

Review of Perfluorochemical Epidemiology Studies

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Epidemiology

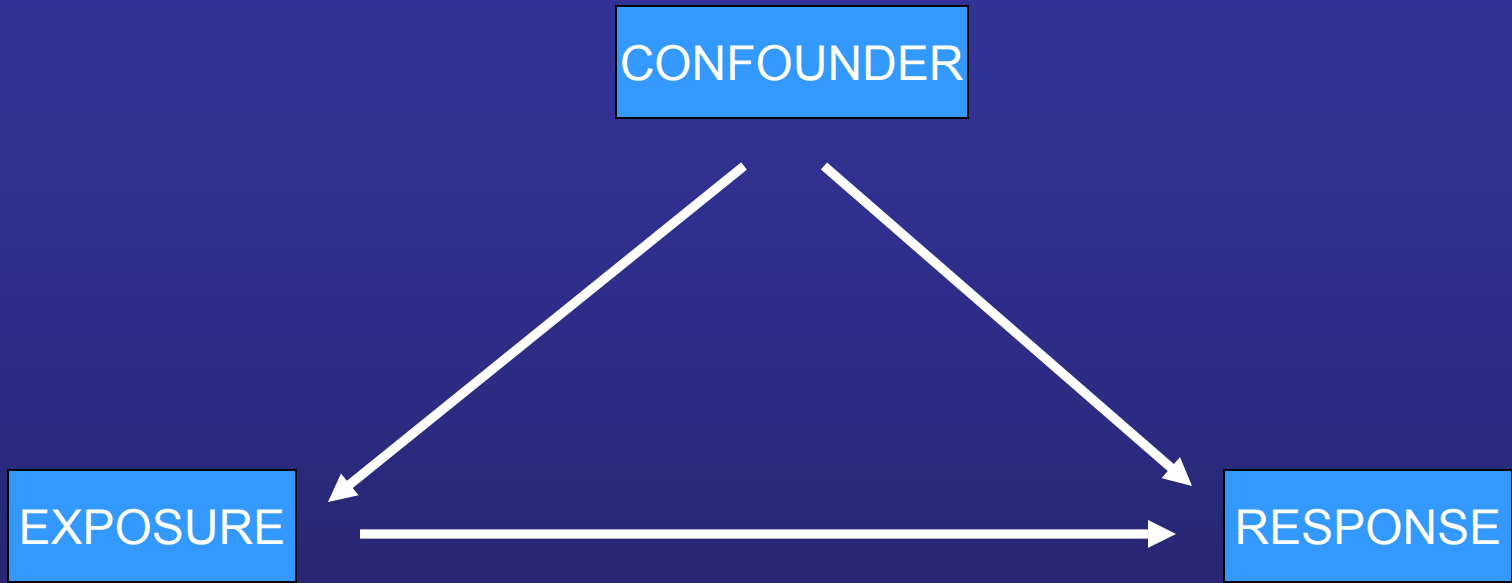
- Epidemiology has been defined as the study of the distribution and determinants of disease in a population(s).
- The foundation of epidemiology is its methods.
- Experimental vs. observational methods.

Epidemiology

- Estimate of effects (e.g., relative risks, odds ratios, standardized mortality ratios) relate the exposure in one or more groups to a referent (least or nonexposed) group.
- Measures of precision (e.g., 95% confidence intervals)

Interpretation of these estimates depends on . . .

- Study design
- Selection
- Disease classification
- Exposure classification
- Misclassification
 - Differential
 - Nondifferential
- Confounding



“Causal Model”

'Weight of the Evidence' Evaluation

- Strength
- Consistency
- Specificity
- Temporality
- Biologic gradient
- Plausibility
- Coherence
- Experimental Evidence

Two roads diverged in a yellow wood,
And sorry I could not travel both . . .

Two roads diverged in a wood, and I--
I took the one less traveled by,
And that has made all the difference

...Robert Frost

How to Present the Epidemiology Literature?

‘Study by Study’

OR

‘Outcome by Outcome’

Presentation Outline

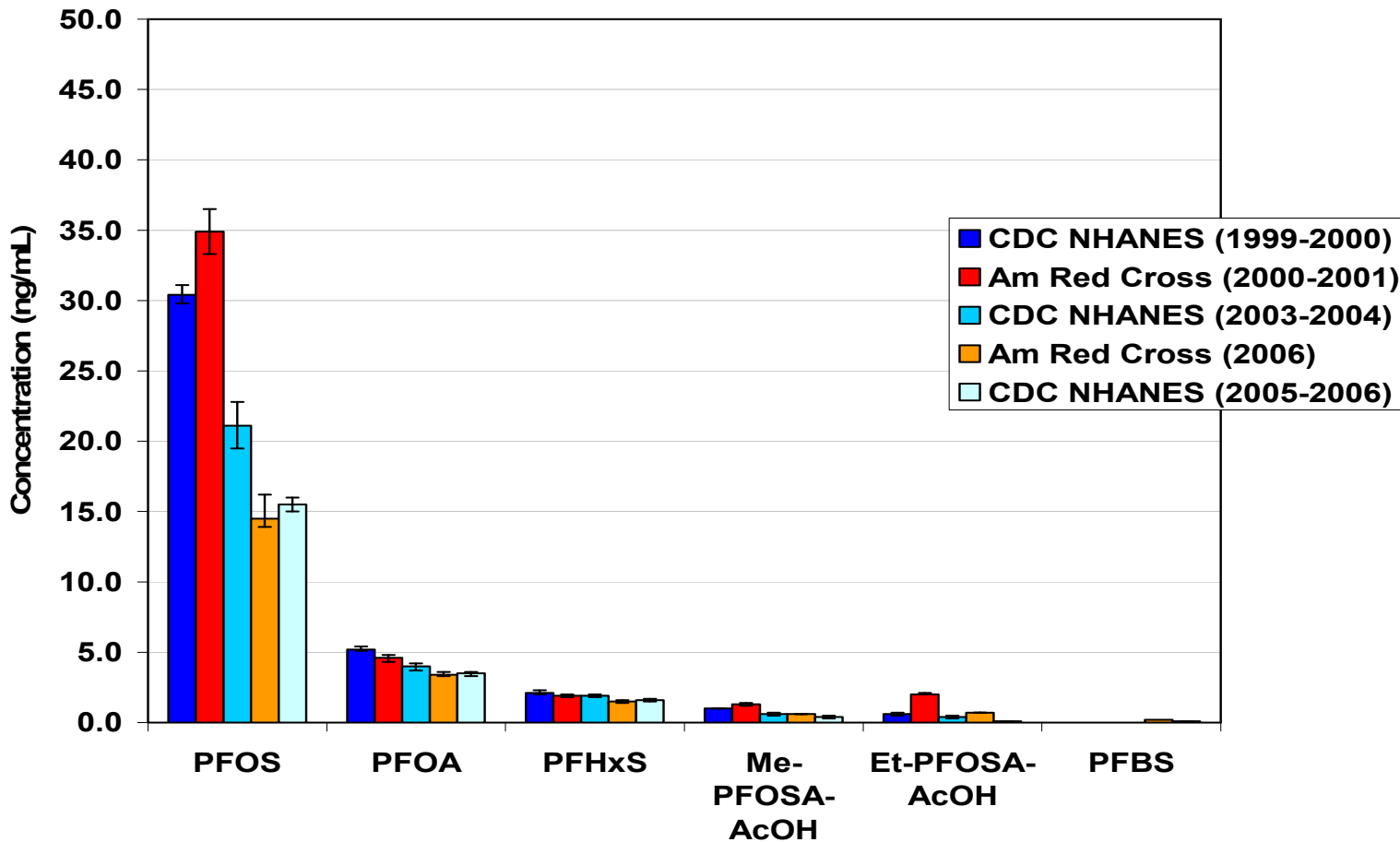
'Outcome by Outcome'

- **Biomonitoring Data for PFOA and PFOS**
- **Health Outcomes**
- **Clinical Chemistries**
- **Developmental Outcomes**

Biomonitoring

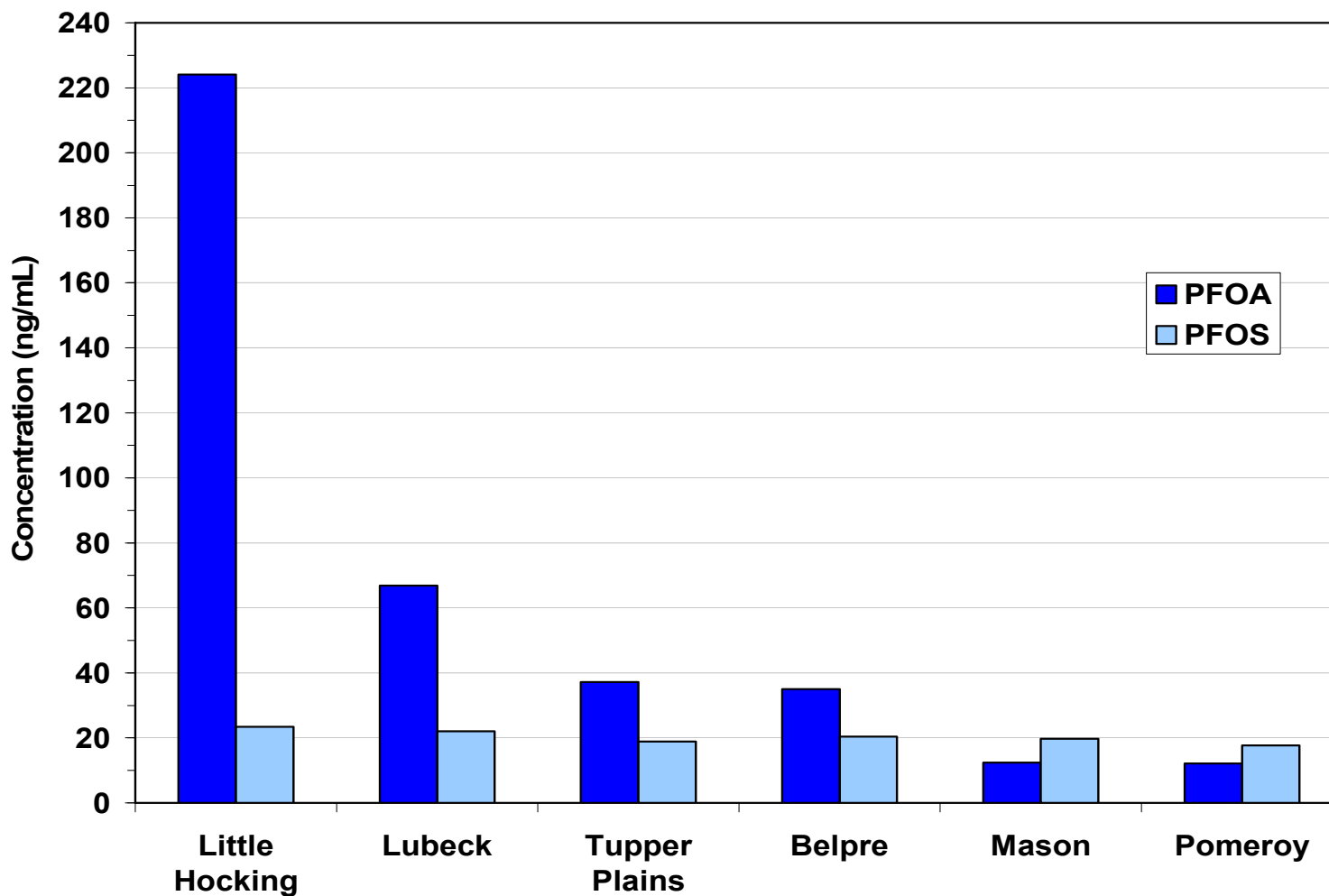
Geometric Mean (95% CI) Concentrations, CDC NHANES and American Red Cross Studies, 1999-2006

Olsen et al. EHP 2003;111:1892-1901
Calafat et al. ES&T 2007;41:2237-2242
Calafat et al. EHP 2007;115:1596-1602
Olsen et al. 2008; ES&T 42:4989-4995
Calafat et al. CDC NHANES website (Aug 2009)



Median PFOA Concentrations by Current Water District, C8 Health Project

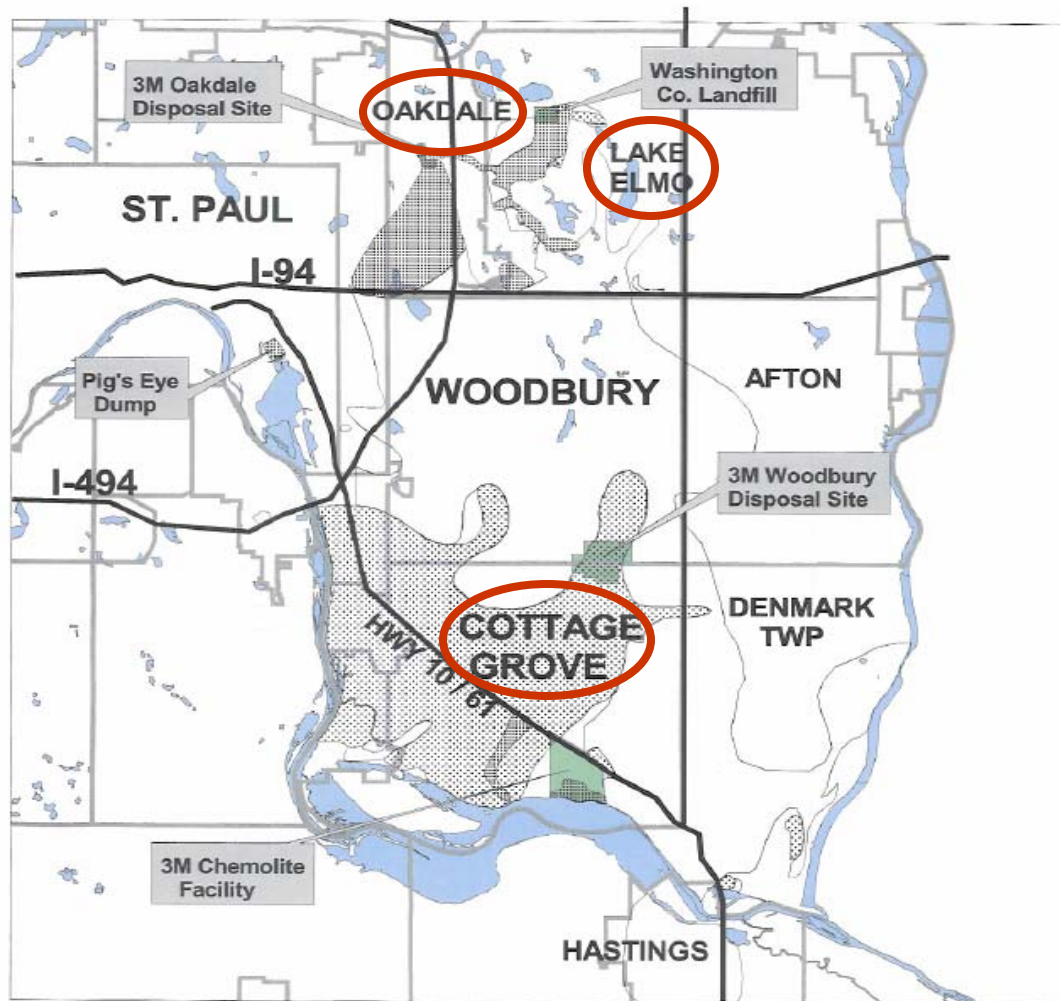
Steenland et al. EHP 2009;117:1083-1088
See also C8 Health Project Website (U of W.V.)







