

Experiences from a PFAS hot spot in Sweden

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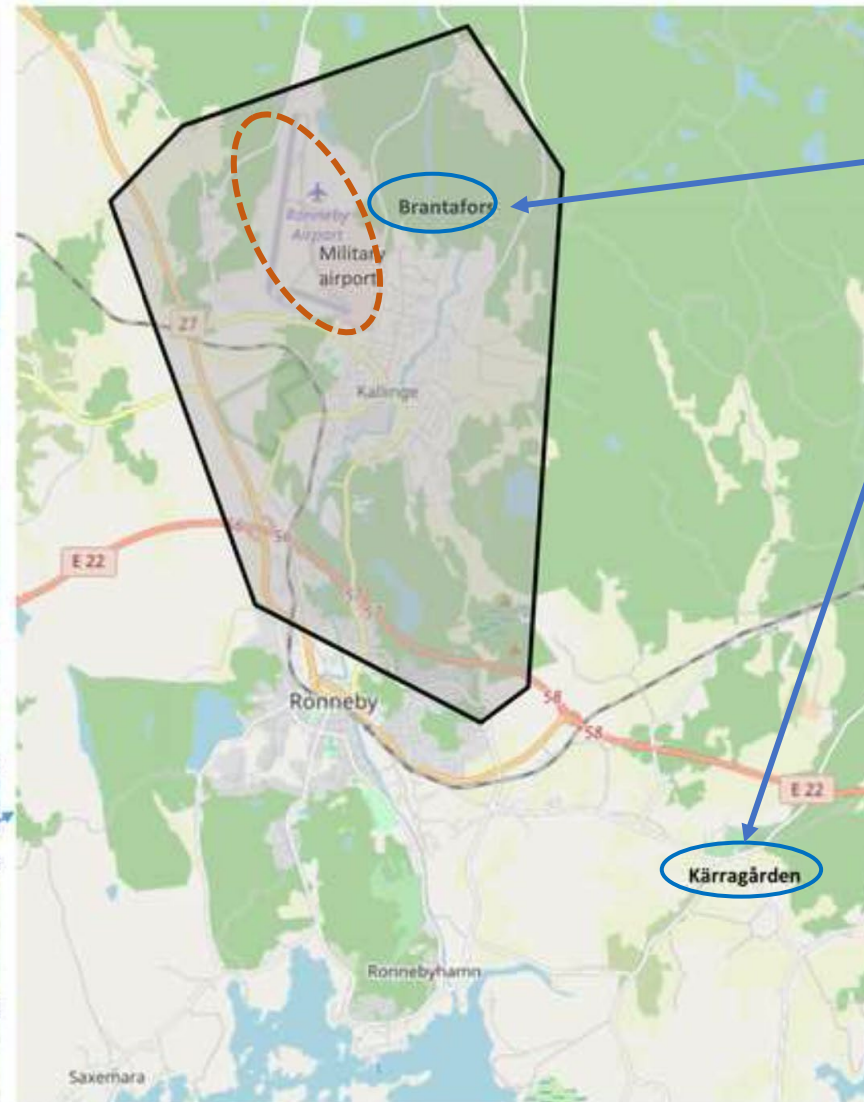
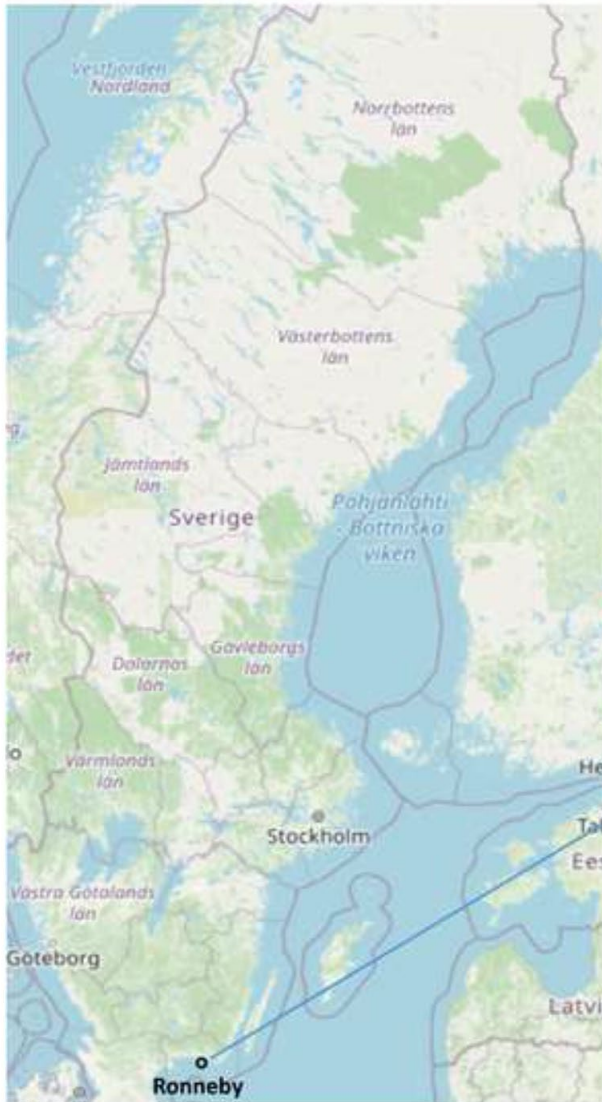
This presentation at a glance

Ronneby PFAS Research Program (RPRP)

