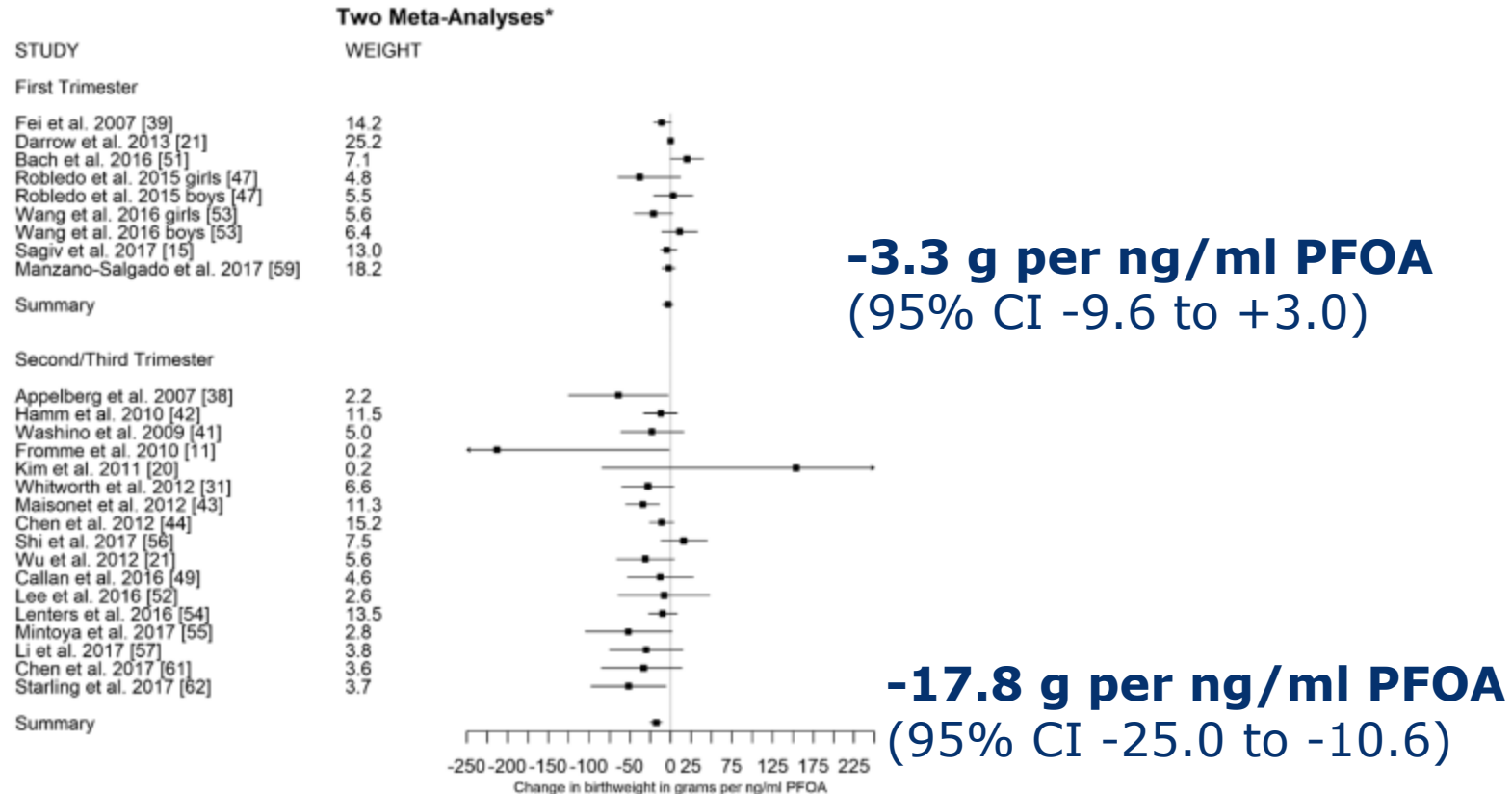
Challenge: Are epidemiological associations causal or due to confounding?