Community Studies



Washington County,
Minnesota

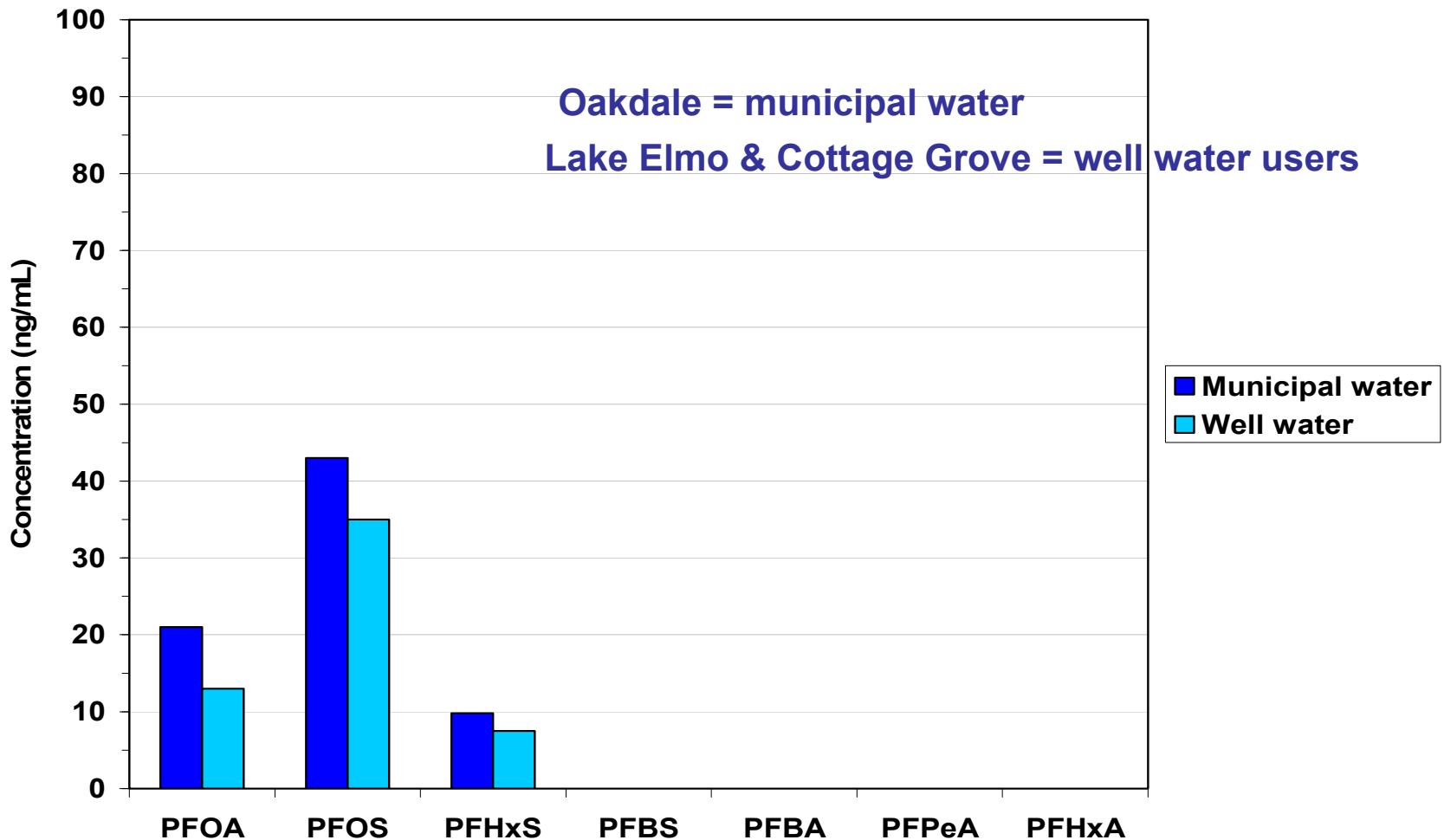


General Distribution of PFCs in the Southeast Metro

-  Two or more PFCs
-  PFBA greater than 1.0 ppb
-  PFBA less than 1.0 ppb
-  No PFCs detected

Note: This map combines sample results from four aquifers. Not all wells in an area shown to have PFCs may be contaminated.

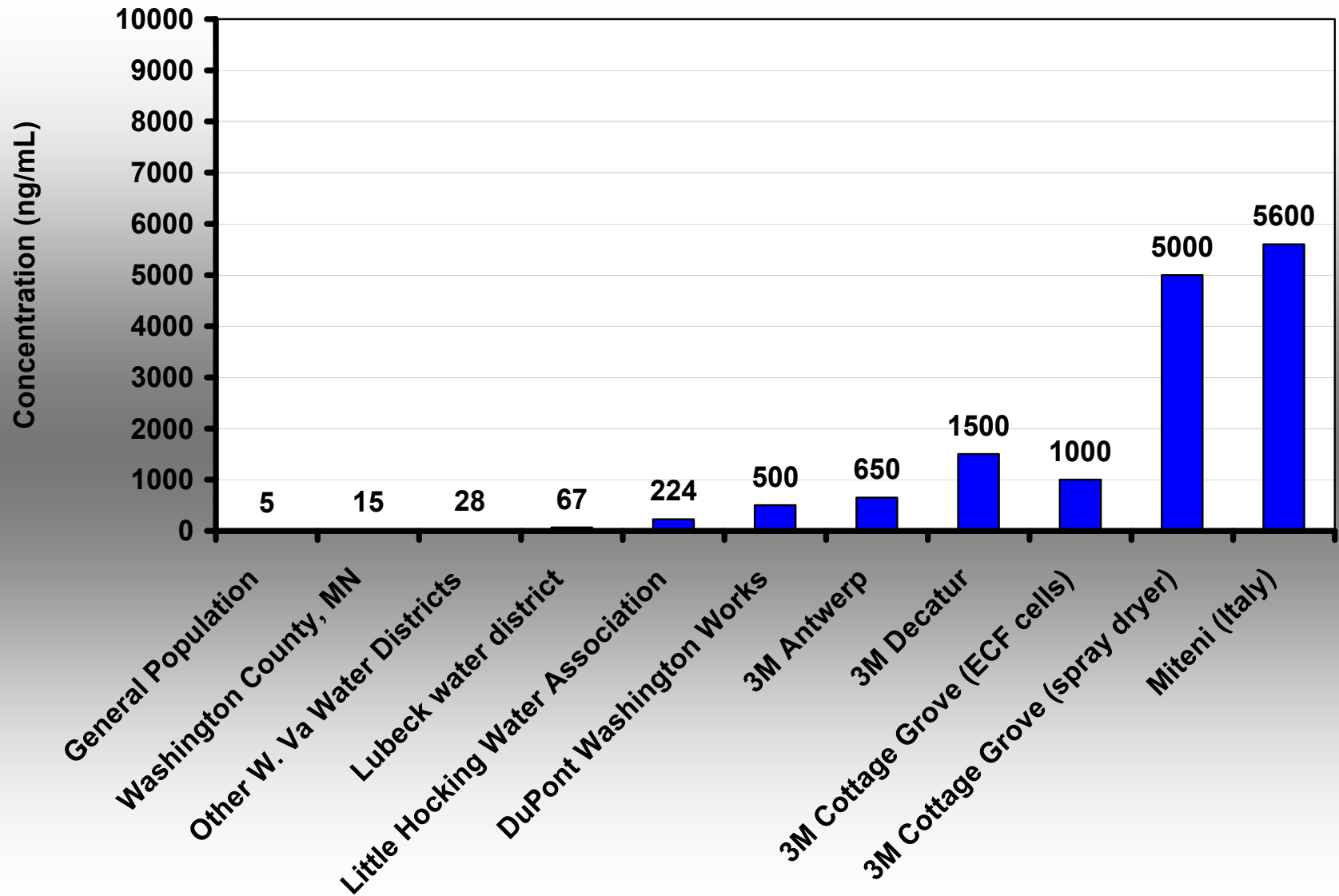
Median Perfluorochemical Concentrations (ng/mL) of Municipal and Well Water Users, MDH East Metro Biomonitoring Study



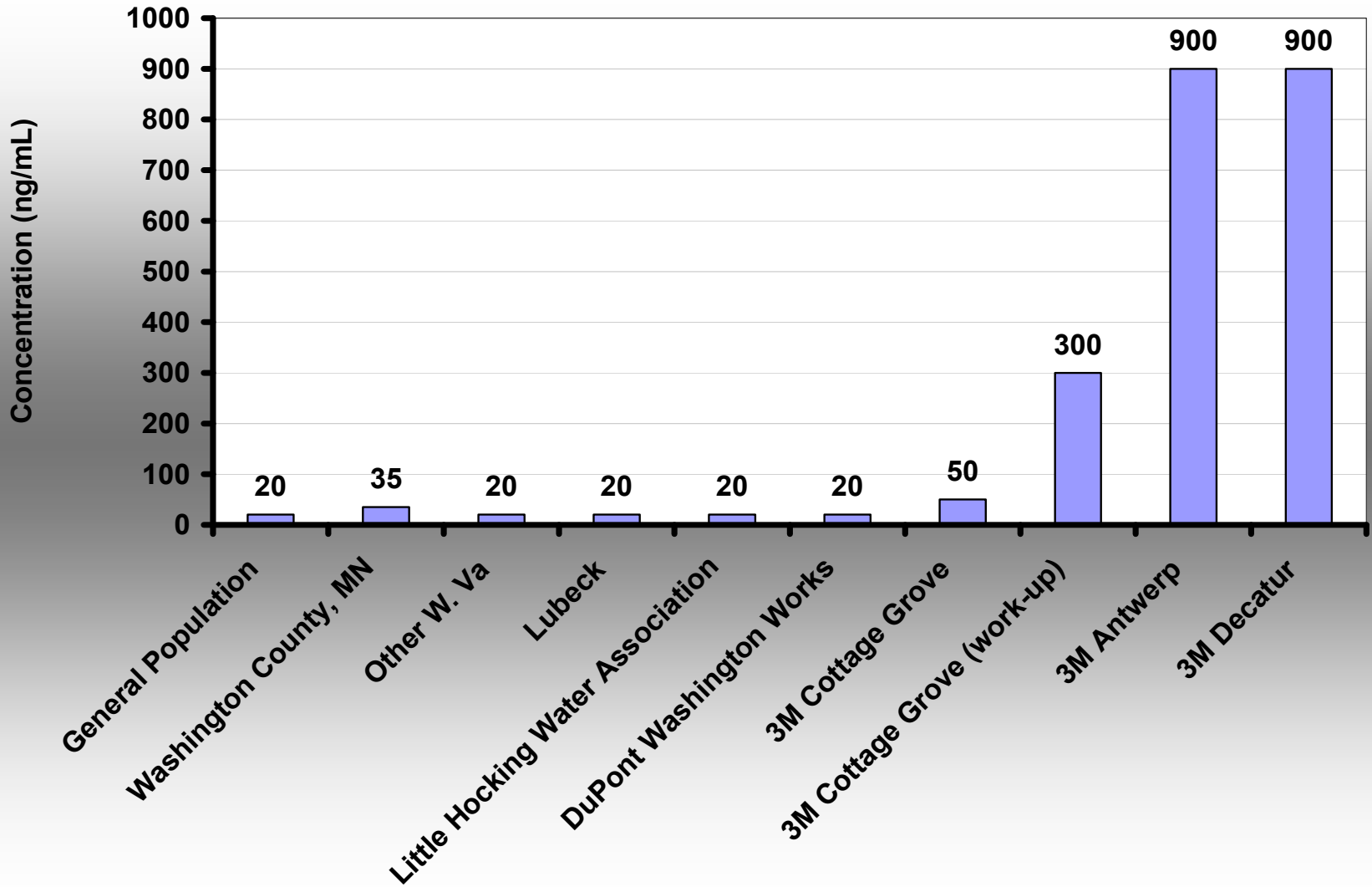
Half-lives of Serum Elimination in Human Studies

Compound	Half-life	95% CI	Reference
PFBA	2.7 days	1.9 – 3.8	Chang et al. Tox Sci 2008
PFBS	25.8 days	16.6 – 40.2	Olsen et al. Toxicol 2008
PFOA	3.5 yrs	3.0 – 4.1	Olsen et al. EHP 2007
	4.8 yrs	2.6 – 9.7 (range)	Costa et al. JOEM 2009
	2.3 yrs	2.1 – 2.4	C8 Science Panel 2009
PFOS	4.8 yrs	4.0 – 5.8	Olsen et al. EHP 2007
PFHxS	7.3 yrs	5.8 – 9.2	Olsen et al. EHP 2007

Approximate Average PFOA Concentrations (ng/mL)



Approximate Average PFOS Concentrations (ng/mL)



Health Endpoints Covered Here

- Liver cancer
- Pancreatic cancer
- Bladder cancer
- Prostate cancer
- Ischemic heart disease
- Cerebrovascular disease
- Diabetes

Occupational Epidemiology Studies

Authors	Source	Year	Location	Study Design	Period
Alexander et al.	OEM	2003	3M Decatur Mfg Plant	Cohort mortality	1961-1998
Alexander & Olsen	Annals Epidemiology	2007	3M Decatur Mfg Plant	Cohort morbidity (validated bladder cancer reports)	1961-2002
Grice et al.	JOEM	2007	3M Decatur Mfg Plant	Cohort morbidity (Self-reports, some validated)	1961-2002
Lundin et al.	Epidemiology	2009	3M Cottage Grove Mfg Plant	Cohort mortality	1948-2002
Leonard et al.	Annals Epidemiology	2007	DuPont Washington Works Plant	Cohort mortality	1947-2002
Sakr et al.	OEM	2009	DuPont Washington Works	Cohort mortality (ischemic heart disease)	1947 - 2002

Community and General Population Studies

Authors	Source	Year	Location	Study Design	Period
Emmett et al.	JOEM	2006	Washington County, OH	Cross-sectional (liver, thyroid diseases)	2004-2005
C8 Health Project & C8 Science Panel	Website	2007	C8 Health Project water districts	Cross-sectional (self-reports)	2005-2006
MacNeil et al.	Environmental Research	2009	C8 Health Project water districts	Cross-sectional (validated type II diabetes)	2005-2006
Colsher et al. & W.V. Dept of Health	Final Reports	2006	3 W.V. counties	Cancer incidence report	1993-2002
Ohio Dept. of Health	Final Report	2008	Washington & Meigs County, OH	Cancer incidence report	2001-2005
Minnesota Dept. of Health	Final Report	2007	2 MN counties and 8 cities	Cancer incidence report of county & communities	1988-2002
Eriksen et al.	JNCI	2009	Denmark	Case-cohort study of liver, pancreas, bladder, and prostate cancer incidence.	1993-2006

Eriksen et al. (JNCI 2009)

Study Methods

- Cohort defined
 - 57,053 individuals age 50-65 with no history of cancer
 - Enrolled December 1993 – May 1997
 - Questionnaire and plasma samples obtained
- Follow-up for cancer diagnoses
 - Danish Cancer Registry and Danish Pathology Data Bank
 - December 1993 – July 2006
 - Median follow-up 7 years

Eriksen et al. (JNCI 2009)

Study Methods

- Cancers identified during follow-up
 - Prostate (n = 713)
 - Bladder (n = 332)
 - Pancreatic (n = 128)
 - Liver (n = 67)
- Comparison population
 - From same cohort, randomly selected a subcohort of 680 men and 92 women, approximating the male-to-female ratio among the cancer patients.
 - “Case-cohort” study design

Eriksen et al. (JNCI 2009)

Study Methods

- Data analysis
 - Data analyzed according to case-cohort design
 - Adjusted incidence rate ratios for quartiles of PFOS and PFOA concentrations (ng/mL) were calculated based on the distribution of patients specific to the analysis of each cancer
 - Depending upon specific cancer, confounders may have included age, sex, smoking history, alcohol, BMI, dietary fat intake, fruit and vegetable intake, education level, and occupational histories at risk for this type of cancer.