- Background
- Findings and ongoing research

Associations between PFAS exposure and health outcomes

- Findings in background vs hotspot populations
- Dose-response relationships
- Implications for risk assessment in different situations



- PFAS in a municipal waterworks was unexpectedly discovered
- Clean drinking water was immediately provided from the other waterworks
- 1/3 of the households had been provided with contaminated water for decades
- Military airport in the middle of a large groundwater basin
- AFFF used since the mid-1980s but no details were available

Two waterworks in the municipality ($\approx 30\,000$ inhabitants)

PFAS	Brantafors, Contaminated Waterworks in Ronneby (ng/L) ^a	Kärragården, Minimally contaminated waterworks in Ronneby (ng/L) ^a
PFPeA	38	10
PFHxA	320	3.6
PFHpA	32	1.4
PFOA	100	1.0
PFNA	<1	<1
PFDA	<1	<1
PFUnDA	<10	<10
PFDoDA	<10	<10
PFBS	130	<2.6
PFHxS	1700	4.6
PFHpS	60	<1
PFOS	8000	27
Sum of PFAS ^d	10,380	47.6

> 10 000 ng/L

≈ 50 ng/L

- No previous analyses of PFAS in groundwater wells or in the outgoing drinking water

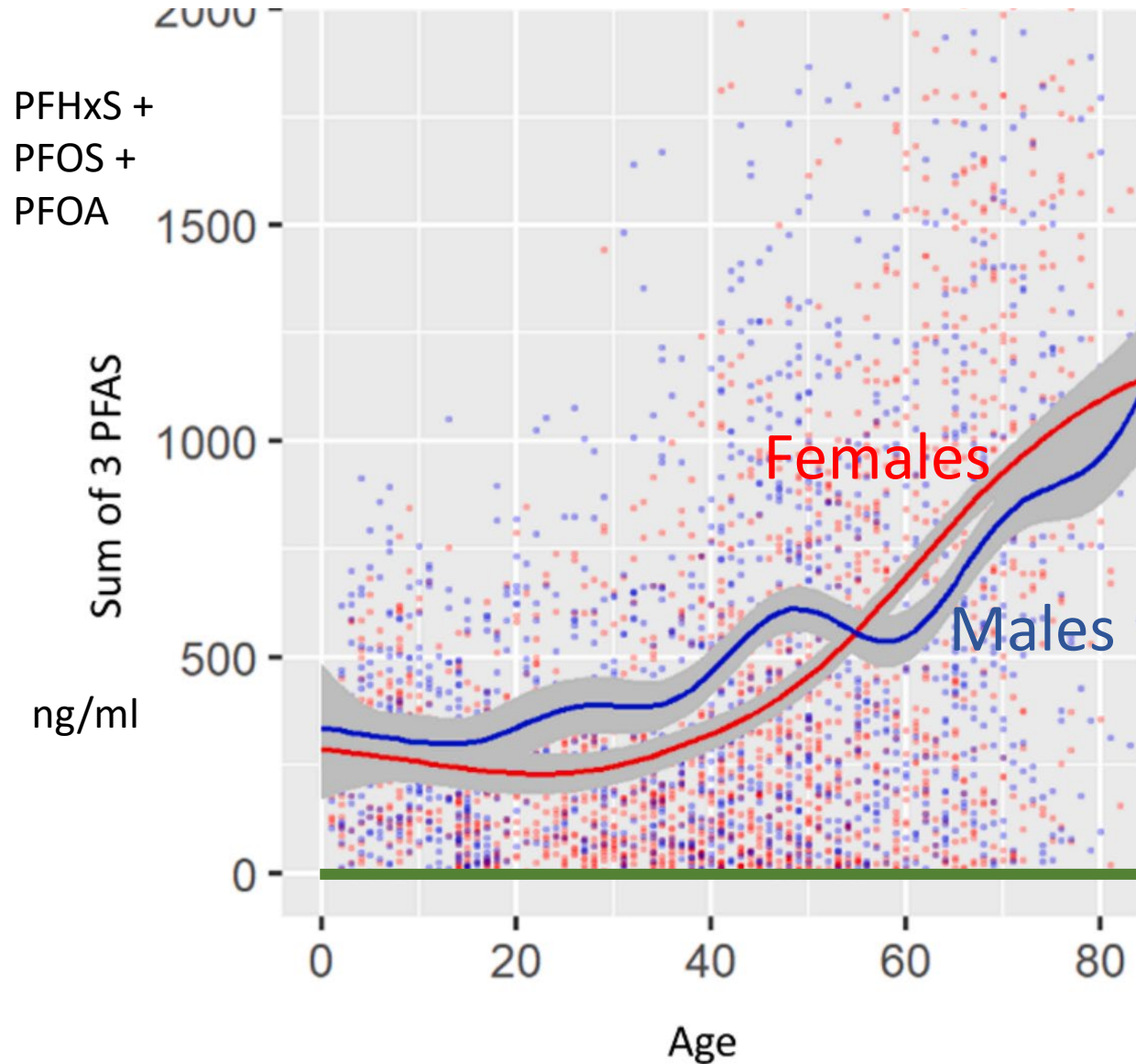
+ Yearly address information on drinking water distribution from the two waterworks

+ Personal ID and yearly address information for the entire Ronneby population since 1980 ($n \approx 65,000$)

**RPRP
cohort**

1/3 of the households had been provided with contaminated water for decades – a natural experiment