Women with decreased filtration during pregnancy are more likely to give birth to infants with lower birth weights and are also more likely to have higher concentrations of PFOA during the third trimester of pregnancy, both due to the altered filtration rate.

Physiological bias (a.k.a., pharmacokinetic bias) may explain associations with clinical measures at PFAS blood concentrations seen in the general population

Epidemiological associations of PFOA and decreases in birth weight



Source: Steenland et al. 2018. Serum Perfluorooctanoic Acid and Birthweight: An Updated Meta-analysis With Bias Analysis. Epidemiology 29: 765-776.

Null association with birth weight when maternal serum sampled before or in first trimester

Small decrease in birth weight when maternal serum sampled late in pregnancy

Can pharmacokinetic bias explain associations between PFAS and decreased vaccine response?

- Zhang et al. (2023) reported associations between total PFAS and decreased response to rubella and mumps vaccine in children with lower folate serum concentrations
 - In children with higher folate serum levels, no association is seen between PFAS and response to rubella and mumps vaccine
- Folate deficiency is known to impair cell-mediated immune response.
 - Humans and animals with folate deficiency have shown decreased T lymphocyte response (Dhur et al. 1991)
- OATP1B1 also plays an important role in the uptake of folate (Trevino et 2009) and PFOA

Hypothesis: Is the association between PFAS and decreased vaccine response confounded by competitive inhibition of transport?

Time for a reality check...

Critical effect	Study population	Serum concentrations	Reference
Decreased vaccine response	537 children, born 1997-2000, Faroe Islands (408 children followed to age 7, 2007)	GM PFOA (age 5), 4.06 ng/mL GM PFOS (age 5), 16.7 ng/mL	Budtz-Jørgensen and Grandjean 2018; Grandjean et al. 2012
Increased total cholesterol	8,814 adults, NHANES, United States, 2003-2014	Mean PFOA, 3.7 ng/mL Mean PFOS, 15.6 ng/mL	Dong et al. 2021
Decreased birth weight	1533 infants, prenatal exposure, Sweden, 2007-2010	Maternal median PFOA, 1.61 ng/mL Maternal median PFOS, 5.38 ng/mL	Wikström et al. 2020

The critical effects from epidemiological studies occur at exposure concentrations seen in the general population (0.1 to 30 ng/mL PFOS and <1 to 10 ng/mL PFOA)