Health Endpoints Covered

Liver Cancer

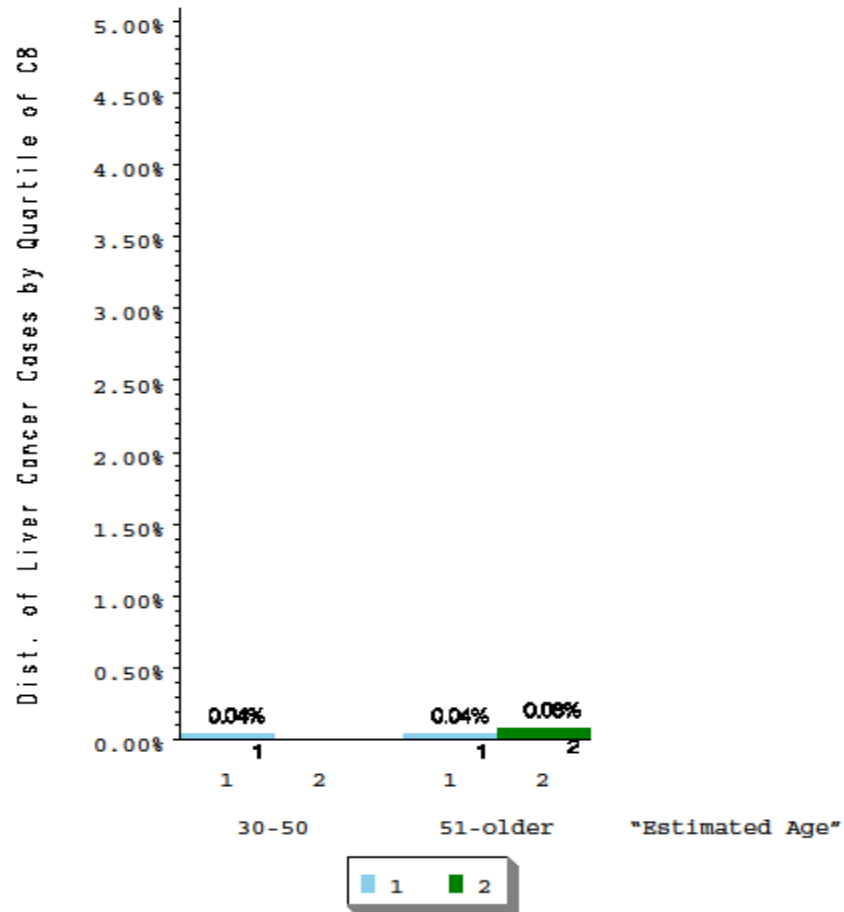
Occupational Studies

Liver Cancer

Study	Categorization	Obs	Exp	SMR	95%CI
Alexander et al.	3M Decatur Facility (AL comparison)	2	1.2	1.6	0.2 – 5.8
	“Not exposed PFOS job”	0	0.5	0.0	
	Ever “Low exposure”	1	0.3	3.9	0.1 – 21.9
	Ever “High exposure”	1	0.5	2.0	0.1 – 11.1
Lundin et al.	3M Cottage Grove Facility (MN comparison)	3	6.4	0.5	0.3 – 0.9
	“Not exposed PFOA job”	1	3.0	0.3	0.0 – 1.8
	Ever “Probable exposure”	2	2.8	0.7	0.2 – 1.6
	Ever “Definite exposure”	0	0.5	0.0	0.0 – 7.6
Leonard et al.	Washington Works Facility (W.V. comparison)	8	6.9	1.2	0.5 – 2.3
	Washington Works Facility (DuPont comparison)	8	5.5	1.4	0.6 – 2.9

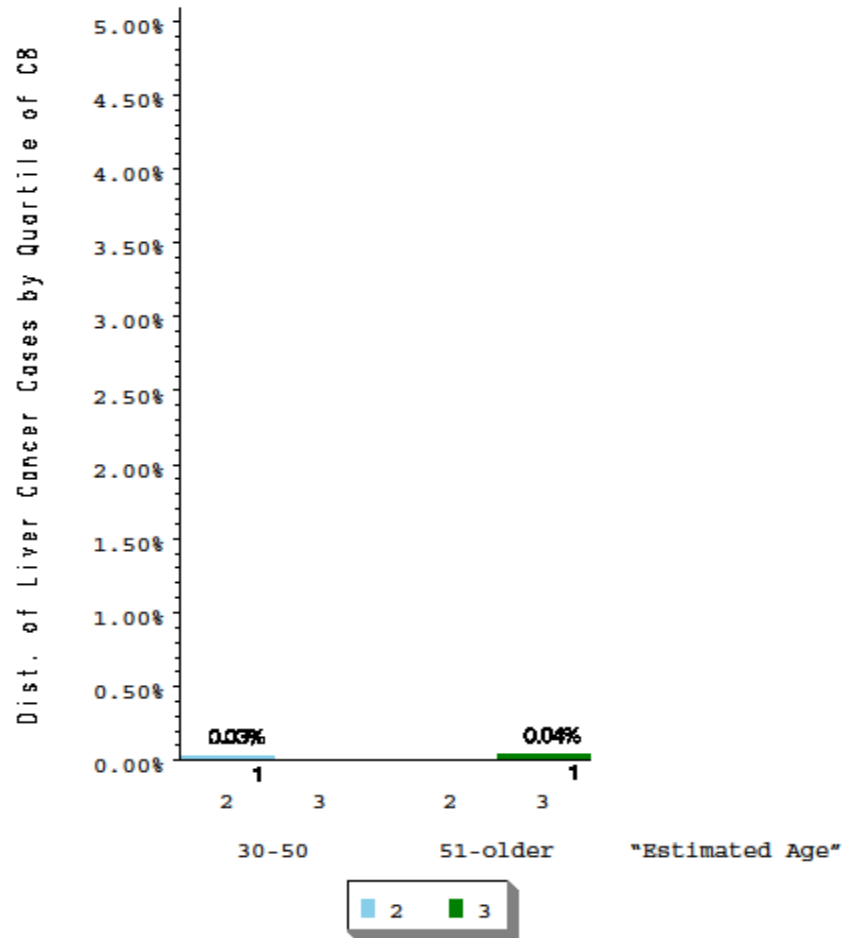
C8 Health Project

*Self- Reported Diagnosis of Liver Cancer in Male Adults
Stratified by Age*

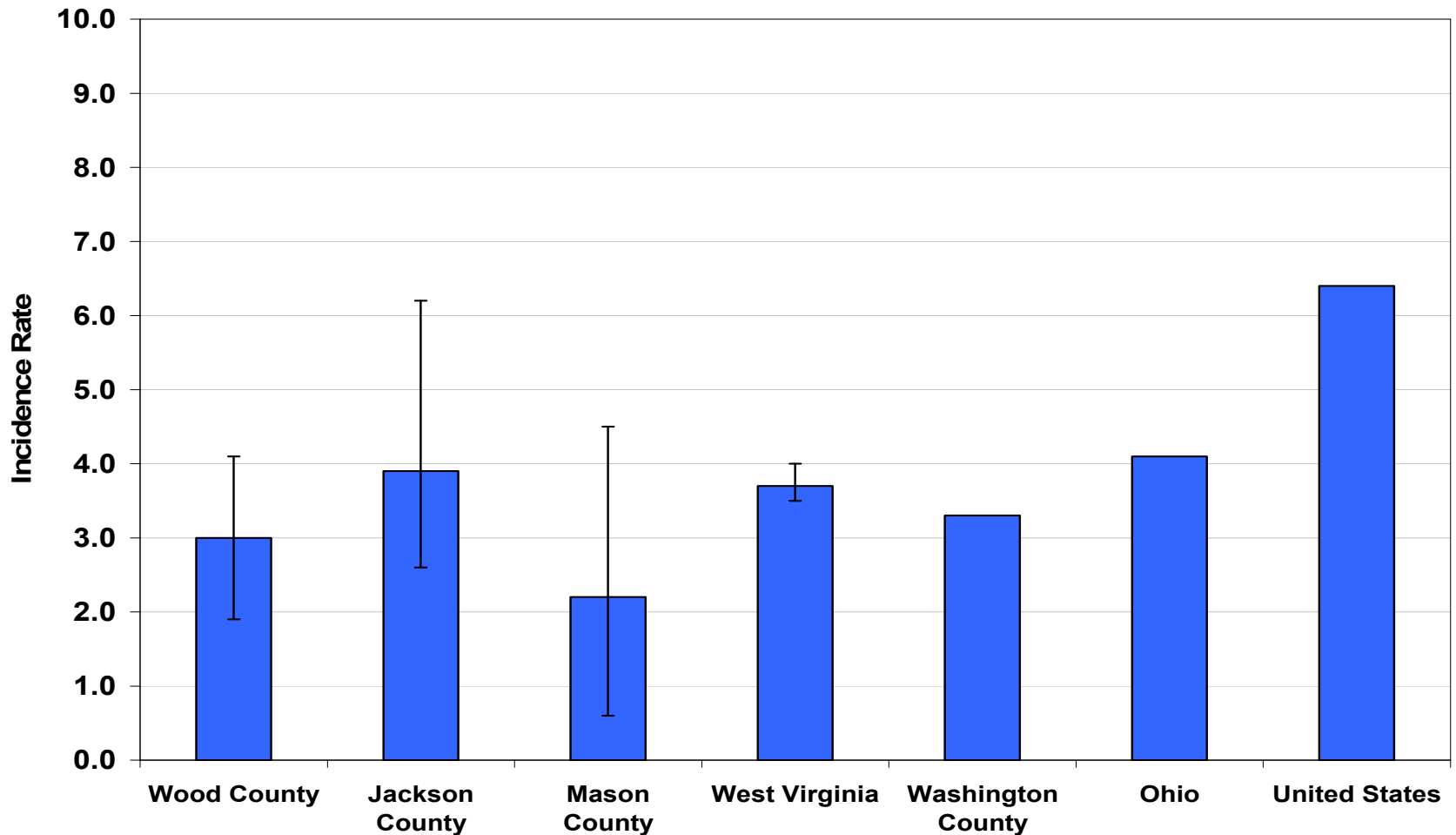


C8 Health Project

*Self- Reported Diagnosis of Liver Cancer in Female Adults
Stratified by Age*



West Virginia and Ohio Counties, Average Annual Age-adjusted Liver Cancer Incidence Rates per 100,000 (95% CI) (1993-2002 and 2001-2005, respectively)

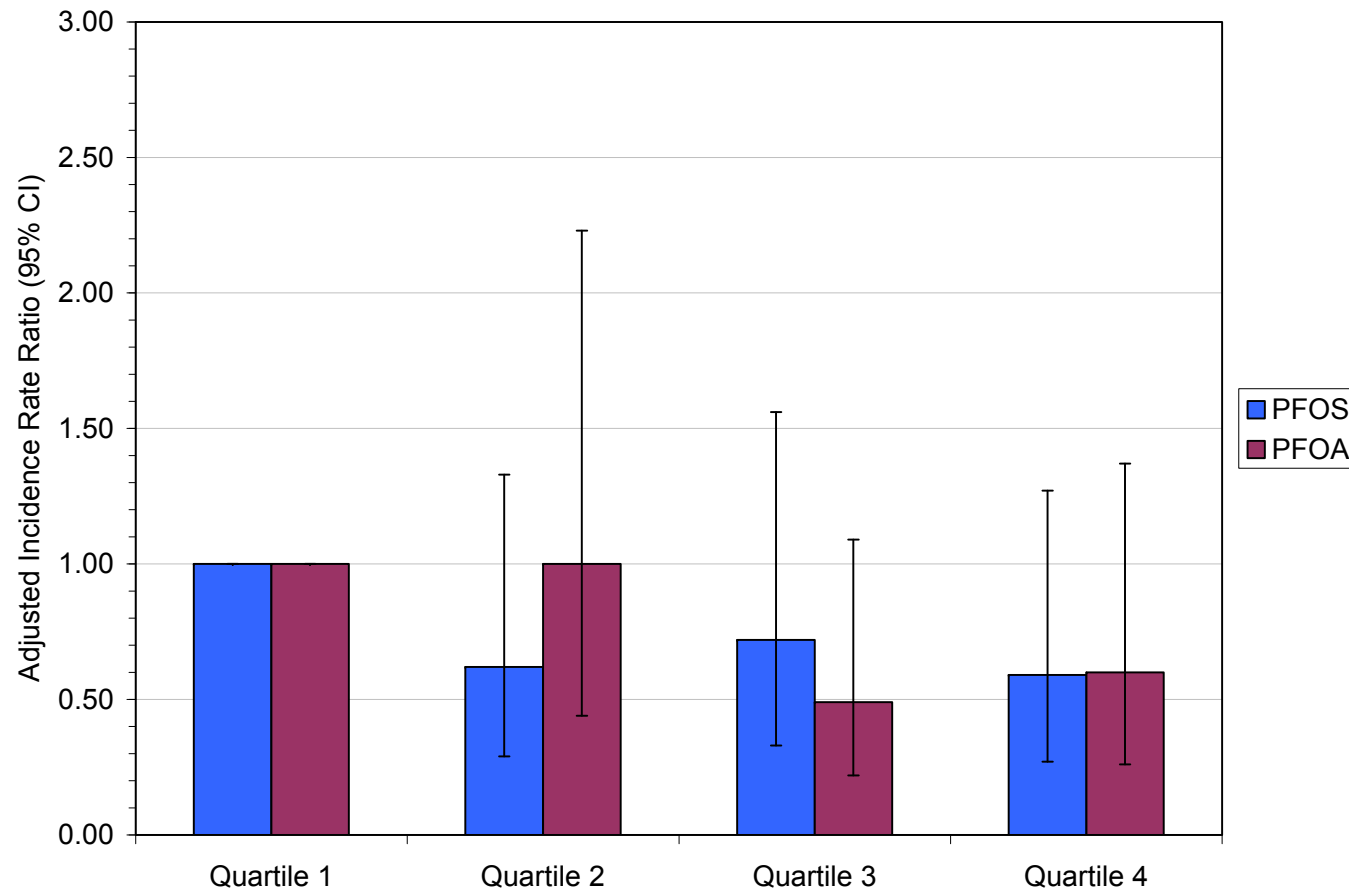


**Minnesota Department of Health
East Metro Communities with Biomonitoring Data,
Liver Cancer Incidence,
1996 – 2004**

<u>Community</u>	<u>Obs</u>	<u>Exp*</u>	<u>SIR</u>
Oakdale	9	7	1.3
Lake Elmo	0	3	0.0
<u>Cottage Grove</u>	6	7	0.9

*Expected number based on metro area cancer incidence rates

Eriksen et al. (Denmark)
Age-adjusted Incidence Rate Ratios (95% CI)
by Plasma Concentration of PFOS and PFOA
for Liver Cancer (N = 67 cases)



Liver Cancer

- **Conclusion**

- No epidemiologic report associated PFOA or PFOS with liver cancer.