Ronneby PFAS Biomarker Cohort

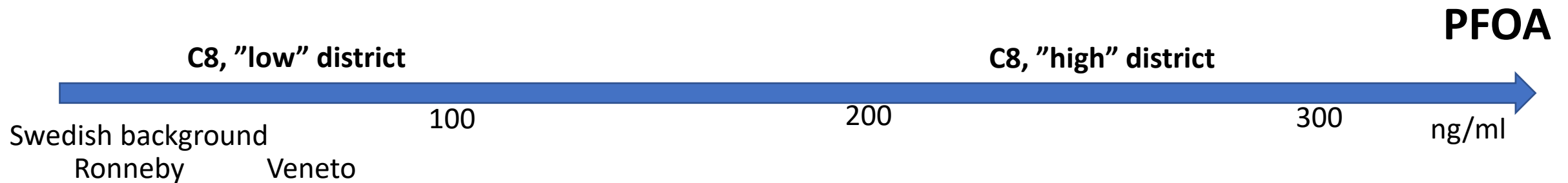


Assessment of exposure:
Open blood sampling 2014-2015

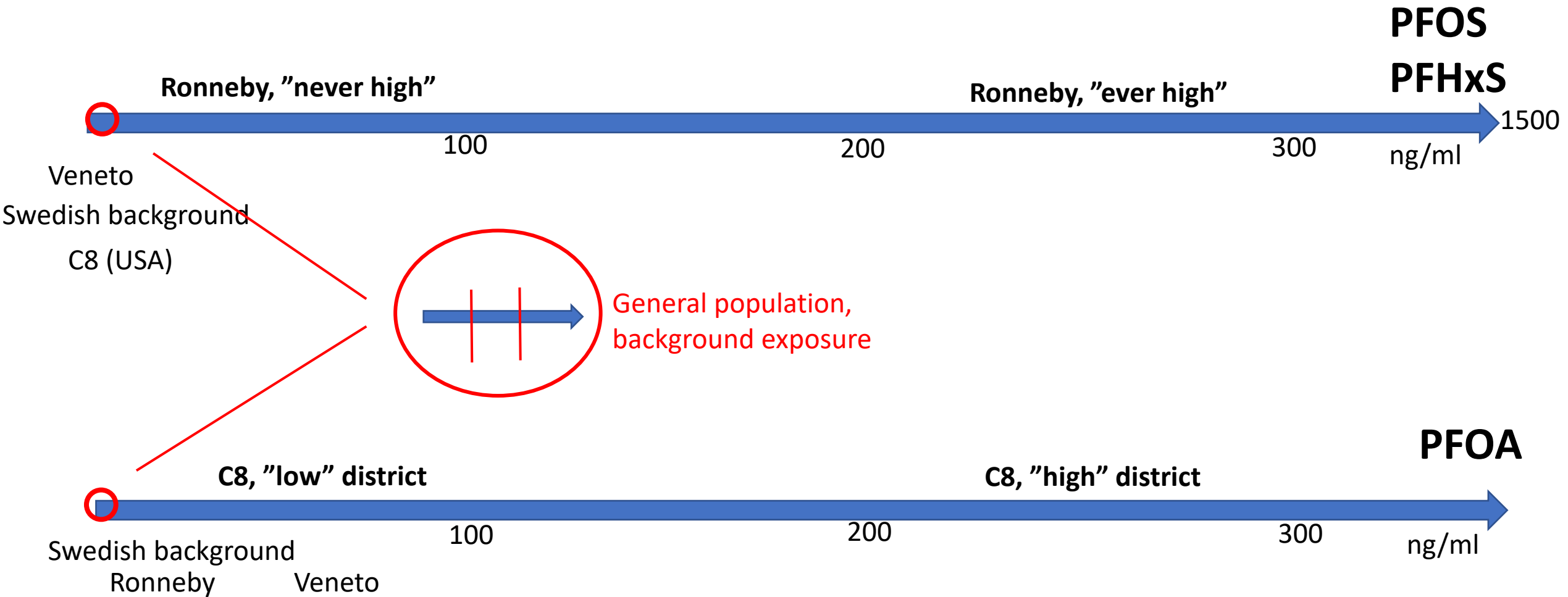
Biobank for research; N=3,293

Reference group from Karlshamn,
background exposure only; N=219

Average serum levels in population-based studies



Average serum levels in population-based studies



Most previous studies: associations at background exposure levels

- Simultaneous measurement of exposure and outcome
 - Cross-sectional prevalence studies
 - Case-control studies
- Longitudinal studies
 - Children: Mother-child cohorts
 - Adults: Re-use of other cohorts with biobanked serum samples

Can studies with larger exposure contrasts help the evaluation of causality?

Outcomes of interest – RPRP publications at present

Sperm function

Blood lipids

Endometriosis

Childhood neurodevelopment

Functional change, reversible

Kidney cancer

Childhood obesity

Prostate cancer

Liver enzymes

Breast cancer

Breastfeeding

Functional change, reversible but risk factor for disease

Reproductive hormones

Testicular cancer

Glomerular filtration

Birth weight

Gestational diabetes

Disease

Thyroid cancer

Bone density

PCOS

Preeclampsia

Diabetes

Hyperthyreosis

Thyroid hormones

Hypothyreosis

Ulcerous colitis

Antibody response after childhood vaccinations

Childhood infections

Cardiovascular disease

Allergies

Osteoporotic fractures

Antibody response after adulthood vaccinations

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Can studies with larger exposure contrasts help the evaluation of causality?