Concentrations are consistent with those seen in the general population

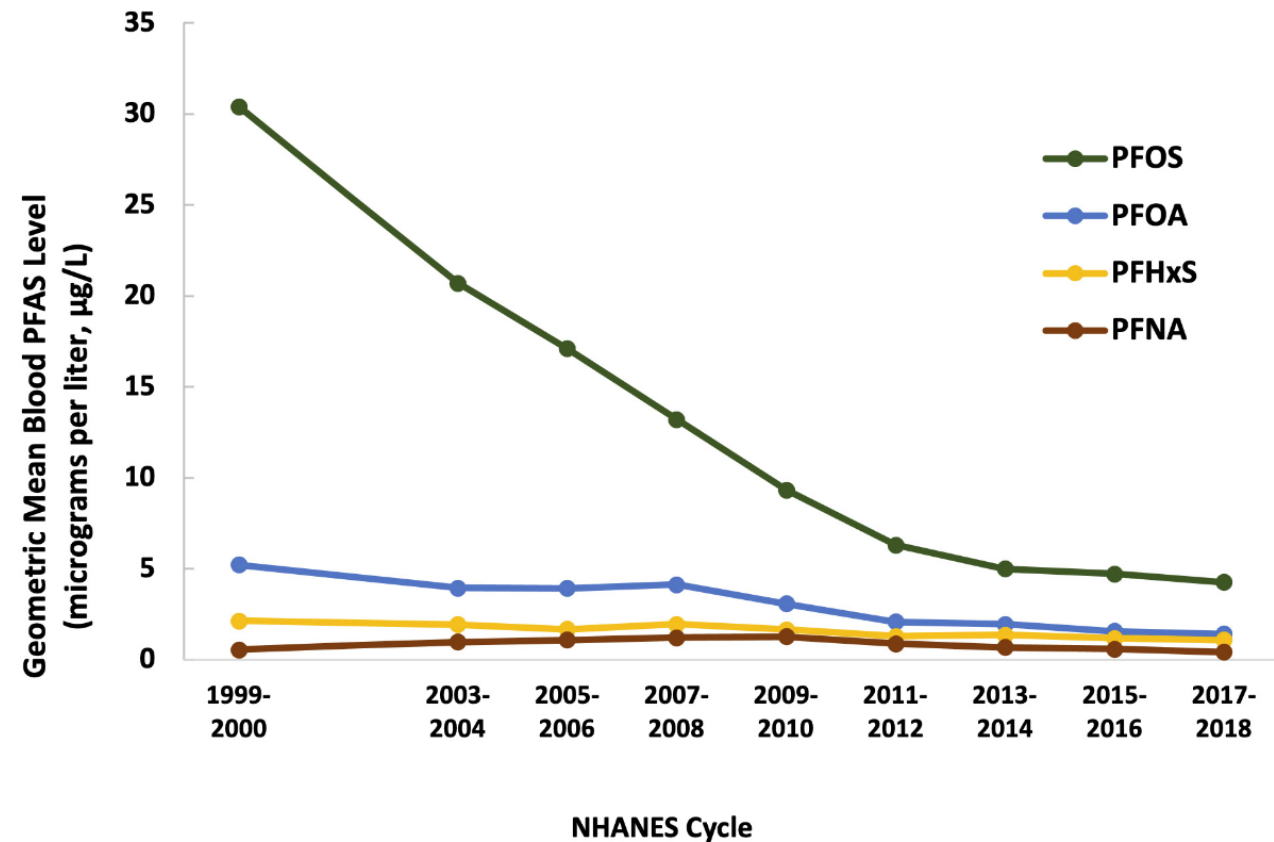
GM	1974*	1989*	2001†
PFOS	30.1	33.3	34.9
PFOA	2.1	5.5	4.5
PFHxS	1.5	2.5	1.9

Sources:

*Olsen et al. 2005; 178 samples, community health study participants, Washington County, MD