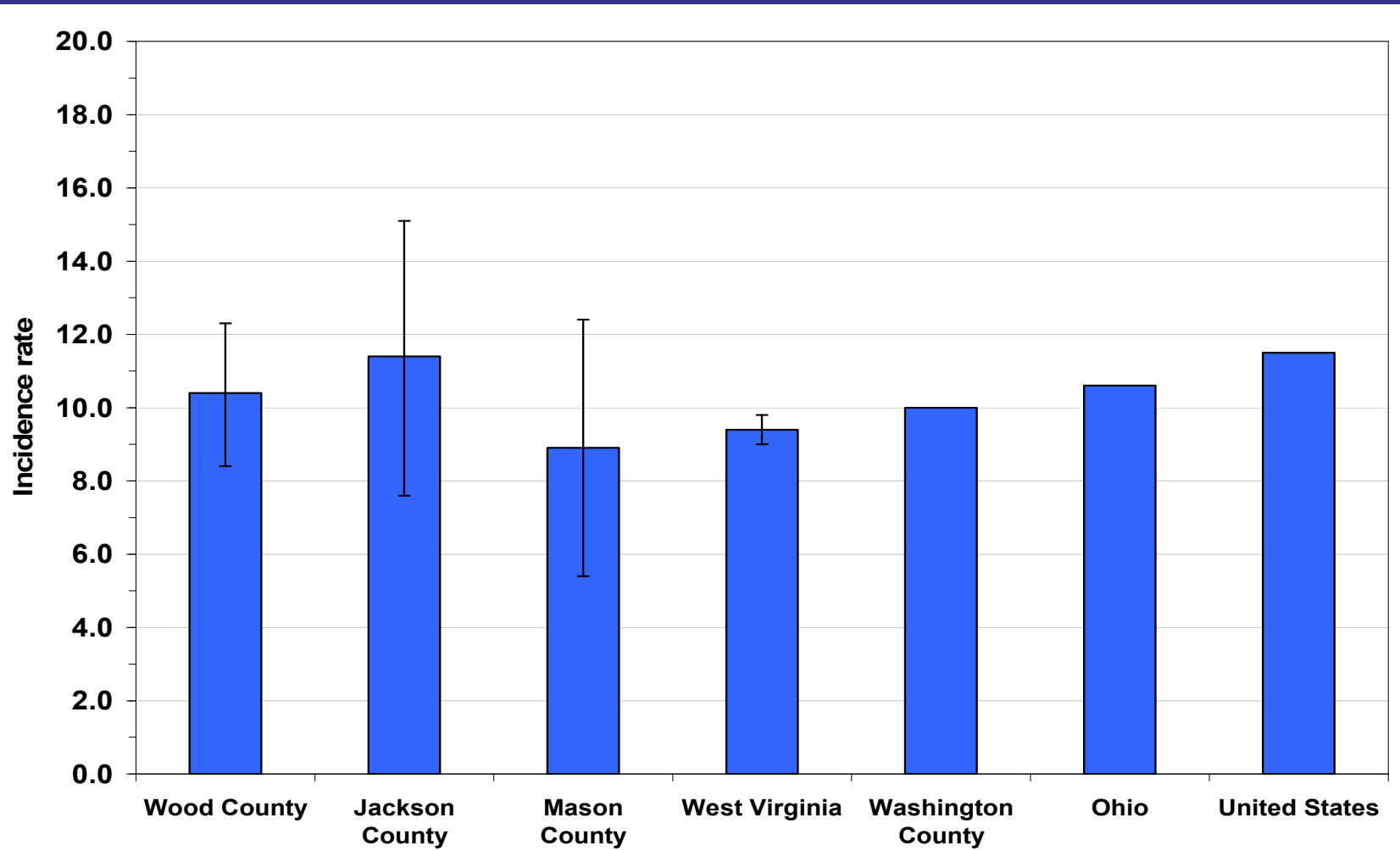
Health Endpoints
Covered

Pancreatic Cancer

Occupational Studies Pancreatic Cancer

Study	Categorization	Obs	Exp	SMR	95%CI
Alexander et al.	Decatur Facility (AL comparison)	0	-	-	-
Lundin et al.	Cottage Grove Facility (MN comparison)	13	15	0.9	0.3 – 0.9
	“Not exposed PFOA job”	5	7.1	0.7	0.2 – 1.6
	Ever “Probable exposure”	7	6.7	1.0	0.4 – 2.1
	Ever “Definite exposure”	1	1.2	0.9	0.0 – 4.7
Leonard et al.	Washington Works Facility (W.V. comparison)	11	13.7	0.8	0.4 – 1.4
	Washington Works Facility (DuPont comparison)	11	11.2	1.0	0.5 – 1.8

West Virginia and Ohio Counties, Average Annual Age-adjusted Pancreatic Cancer Incidence Rates per 100,000 (95% CI) (1993-2002 and 2001-2005, respectively)

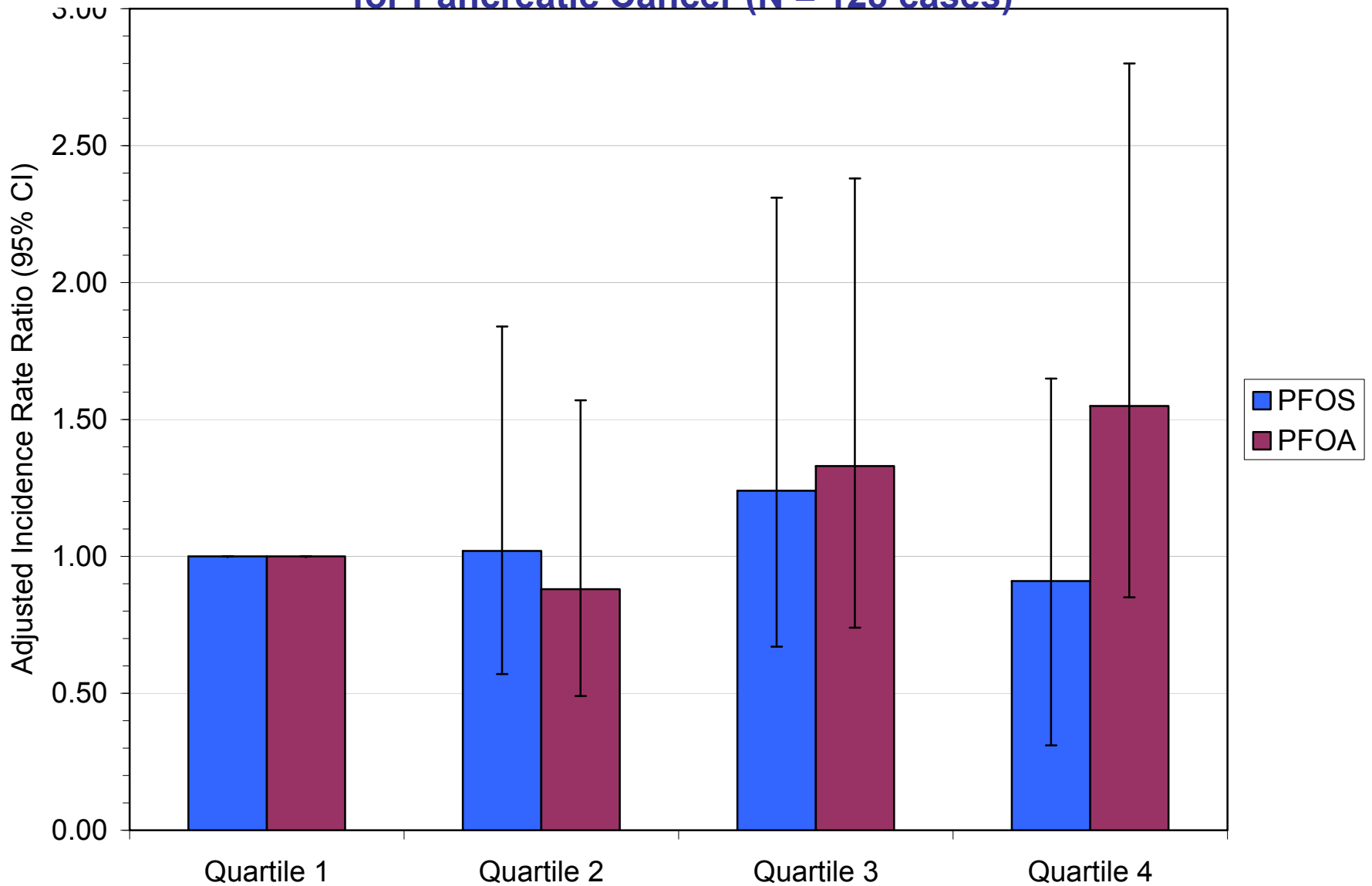


**Minnesota Department of Health
East Metro Communities with Biomonitoring Data,
Pancreatic Cancer Incidence,
1996 – 2004**

<u>Community</u>	<u>Obs</u>	<u>Exp*</u>	<u>SIR</u>
Oakdale	13	16	0.8
Lake Elmo	5	5	1.0
<u>Cottage Grove</u>	16	14	1.1

*Expected number based on metro area cancer incidence rates

Eriksen et al.(Denmark)
Age-adjusted Incidence Rate Ratios (95% CI)
by Plasma Concentration of PFOS and PFOA
for Pancreatic Cancer (N = 128 cases)



Pancreatic Cancer

- Conclusion
 - No epidemiologic report associated PFOA or PFOS with pancreatic cancer.

Health Endpoints
Covered

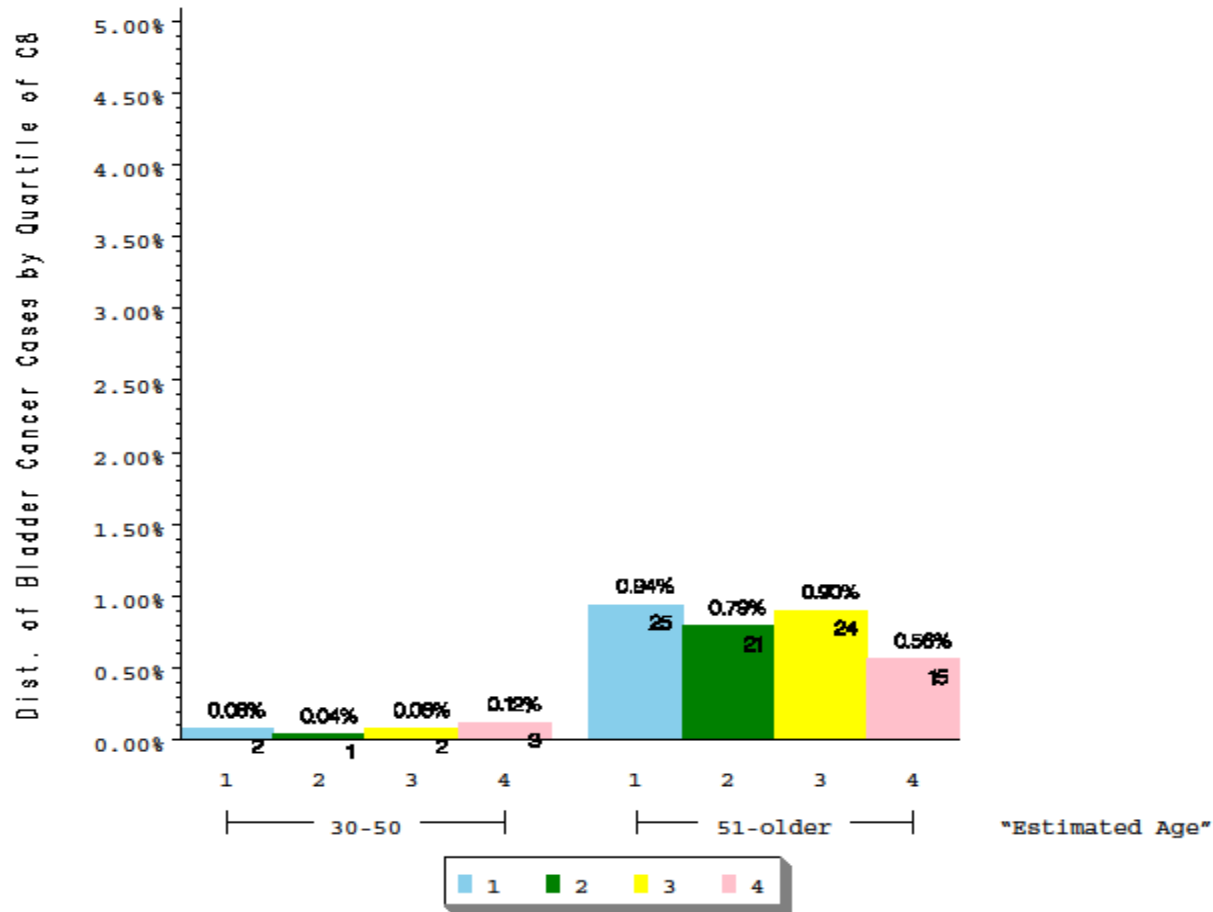
Bladder Cancer

Occupational Studies - Bladder Cancer

Study	Categorization	Obs	Exp	SMR/RR*	95%CI
Alexander et al.	Decatur Facility (AL comparison)	3	0.6	4.8	1.0 – 14.1
	“Not exposed PFOS job”	0	-	-	-
	Ever “Low exposure”	0	-	-	-
	Ever “High exposure”	3	0.2	12.8	2.6 – 37.4
Alexander & Olsen	Decatur Facility (NCI SEER comparison)	11	8.6	1.3*	0.6 – 2.3
	0 - < 1 years (internal ref)	2	-	1.0* (ref)	-
	1 – 5 years (high exposure)	4	-	0.8*	0.2 – 4.7
	5 -< 10 years (high exposure)	3	-	1.9*	0.3 – 12.1
	≥ 10 years (high exposure)	2	-	1.5*	0.2 – 10.11
Lundin et al.	Cottage Grove Facility (MN comparison)	7	6.8	1.1	0.5 -2.8
	“Not exposed PFOA job”	4	3.0	1.4	0.4 – 3.7
	Ever “Probable exposure”	3	2.8	1.2	0.3 – 3.5
	Ever “Definite exposure”	0	0.5	0.0	0.0 – 7.6
Leonard et al.	Washington Works (W.V. comparison)	7.0	6.8	1.0	0.4 – 2.1
	Washington Works (DuPont comparison)	7.0	5.4	1.3	0.5 – 2.7