	PFOA	PFOS, PFHxS	REPRODUCTION	C8	RPRP	
CANCER	C8	RPRP	Birth weight	no	(no)	
Prostate	no	no				
Breast	no	no	Gest. diabetes	no	no	
Kidney	yes	yes	Preeclampsia	yes	no	
Testicular	yes	(yes)				
Thyroid	(yes)	(yes)	Endometriosis	-	no	
			PCOS	-	yes	
			Uterine fibroids	-	(yes)	
DISEASES	C8	RPRP				
Diabetes	no	yes				
Hypertension	no	-	BIOMARKERS	C8	RPRP	Veneto
Cardiovascular	no	-	Cholesterol	yes	yes	yes
Thyroid	(yes)	no	Thyroid hormones	no	no	no
Fractures	-	yes				
Liver	no	-	Ab after vacc., children	-	-	-
Colitis ulcerosa	yes	no	Ab after vacc., adults	(yes)	no	-

Very different effect estimates for birth weight

Measured; background exposure

-5 g per 1 ng/ml increase in PFOA
(Fei 2007)

-11 g per 1 ng/ml increase in PFOS
(Steenland 2018)

-19 g per 1 ng/ml increase in PFOA
(Johnson 2014)

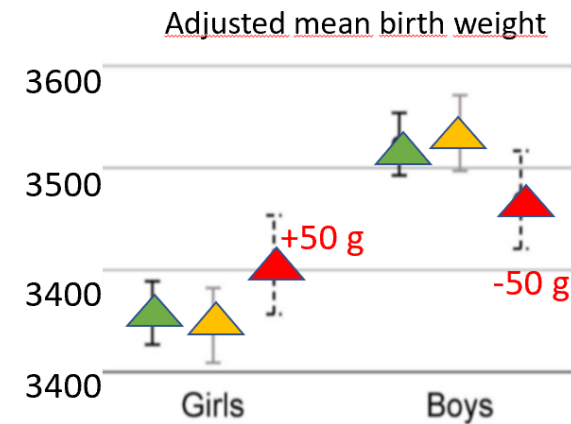
-50 g per 3-fold increase in PFOS
(Negri 2017)

-142 g per 1th to 4th quartile of PFOS (girls only)
(Wikström 2020)

Address based exposure assessment

- ▲ Blekinge county (n=9,692)
- ▲ Ronneby, not highly contaminated water; n=3,452)
- ▲ Ronneby, contaminated water; n=823)

Engström, 2021



Rough estimates for PFOS per 1 ng/mL increase
-0.50 g (boys), +0.50 g (girls)

Only for births 2005-2013;

No difference for births 1995-2004

What is the shape of the dose-response curve?

Extrapolate
"upwards"?

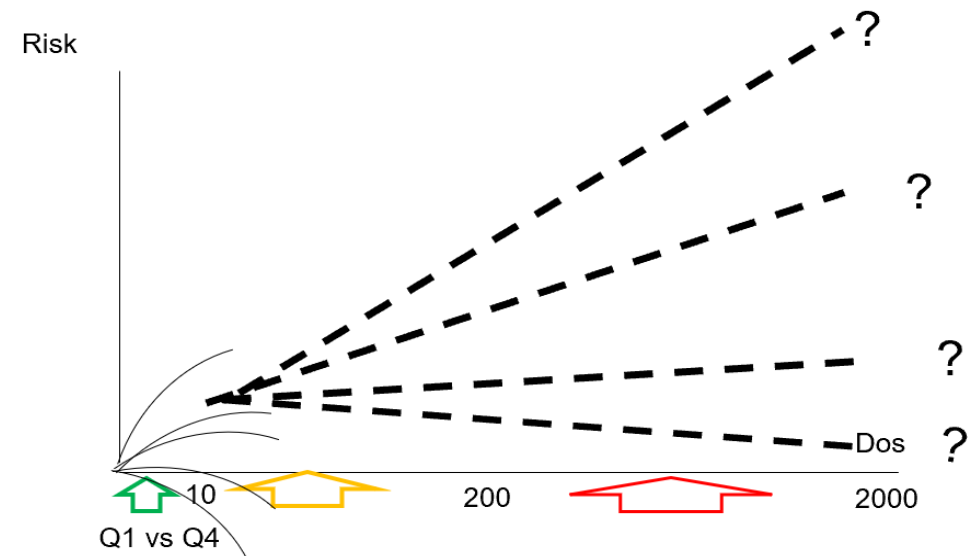


Risk?

PFAS levels

Studies within a narrow exposure range may be more prone to inaccuracy of a measured exposure and misclassifications

Studies using biomarkers of exposure may be more prone to confounding and reverse causation



Non-linear dose-response – PFOA and cholesterol

Danish general population

At an increase of 4 ng/ml PFOA
(median 7 ng/ml)
+2 % (Eriksen et al, 2013)