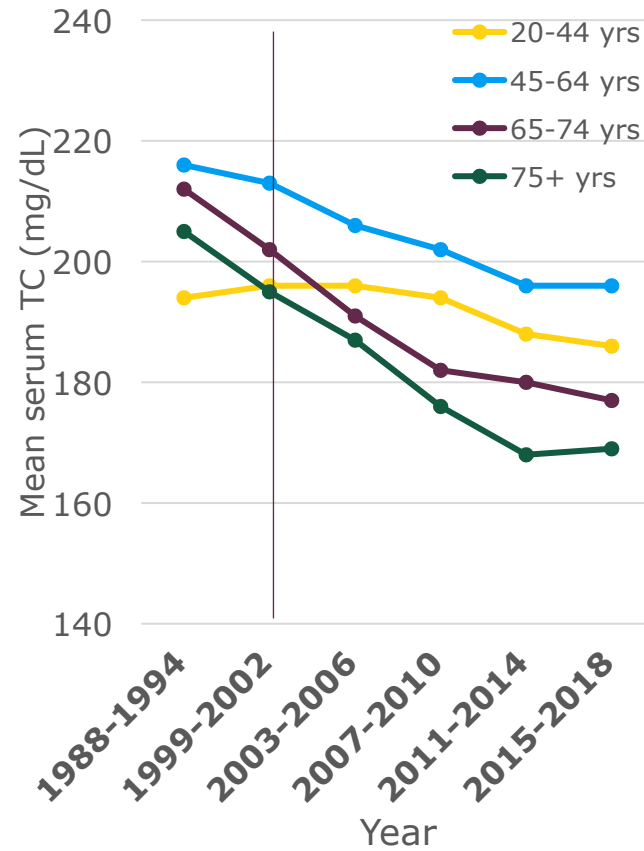
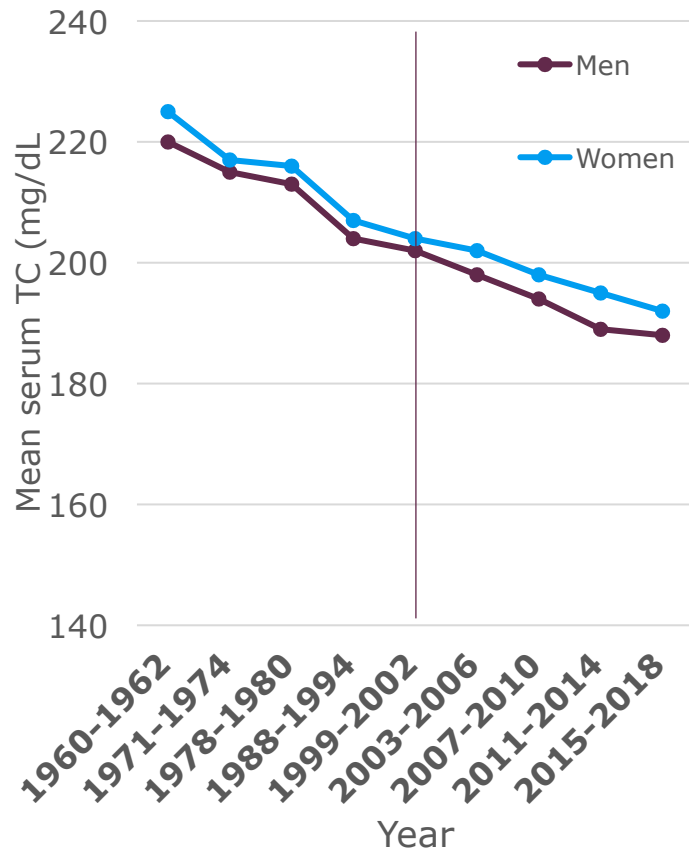
† Olsen et al. 2003; 108 samples, blood donors, Hagerstown, MD

Blood concentrations of the most common PFAS in the US, 1999-2018



Source: Centers for Disease Control and Prevention. National Report on Human Exposure to Environmental Chemicals, Biomonitoring Data Tables for Environmental Chemicals. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