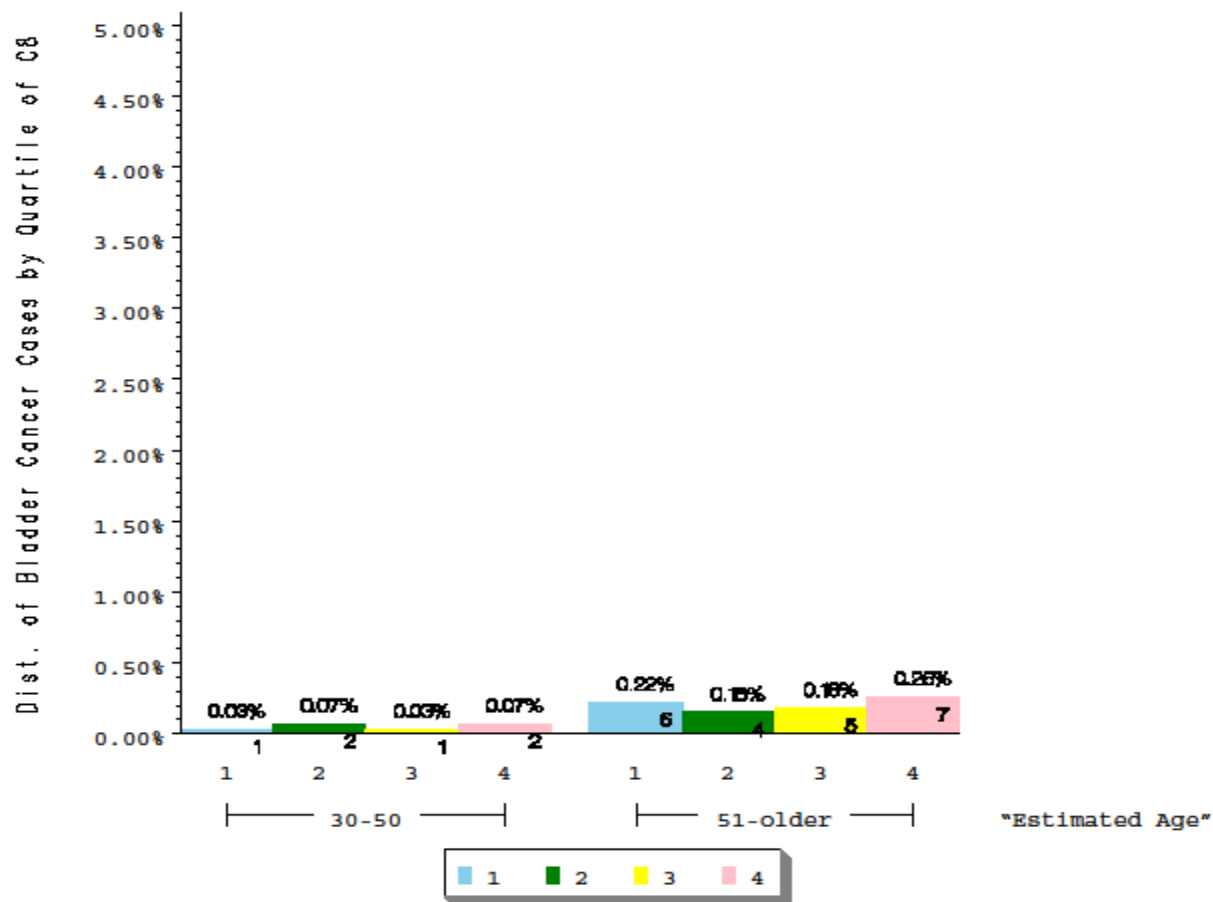
C8 Health Project

*Self- Reported Diagnosis of Bladder Cancer in Male Adults
Stratified by Age*

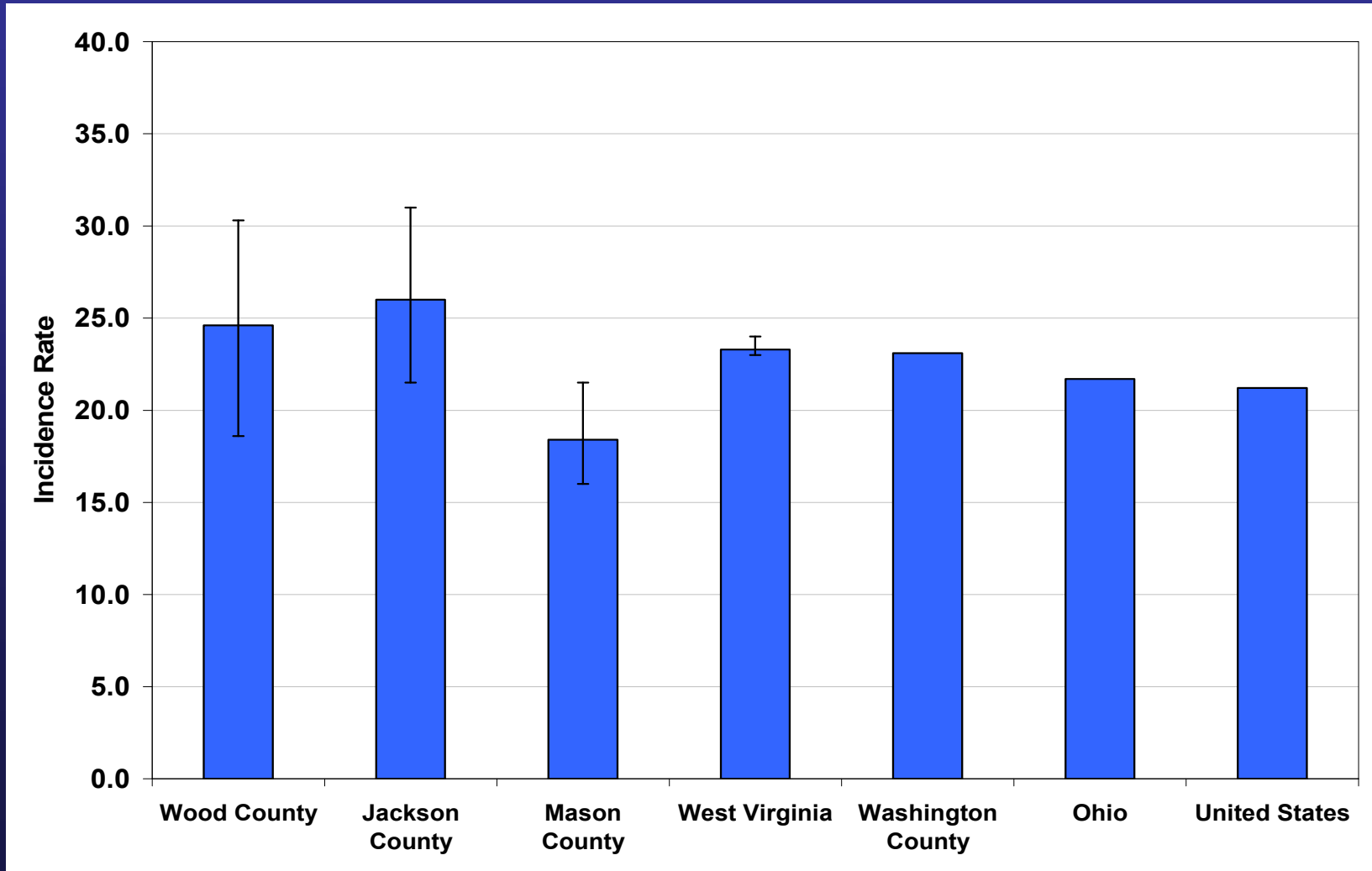


C8 Health Project

*Self- Reported Diagnosis of Bladder Cancer in Female Adults
Stratified by Age*



West Virginia and Ohio Counties, Average Annual Age-adjusted Bladder Cancer Incidence Rates per 100,000 (95% CI) (1993-2002 and 2001-2005, respectively)

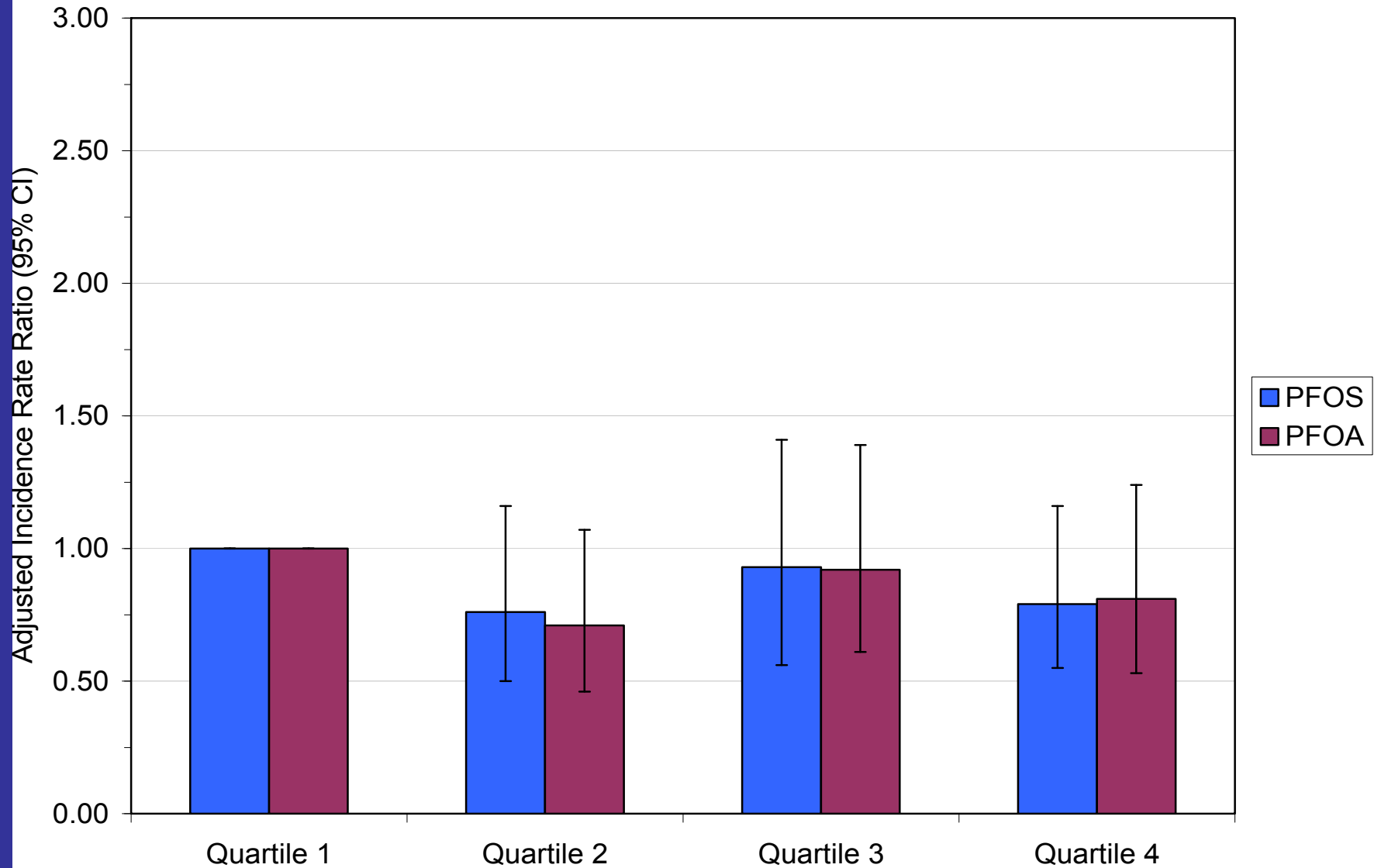


**Minnesota Department of Health
East Metro Communities with Biomonitoring Data,
Bladder Cancer Incidence,
1996 – 2004**

<u>Community</u>	<u>Obs</u>	<u>Exp*</u>	<u>SIR</u>
Oakdale	40	39	1.0
Lake Elmo	5	10	0.5
<u>Cottage Grove</u>	39	30	1.3

*Expected number based on metro area cancer incidence rates

Eriksen et al.(Denmark)
Age-adjusted Incidence Rate Ratios (95% CI)
by Plasma Concentration of PFOS and PFOA
for Bladder Cancer (N = 332 cases)



Bladder Cancer

- Conclusion

- One epidemiologic report (Alexander et al.) associated bladder cancer mortality with having worked in a high POSF job area.
- This finding was not substantiated by Alexander and Olsen who conducted a more in-depth investigation of bladder cancer incidence of the same workforce.
- No other reports have associated PFOS or PFOA exposure with bladder cancer – epidemiological or toxicological.