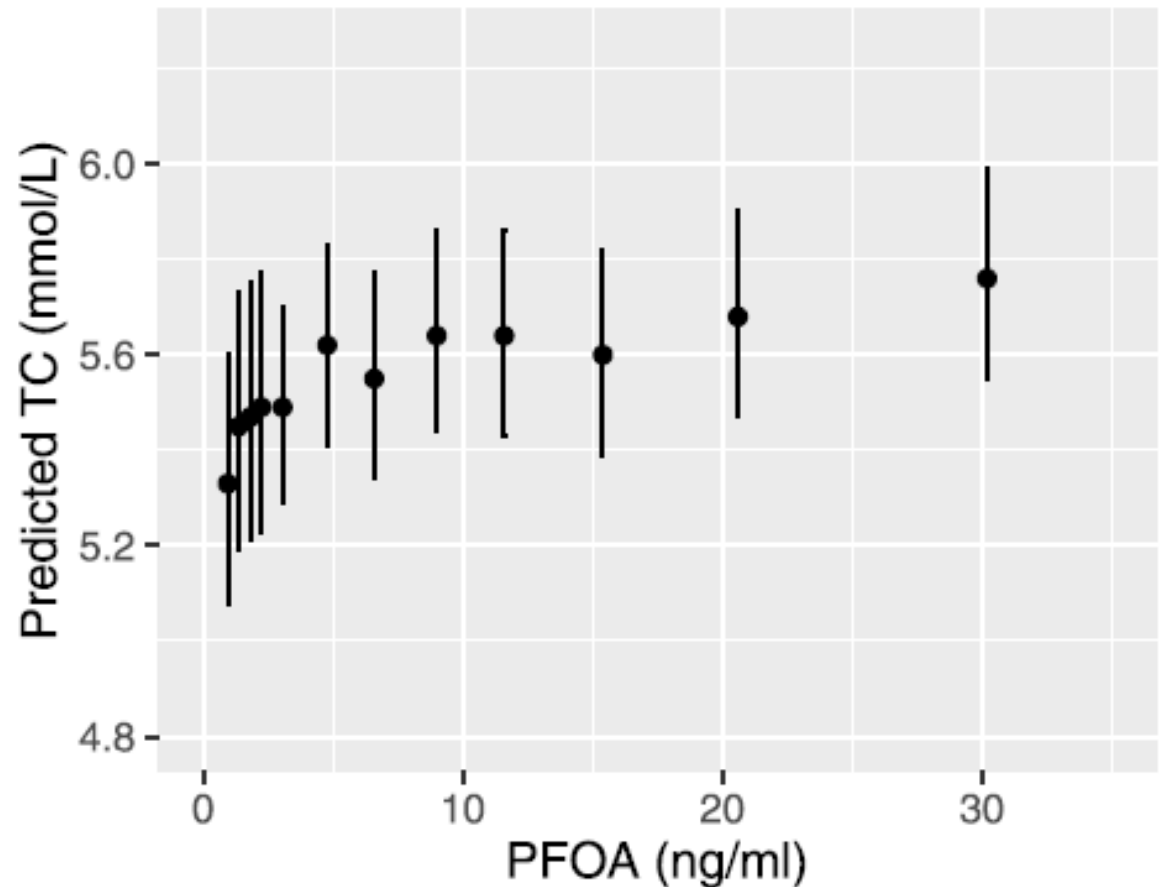
C8 population, PFOA

At an increase of 15 ng/ml
(lowest decile to median 27 ng/ml)
+3-4 % (Steenland et al 2009)

PFOA workers

At an increase of 1000 ng/ml
+3% (Olsen et al 2003)
+2% (Sakr 2007)

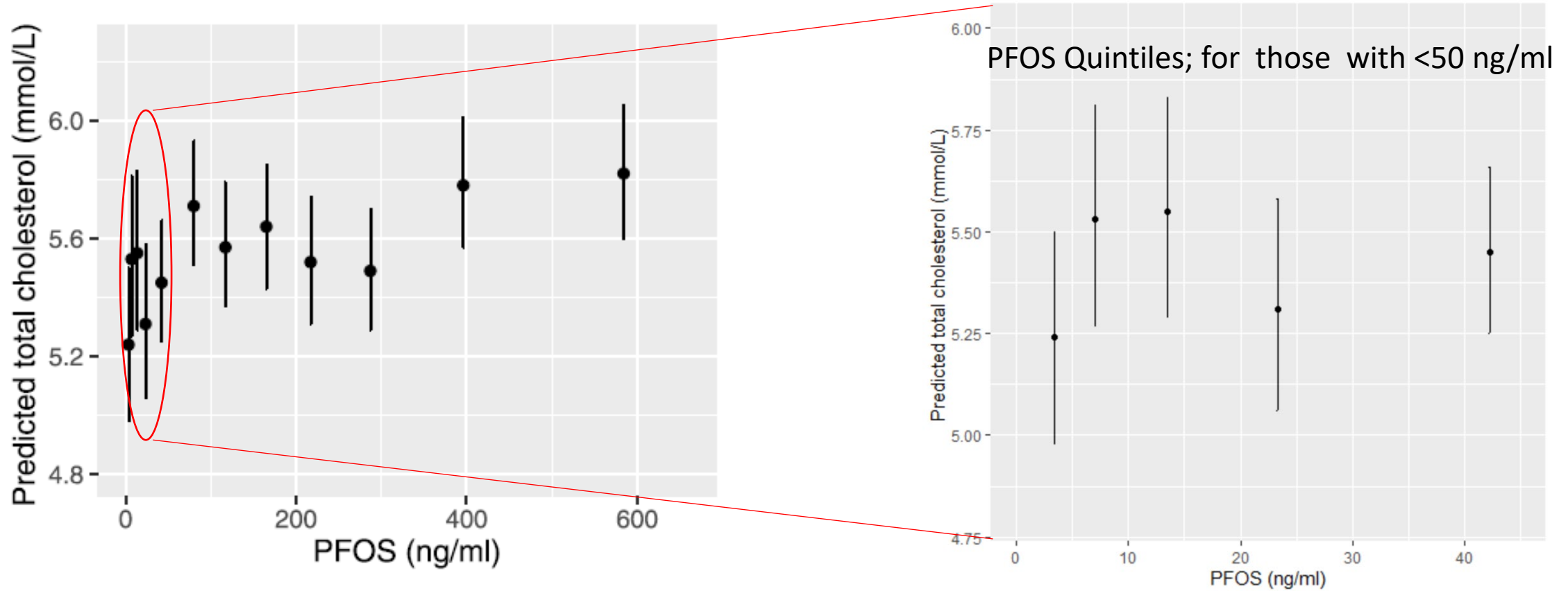
RPRP biomarker study, Li et al, 2020



Steeper rise at low levels, but not over the whole range of exposures

(predicted TC, adjusted)