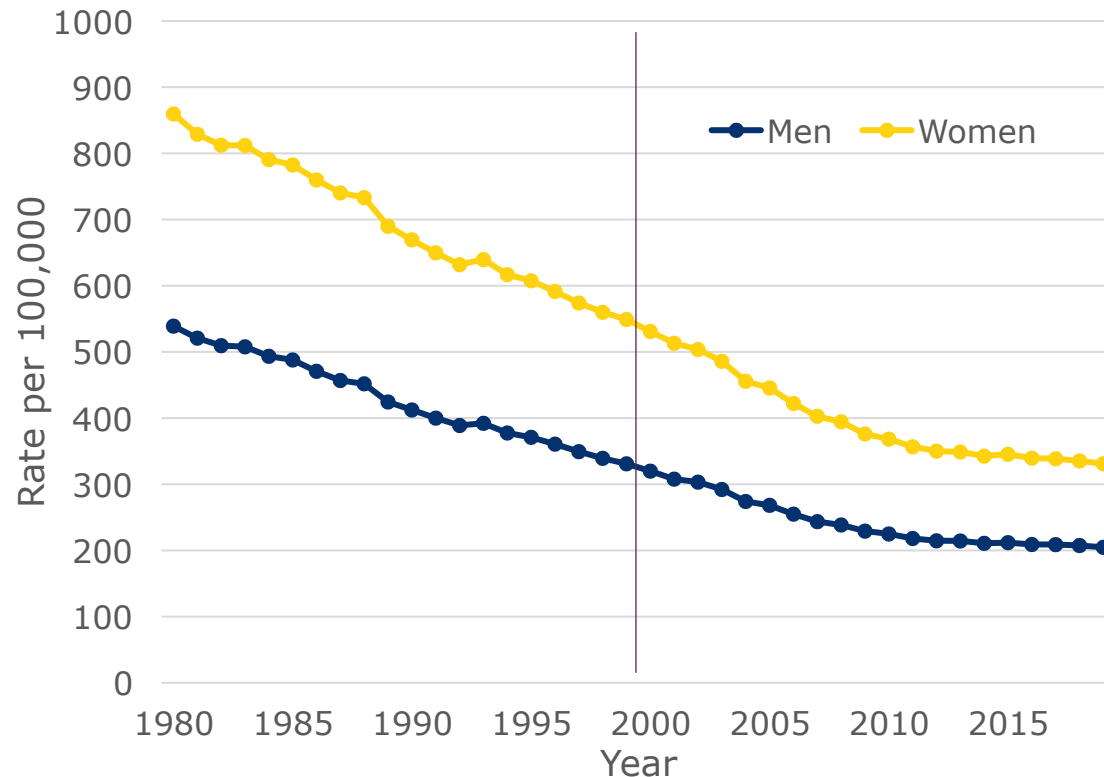
Average total cholesterol in the United States, adults 20 years and older, 1988-2018



Cholesterol levels have decreased since the early 1960s because of changes in lifestyle, diet, and introduction of cholesterol lowering medications

Source: National Center for Health Statistics. Health, United States, 2019: Table 23. Cholesterol among adults aged 20 and over. Hyattsville, MD. 2019. Available from: <https://www.cdc.gov/nchs/hus/data-finder.htm>