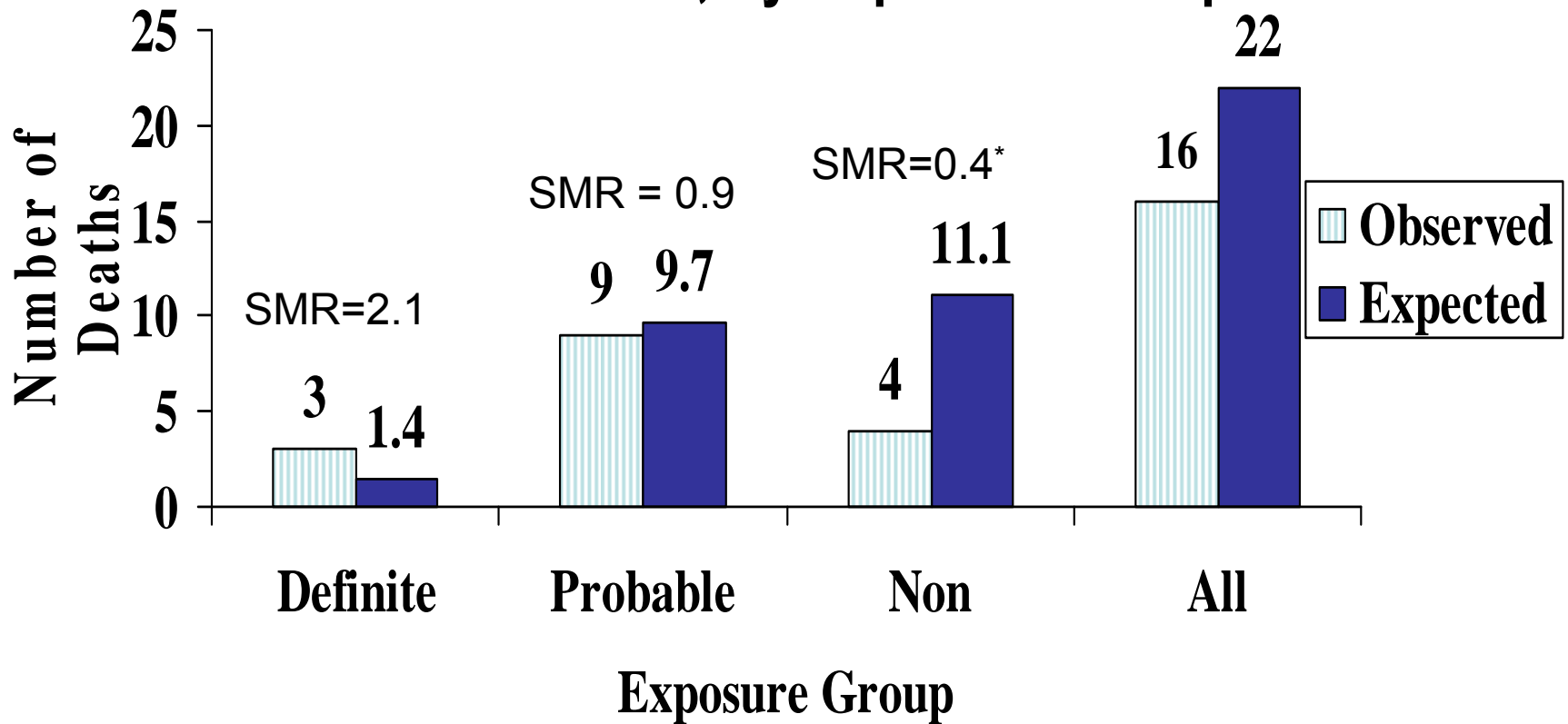
Health Endpoints
Covered

Prostate Cancer

Occupational Studies Prostate Cancer

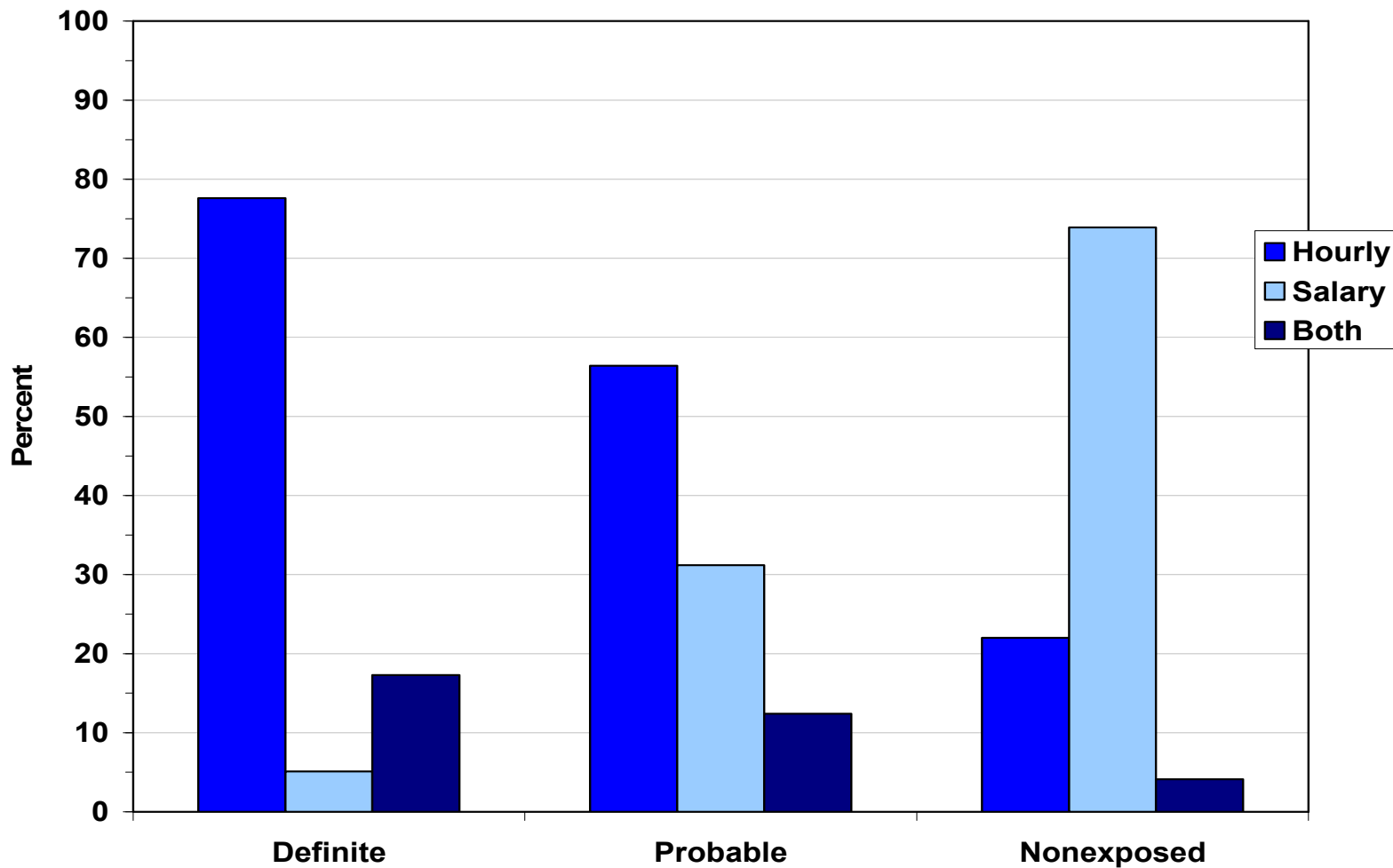
Study	Categorization	Obs	Exp	SMR or OR*	95%CI
Alexander et al.	Facility (AL comparison)	0	-	-	-
Grice et al.	“Not exposed PFOS job”	10	-	1.0 (ref)	-
	Low or high (≥ 1 year)	16	-	1.4*	0.6 – 3.0
	High (> 1 year)	9	-	1.1*	0.4 – 2.7
Lundin et al.	Facility (MN comparison)	16	22	0.5	0.3 – 0.9
	“Not exposed PFOA job”	4	11.1	0.4	0.1 – 0.9
	Ever “Probable exposure”	9	9.7	0.9	0.4 – 1.8
	Ever “Definite exposure”	3	1.4	2.1	0.4 – 6.1
Leonard et al.	Facility (W.V. comparison)	12	20.9	0.6	0.3 – 1.0
	Facility (DuPont comparison)	12	18.4	0.7	0.3 – 1.1

3M Cottage Grove Observed and Expected Deaths for Prostate Cancer, by Exposure Group



*=Statistically lower than expected compared to the rest of Minnesota

Percent Hourly vs Salary Status of 3M Cottage Grove Cohort by PFOA Exposure Group



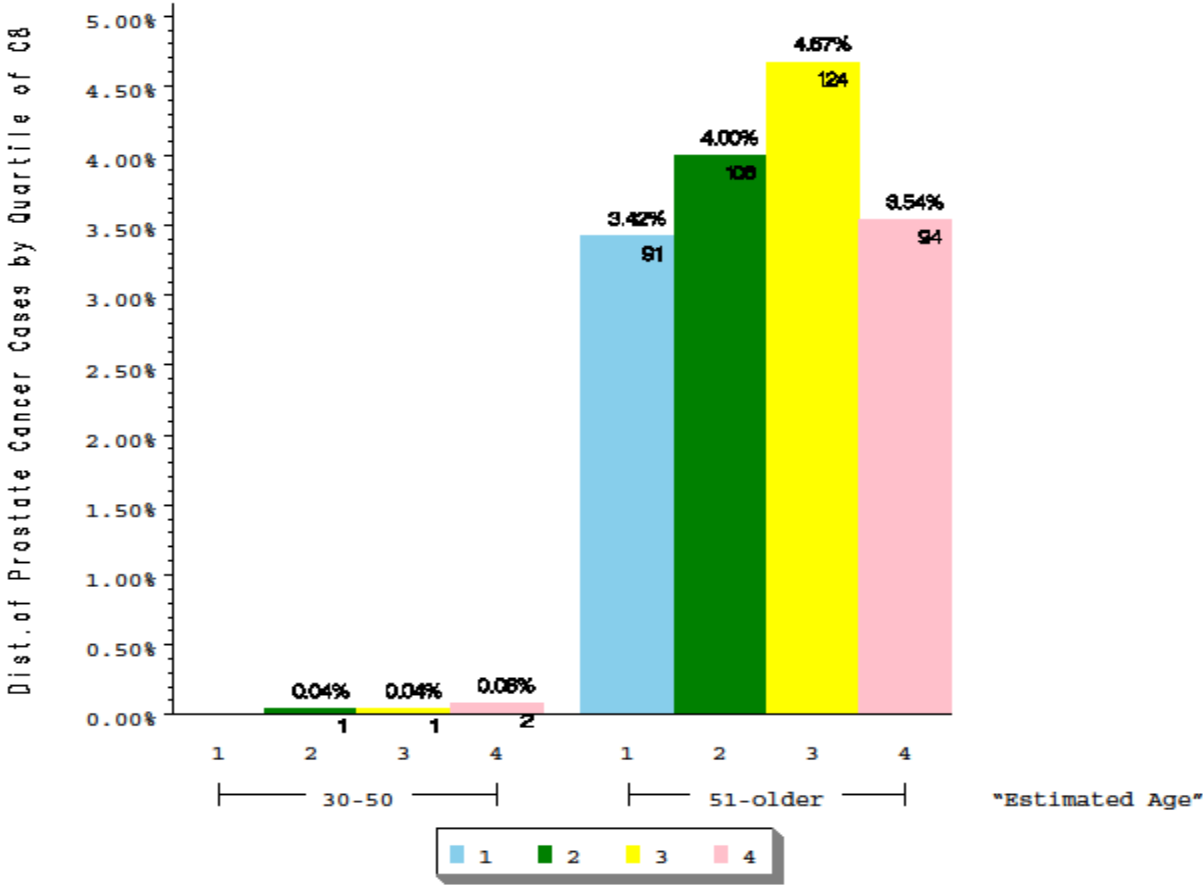
Lundin et al.

**Prostate Cancer: Comparing Exposure
within the 3M Cottage Grove Study,
Results from Cox Proportional Hazard Model**

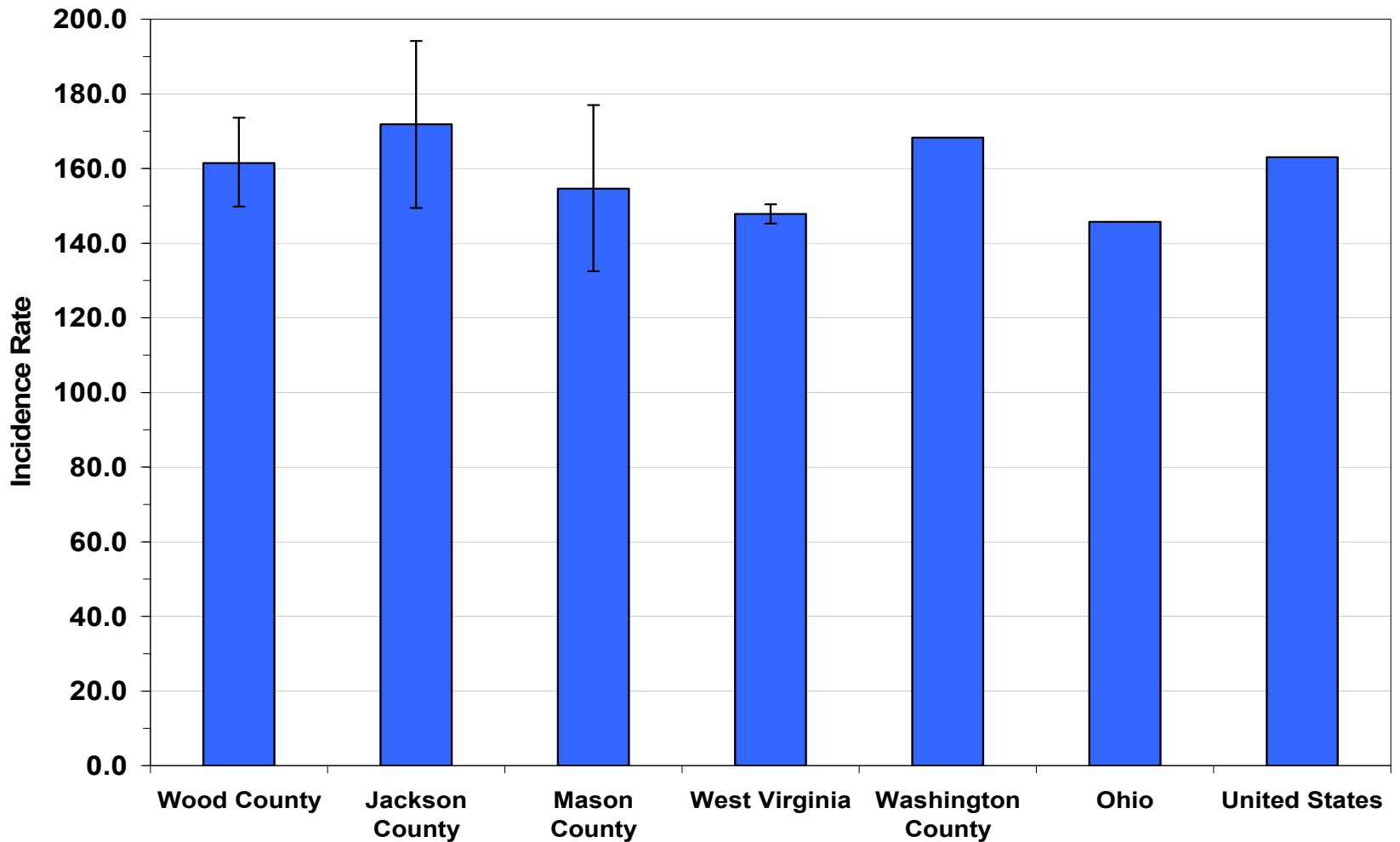
Exposure classification	N	RR	95% CI
Job levels			
High	2	6.6	1.1 - 37.7
Moderate	10	3.0	0.9 - 9.7
Low	4	1.0	-
High exposure job equivalents			
≥5 years	7	3.7	1.3 - 10.4
1-4 years	1	0.4	0.1 - 3.6
<1 Years	8	1.0	-

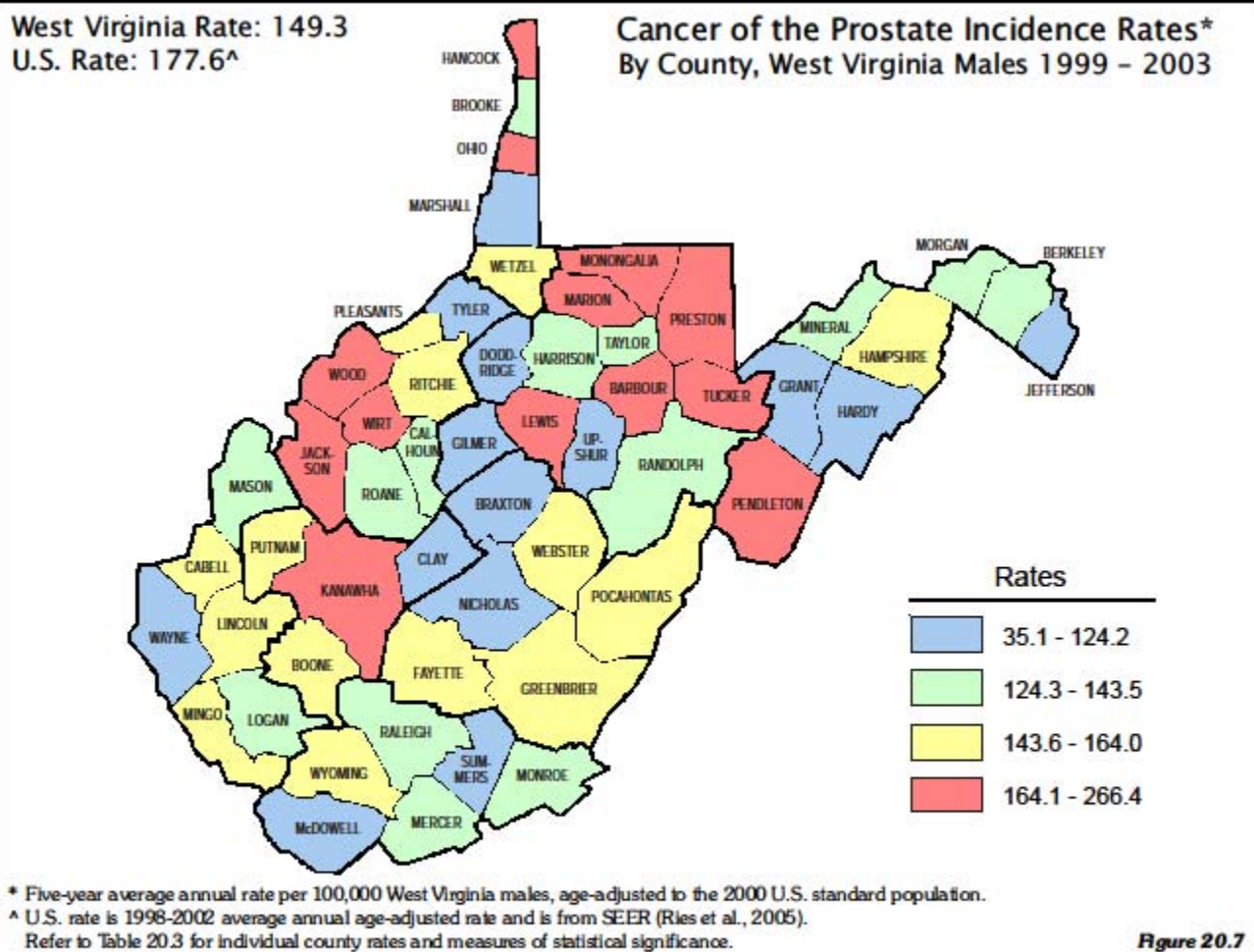
C8 Health Project

Self- Reported Diagnosis of Prostate Cancer in Male Adults Stratified by Age



West Virginia and Ohio Counties, Average Annual Age-adjusted Prostate Cancer Incidence Rates per 100,000 (95% CI) (1993-2002 and 2001-2005, respectively)