RPRP biomarker study, Li et al, 2020



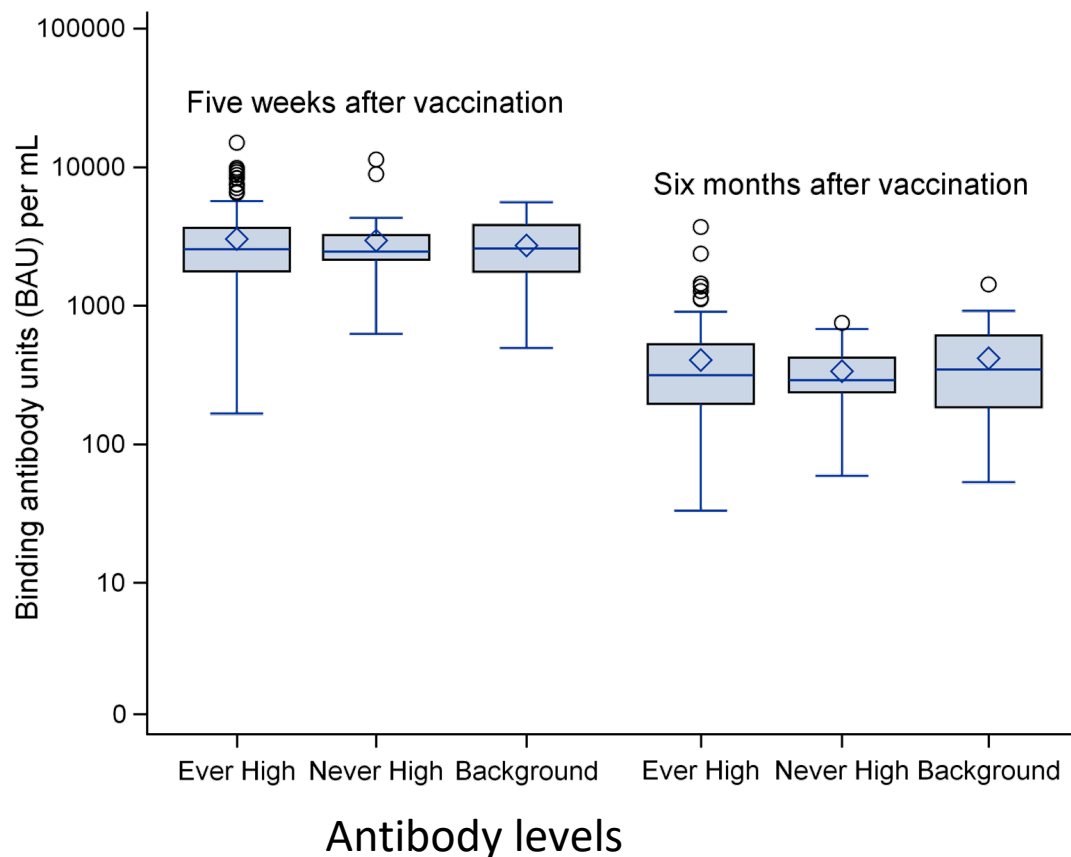
RPRP in summary so far....

- Some previously reported associations were confirmed, others not.
- Some new findings which need replication

- Manifold higher exposure levels did not result in manifold higher observed risks

- Decreased vaccination responses in childhood may not remain in adulthood

No decreased immune response in adults after vaccination against SarsCoV-2 (mRNA vaccine; Anderson et al. Env Health Perspect 2023)



Compound	Median (ng/mL)		
	Ronneby		Karlshamn
	Ever High n=245	Never High n=63	Background n=40
PFHxS	56	10	0.9
PFOS	54	14	4
PFOA	2	1	1
PFHpS	3	0.6	0.1
PFNA	0.4	0.4	0.4
PFDA	0.2	0.2	0.2
PFUnDA	0.1	0.1	0.1

The findings are supported by others:
 Shih et al. 2021; Faroe young adults, hepatitis A and B
 Porter et al. 2022; Covid, various vaccines; workers
 Bailey et al. 2023; Covid, mRNA

Risk assessment and risk communication in two very different situations

Tolerable Weekly Intake,
drinking water standards

Protect a population over
generations

”Hotspot ”

Risk assessment and risk
communication in a defined
population with higher than
background exposure

Sweden 2014: Drinking water 900 ng/L
action limit: 90 ng/L

Sweden 2022: DW 4 ng/L

US EPA 2022: ”health advisory” 0.004 ng/L för PFOA,
0.02 ng/L för PFOS

Why is it important to assess the shape of the dose-response curve?

Extrapolate
"upwards"?



Risk?



Extrapolate
"downwards"?