Age-adjusted cardiovascular disease mortality in the United States, 1980-2019

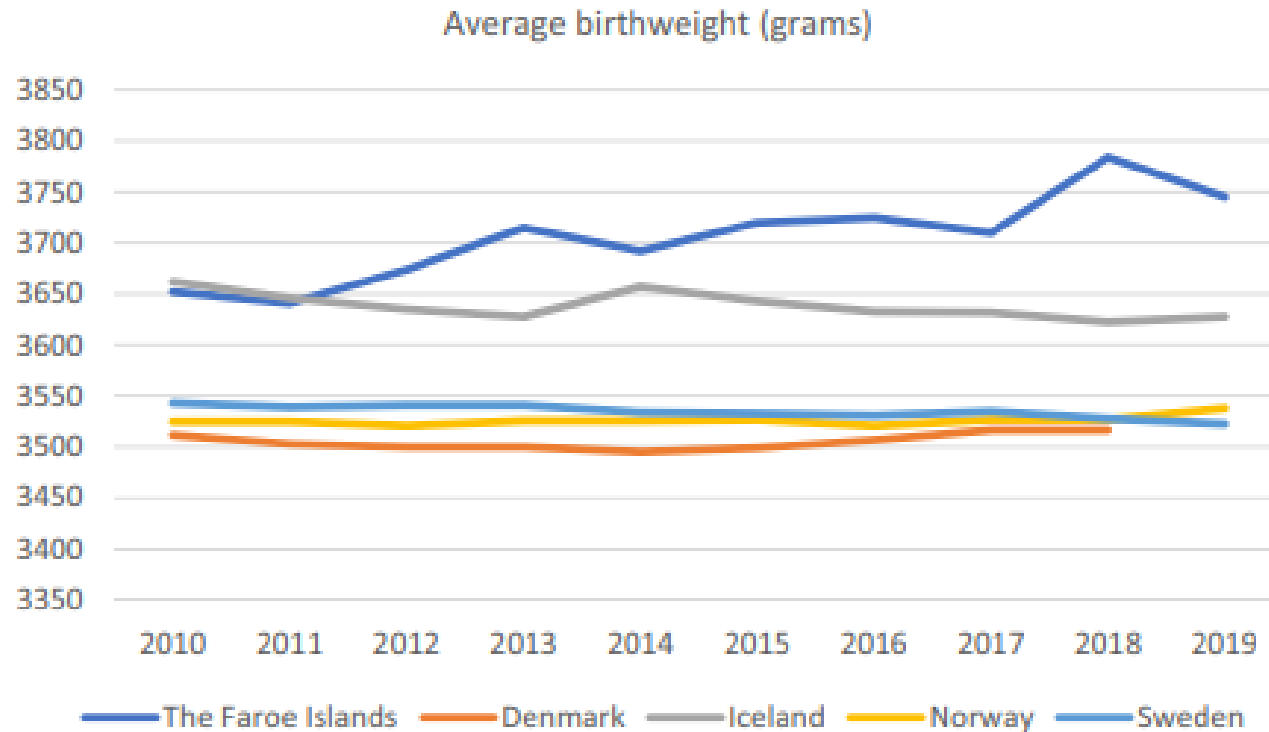


SOURCE: National Center for Health Statistics, National Vital Statistics System; Grove RD, Hetzel AM. Vital statistics rates in the United States, 1940–1960. 1968; numerator data from National Vital Statistics System, annual public-use Mortality Files; denominator data from U.S. Census Bureau national population estimates; and Xu JQ, Murphy SL, Kochanek KD, Arias E. Deaths: Final data for 2019. National Vital Statistics Reports; vol 70 no 8. Hyattsville, MD: National Center for Health Statistics. 2021. Available from: <https://www.cdc.gov/nchs/data/nvsr/nvsr70/nvsr70-08-508.pdf>. See Sources and Definitions, National Vital Statistics System (NVSS).

Mortality rates from cardiovascular diseases have decreased since 1980 (and earlier)

Average birth weight in Scandinavian countries, 2010-2019

AOGS
Acta Obstet Gynecol Scand
511



Source: Olsen et al. 2023, *Acta Obstet Gynecol Scand*.

Clinical relevance
of small
decreases in birth
weight is
uncertain

The average birth weight of 10,132 liveborn infants delivered in the Faroes during the period 1969-81 was 3610 grams, which is the highest average weight reported by 33 countries from which we were able to obtain information.

Olsen and Joenson, 1985

Conclusions from epidemiological studies

- Epidemiological studies have shown associations with precursors to adverse health effects
 - Increases in total cholesterol
 - Decreases in vaccine response
 - Decreases in birth weight
- The adverse clinical effects of these epidemiological associations are uncertain
 - Increased risks of cardiovascular diseases are not seen
 - Mixed evidence for risks of infectious diseases or infections
 - Increased risks of preterm births or other developmental effects associated with birth weight are generally not seen

Physiological processes may bias the observed associations between PFAS blood concentrations and clinical measures that are precursors to adverse outcomes

Take aways

- PFOA and PFOS blood concentrations have decreased over the past 20 years or more
- Although PFAS exposure may be reduced through regulations, the physiological determinants of internal dose (i.e., blood concentrations at general population levels) cannot be manipulated (interindividual variation)
- More epidemiological studies of PFAS blood concentrations and the same clinical measures are not needed
 - Do not “strengthen the evidence” by demonstrating consistent associations
 - Consistent associations may be seen because of reverse causality and confounding by physiological processes (e.g., pharmacokinetic bias)
- Epidemiological and experimental studies that test hypotheses related to postulated mechanisms and mode of action or PK bias are needed

The science is not settled regarding the health effects of PFAS at concentrations seen in the general population

Uncertainties exist

Questions?

Idell@ramboll.com

+1 413 835 4364

Amherst, Massachusetts