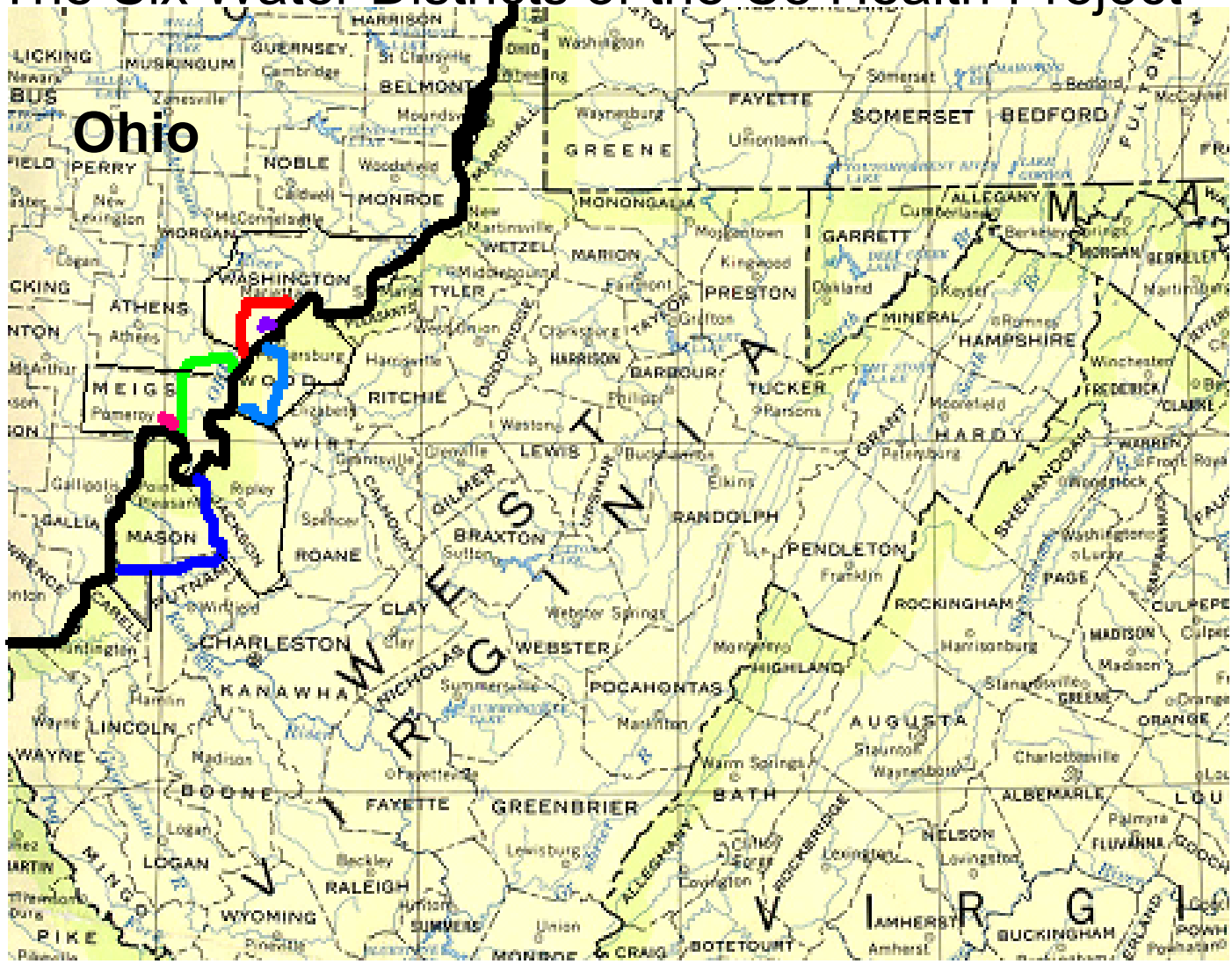




Colsher et al.

- Analyzed prostate cancer (1998-2002) by residential zip code at diagnosis within the 3 W.V. counties (Wood, Jackson, Mason).
- There was a tendency towards higher than expected numbers of prostate cancer cases (not statistically significant) in all areas except southern Mason county, eastern Jackson county, and eastern Wood county.

The Six Water Districts of the C8 Health Project



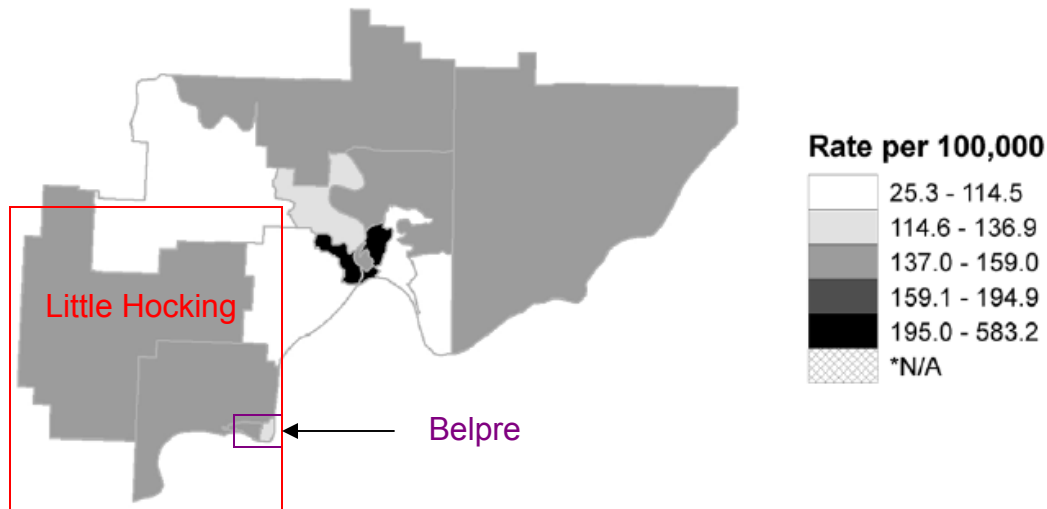
Little Hocking Lubeck Belpre Tupper Plains Pomeroy Mason

Ohio Cancer Incidence Surveillance System

Washington County

Prostate Cancer

Figure 4. Average Annual Age-adjusted Incidence Rates of Invasive Prostate Cancer, by Census Tract, in Washington County, 1996-2005¹⁻⁴



[1] Source: Ohio Cancer Incidence Surveillance System, Ohio Department of Health, 2008.

[2] Rates are per 100,000 and were calculated using vintage 2006 intercensal estimates for July 1, 1996-1999 and postcensal estimates for July 1, 2000-2005, (U.S. Census Bureau, 2007). Rates are direct age-adjusted to the U.S. 2000 standard population.

[3] NOTE: Large census tracts may appear to have higher rates and risks due to their size—interpret with caution.

[4] Cut points for rate quartiles were derived from the distribution for the State of Ohio.

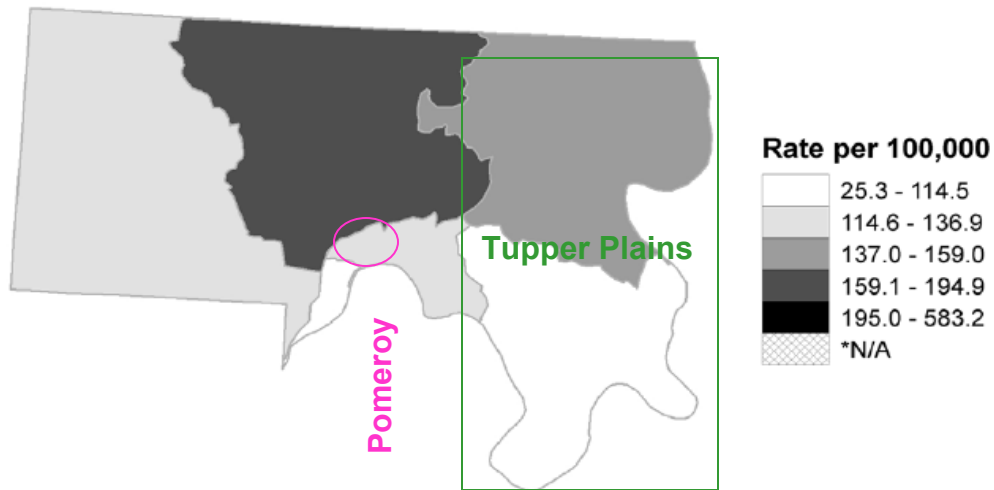
[‡]Rates may be unstable and are not presented when the count for 1996-2005 is less than five (i.e., average annual count is <1). A small number (less than 1%) of unusually high outlying incidence rates are also not presented.

Ohio Cancer Incidence Surveillance System

Meigs County

Prostate Cancer

Figure 4. Average Annual Age-adjusted Incidence Rates of Invasive Prostate Cancer, by Census Tract, in Meigs County, 1996-2005¹⁻⁴



[1] Source: Ohio Cancer Incidence Surveillance System, Ohio Department of Health, 2008.

[2] Rates are per 100,000 and were calculated using vintage 2006 intercensal estimates for July 1, 1996-1999 and postcensal estimates for July 1, 2000-2005, (U.S. Census Bureau, 2007). Rates are direct age-adjusted to the U.S. 2000 standard population.

[3] NOTE: Large census tracts may appear to have higher rates and risks due to their size—interpret with caution.

[4] Cut points for rate quartiles were derived from the distribution for the State of Ohio.

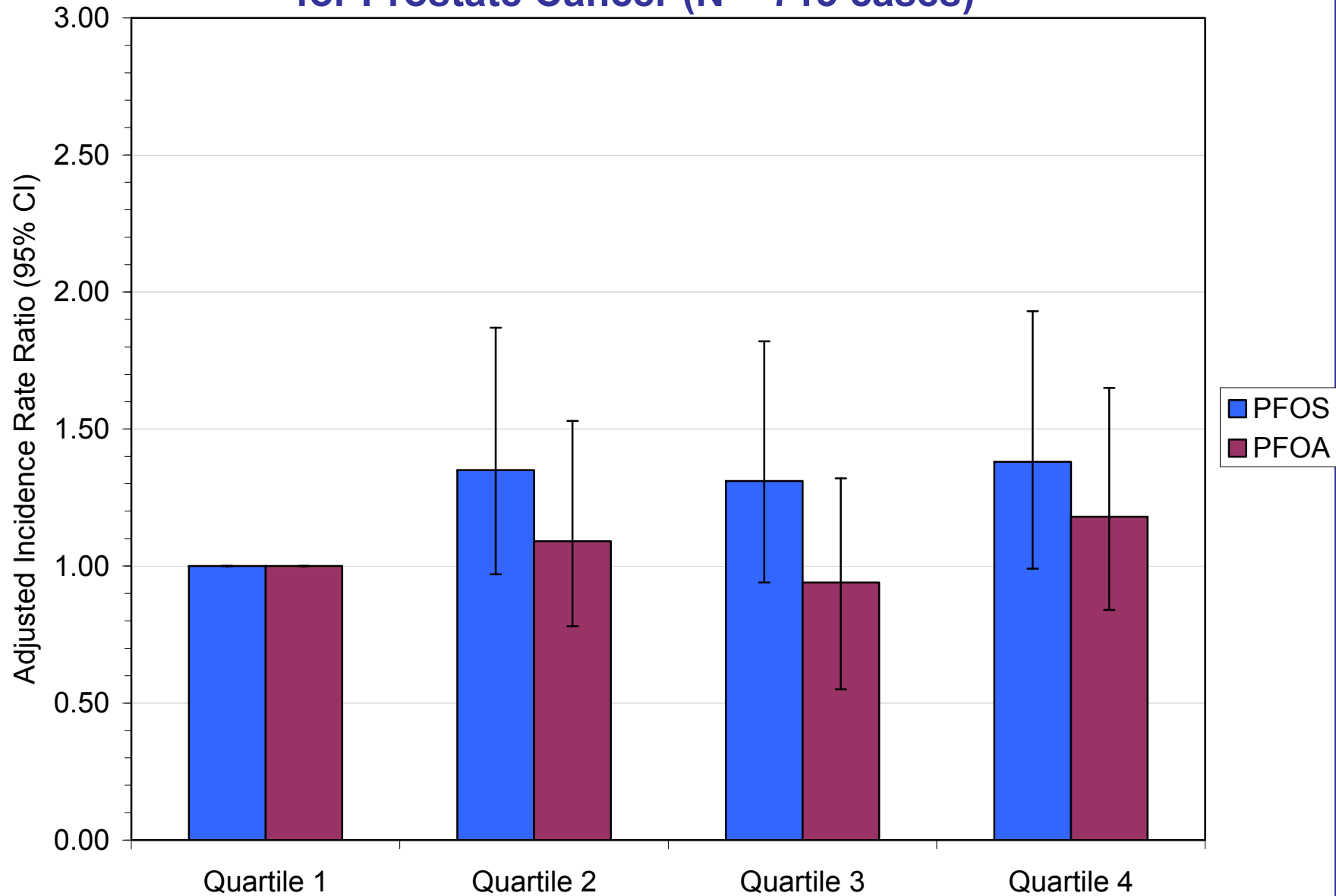
*Rates may be unstable and are not presented when the count for 1996-2005 is less than five (i.e., average annual count is <1). A small number (less than 1%) of unusually high outlying incidence rates are also not presented.

Minnesota Department of Health
East Metro Communities with Biomonitoring Data,
Prostate Cancer Incidence,
1996 – 2004

<u>Community</u>	<u>Obs</u>	<u>Exp*</u>	<u>SIR</u>
Oakdale	132	137	1.0
Lake Elmo	44	43	1.0
<u>Cottage Grove</u>	118	124	1.0

*Expected number based on metro area cancer incidence rates

Eriksen et al.(Denmark)
Age-adjusted Incidence Rate Ratios (95% CI)
by Plasma Concentration of PFOS and PFOA
for Prostate Cancer (N = 713 cases)



Prostate Cancer

- Conclusions

- One epidemiologic report (Lundin et al.) reported an association, albeit inconsistently, with prostate cancer and having exposure to PFOA.
- The inconsistency was due to the fact that the association was magnified by a deficit of prostate cancer mortality among the least exposed.
- This study is being expanded to examine prostate cancer incidence.
- Prostate cancer mortality was higher in two West Virginia counties (Wood and Mason) compared to W.V. (but not U.S.). Prostate cancer rates for the water districts of Little Hocking and Tupper Plains appeared at or below the Ohio average.
- No other reports have associated PFOS or PFOA exposure with prostate cancer – epidemiological or toxicological.