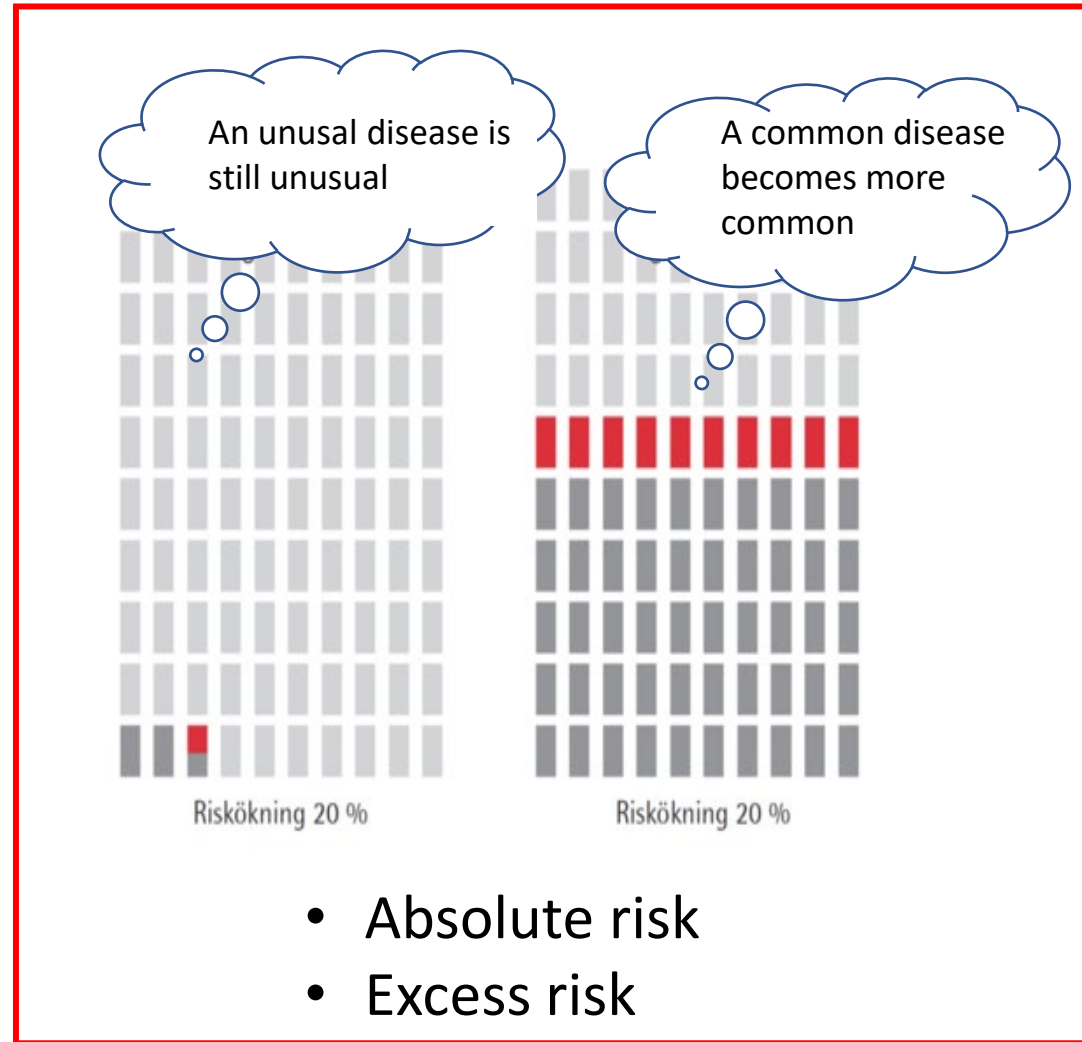
PFAS levels 

Studies within a narrow exposure range may be more prone to inaccuracy of a measured exposure and misclassifications

Studies using biomarkers of exposure may be more prone to confounding and reverse causation

Lack of mechanistical understanding.
Saturation? Threshold?
Other mechanisms?

The risk communication dilemma in a hotspot



- Is my illness due to PFAS
- Will I become ill
- Will my child become ill
- Risk on the individual level

- Absolute risk
- Excess risk

All AAP content is accessible to individuals with disabilities. A fully accessible Section 508-compliant HTML version of this article is available at <http://dx.doi.org/10.1289/ehp.1206372>.

Research | Children's Health

Serum Perfluorooctanoic Acid and Perfluorooctane Sulfonate Concentrations in Relation to Birth Outcomes in the Mid-Ohio Valley, 2005–2010

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BACKGROUND: Previous research suggests perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) may be associated with adverse pregnancy outcomes.

OBJECTIVE: We conducted a population-based study of PFOA and PFOS and birth outcomes from 2005 through 2010 in a Mid-Ohio Valley community exposed to high levels of PFOA through drinking-water contamination.

METHODS: Women provided serum for PFOA and PFOS measurement in 2005–2006 and reported reproductive histories in subsequent follow-up interviews. Reported singleton live births among 1,330 women after 1 January 2005 were linked to birth records ($n = 1,500$) to identify the outcomes of preterm birth (< 37 weeks gestation), pregnancy-induced hypertension, low birth weight (< 2,500 g), and birth weight (grams) among full-term infants.

RESULTS: We observed little or no evidence of association between maternal serum PFOA or PFOS and preterm birth ($n = 158$) or low birth weight ($n = 88$). Serum PFOA and PFOS were both positively associated with pregnancy-induced hypertension ($n = 106$), with adjusted odds ratios (ORs) per log unit increase in PFOA and PFOS of 1.27 (95% CI: 1.05, 1.55) and 1.47 (95% CI: 1.06, 2.04), respectively, but associations did not increase substantially when stratified by gestation. Results of analyses restricted to pregnancies conceived after blood collection were consistent with the main analyses. There was suggestive of a modest negative association between PFOS and birth weight in full-term infants (-29 g per log unit increase; 95% CI: -66 , 7), which became stronger when restricted to births conceived after the blood sample collection (-49 g per log unit increase; 95% CI: -90 , -8).

CONCLUSIONS: Results provide some evidence of positive associations between measured serum perfluorinated compounds and pregnancy-induced hypertension and a negative association between PFOS and birth weight among full-term infants.

CREATION: Darrow LA, Stein CR, Stoenland K. 2013. Serum perfluorooctanoic acid and perfluorooctane sulfonate concentrations in relation to birth outcomes in the Mid-Ohio Valley, 2005–2010. *Environ Health Perspect* 121:1207–1213; <http://dx.doi.org/10.1289/ehp.1206372>

Introduction

Perfluorooctanoic acid (PFOA, or C8) and perfluorooctane sulfonate (PFOS) are synthetic, environmentally persistent perfluorinated compounds (PFCS). PFOA has been used in the manufacture of fluoropolymers such as polytetrafluoroethylene (i.e., Teflon) since the 1940s. PFOS exhibits similar properties and, like PFOA, has been used in a variety of consumer products (e.g., Scotchgard for stains, greases and water-resistant properties).

Biomonitoring of the general U.S. population indicates that exposure to PFOA and PFOS is nearly ubiquitous, with > 99% of people sampled in 2003–2004 showing detectable levels of both PFOA and PFOS in their blood (Calafat et al. 2007).

Previous epidemiologic studies of PFCS and pregnancy outcomes in the general population provide inconsistent evidence of associations with birth outcomes such as birth weight and length of gestation (Apfelberg et al. 2007; Harris et al. 2007; Hamm et al. 2010; Watkins et al. 2009); both PFOA and PFOS cross the placental barrier (Midach et al. 2007). Toxicological studies have reported evidence of reproductive effects in mice and rats, includ-

ing reduced postnatal growth, but at higher exposure levels than measured in human populations with background levels of exposure (Iau et al. 2007). In addition, extrapolation between species is complicated by differences in PFCS metabolism and half-lives among humans, nonhuman primates, and rodents.

In the present study we focused on a population in the Mid-Ohio Valley living near a chemical manufacturing plant in Parkersburg, West Virginia. The DuPont Company's Washington Works factory has used PFOA in the manufacture of fluoropolymer since 1951, with use peaking in the 1990s. Community residents were exposed to high levels of PFOA through ground-water contamination (2005–2006; serum median = 28 ng/mL) with residents in certain water distribution districts more highly exposed than others (Stoenland et al. 2009).

The median PFOA level in the U.S. population in 2003–2004 was 4 ng/mL (Calafat et al. 2007). In 2001 a class action lawsuit led to initiation of the CB Health Project, a survey of 69,030 people who had been exposed to PFOA-contaminated drinking water in specific water districts in Ohio and West

Virginia (Fisher et al. 2009). The survey included collection of demographic information, medical histories, health-care behaviors, clinical laboratory measurements, and serum measurement of PFOA and other PFCS. A subset of participants who were at least 20 years old at the time of enrollment in the CB Health Project ($n = 32,254$) participated in one or two follow-up interviews between 2008 and 2011 as part of the Community Follow-up Study (CB Science Panel 2013).

For the present study, we examined outcomes among births to Community Follow-up Study participants that occurred after 1 January 2005; outcomes of births that occurred before 2005 were examined previously (Stein et al. 2012b).

Four recent retrospective cohort studies have examined relationships between PFOA and pregnancy outcomes in this highly-exposed Mid-Ohio Valley region (Nolan et al. 2010; Savitt et al. 2012a, 2012b; Stein et al. 2009). Two studies of birth outcomes among women who were enrolled in the CB Health Project or resided in the study area in relation to modeled historical estimates of personal

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This research was funded by the CB Class Action Settlement Agreement (Circuit Court of Wood County, West Virginia) between DuPont and Fluorocell, which resulted from claims of perfluorooctanoic acid (PFOA, or C8). C.S. is one of three members of a Court approved CB Science Panel established under the Settlement Agreement to describe if there are probable links (as defined in the Settlement Agreement) between PFOA and disease. Funds are administered by an agency that reports to the Court, and work is independent of either party to the lawsuit. Probable link determinations of the CB Science Panel are available on the CB website (<http://www.cbhealthproject.org/>). C.S.'s research was supported by the National Institute of Environmental Health Science (R01ES019164).

The authors declare they have no actual or potential competing financial interests.

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Longitudinal registry studies

Around 65 000 persons ever registered in Ronneby 1980-2013. Yearly addresses linked to

Extended exposure modelling using reconstruction of historical exposures

- Inpatient and outpatient hospital diagnoses, primary health care diagnosis

- Focus on low-median exposure levels

- Cancer incidence causes of death

- Pharmaceutical registry 2005

- Educational achievements, working life attachment

All children in Blekinge
- Medical birth registry

Child health care*

All children in the municipality 1990-on

Childhood growth

Speech and psychomotor development

Mother-child cohort*

Transfer of PFAS mother-child

Duration of follow-up
Follow-up during childhood

Childhood growth

Speech and psychomotor development

Longitudinal vaccination response*

Routine vaccination program in children
Sars-CoV-2 in adults

Biobank*

(serum, blood, urine, faeces, placenta, breast milk)

Exposure assessment

Biomarkers for (subclinical) effects
Collaborations

Mechanistical studies (genetics, metalomics, immunology, epigenetics)

Reconstruction of historical exposures

Dry blood spots from neonates

Environmental investigations

* Includes reference population from Karlshamn with background levels of PFAS

Thank you for your attention

Ronneby PFAS Research Program (RPRP)



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