Health Endpoints Covered

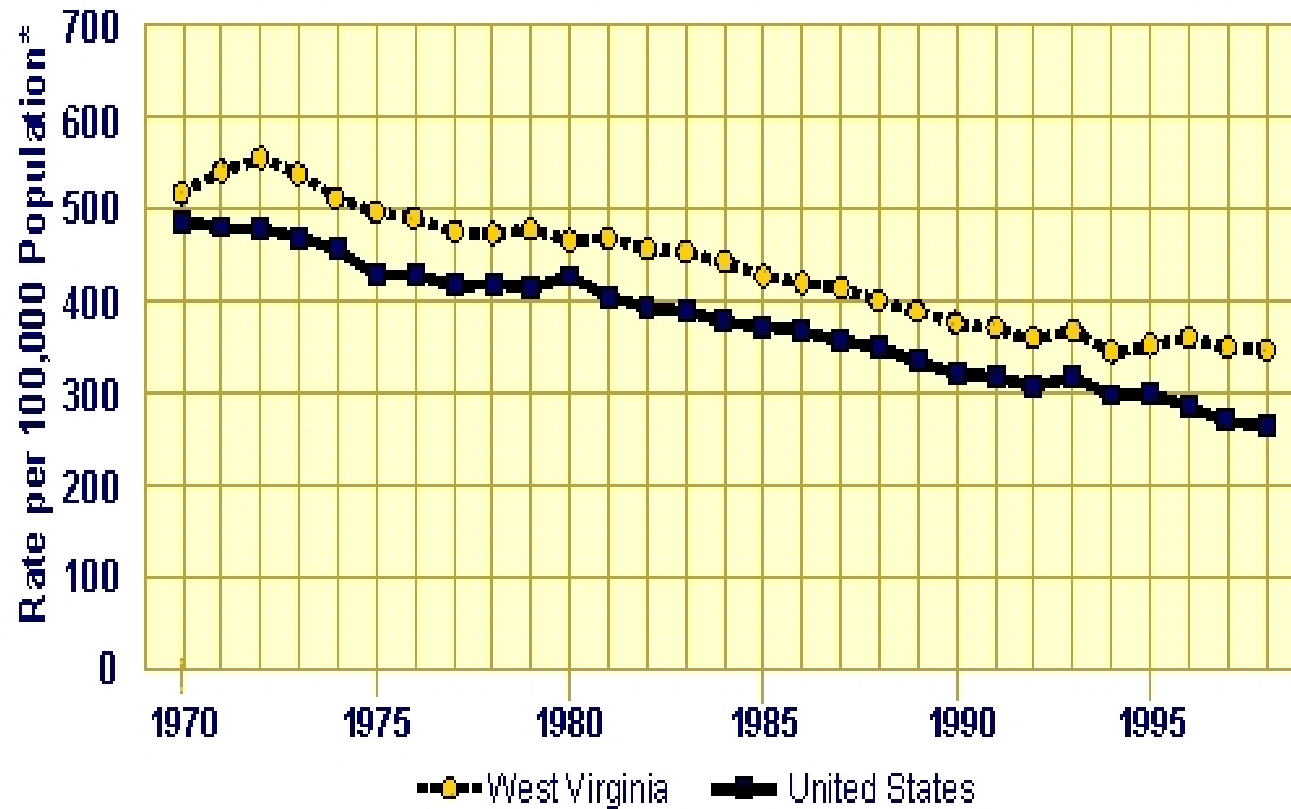
Ischemic Heart Disease

Occupational Studies, Ischemic Heart Disease*

Study	Categorization	Obs	Exp	SMR	95%CI
Alexander et al.	Decatur Facility (AL comparison)	35	62.5	0.6	0.4 – 0.8
	“Not exposed PFOS job”	14	16.7	0.8	0.5 – 1.4
	Ever “Low exposure”	7	12.9	0.5	0.2 – 1.1
	Ever “High exposure”	14	24.8	0.6	0.3 – 1.0
Lundin et al.	Cottage Grove Facility (MN comparison)	201	259.2	0.8	0.7 – 0.9
	“Not exposed PFOA job”	125	156.3	0.8	0.7 – 0.9
	Ever “Probable exposure”	93	116.3	0.8	0.7 – 1.0
	Ever “Definite exposure”	16	20.0	0.8	0.5 – 1.4
Leonard et al.	Washington Works Facility (W.V. comparison)	239	348.1	0.7	0.6 – 0.8
	Washington Works Facility (DuPont comparison)	239	218.2	1.1	1.0 – 1.2
Sakr et al.	Washington Works Facility	see	next	slides	

*Decatur facility = All Heart Disease

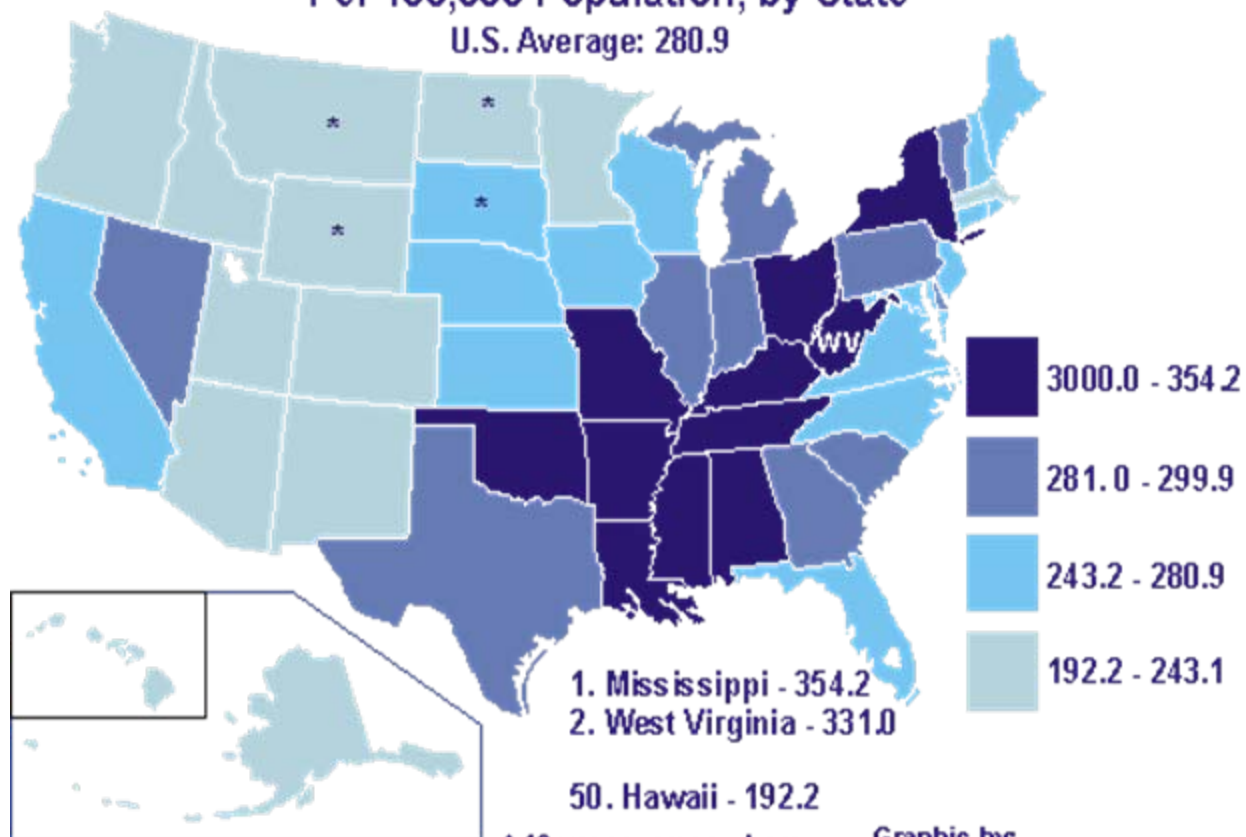
**Figure 4.2. Heart Disease Mortality
West Virginia and United States, 1970-1998
Both Genders**



*Rates are adjusted by age to the 2000 U.S. Standard million.

1995-97 Heart Disease Mortality Per 100,000 Population, by State

U.S. Average: 280.9



Source: 1995-97 Centers for
Disease Control and Prevention

Graphic by:
WV Health Statistics Center

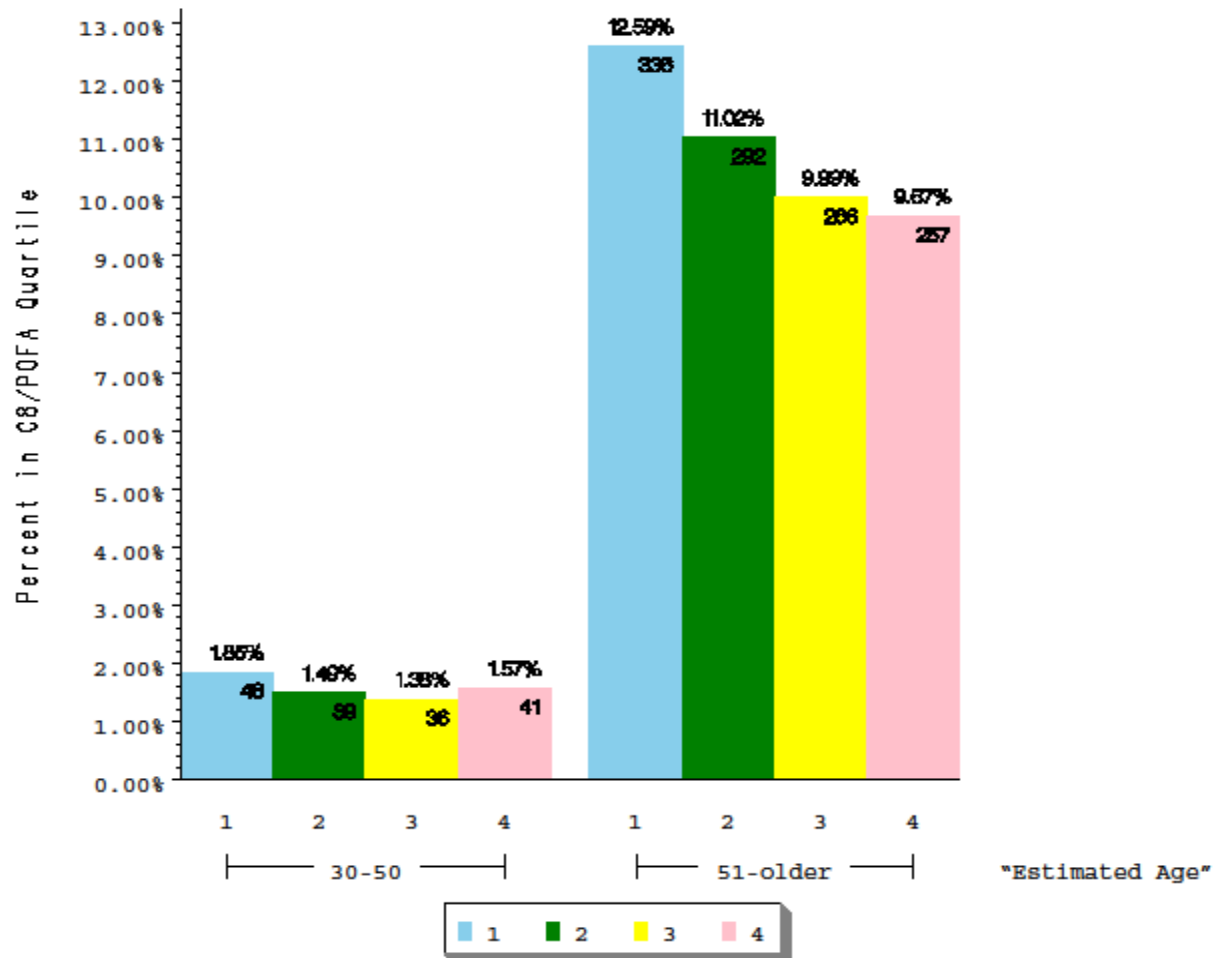
Occupational Studies (continued)

Ischemic Heart Disease

Sakr et al.	Exposure (ppm-yrs)	No lag	5-year lag	10-year lag	15-year lag	20-year lag
DuPont Washington Works	Approximate Cumulative (PFOA)	No lag	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Qtr 1	<2.1 ppm-yrs	1.0	1.0	1.0	1.0	1.0
Qtr 2	2.1 – 5.0 ppm-yrs	0.8 (0.5,1.2)	1.0 (0.6,1.6)	1.0 (0.7,1.6)	1.0 (0.7,1.6)	0.9 (0.6, 1.4)
Qtr 3	5.1 – 6.5 ppm-yrs	1.0 (0.6,1.6)	1.2 (0.8,2.0)	1.4 (0.9,2.4)	1.4 (0.8,2.4)	1.4 (0.8, 2.2)
Qtr 4	>= 6.5 ppm-yrs	0.9 (0.5,1.5)	1.1 (0.7,2.0)	1.6 (0.9,2.7)	1.2 (0.7,2.1)	1.3 (0.8, 2.3)
P- value for trend		0.98	0.58	0.06	0.62	0.23

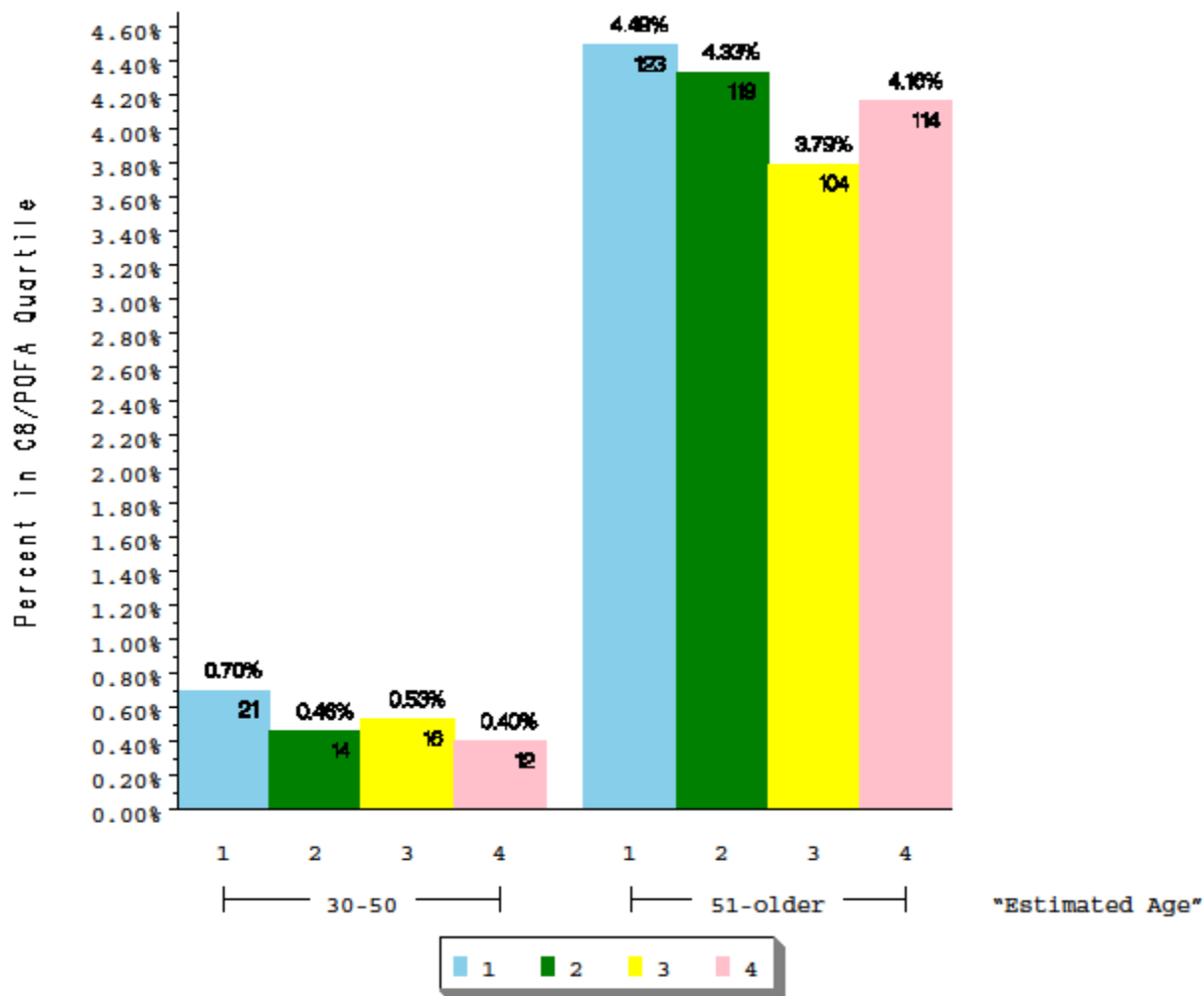
C8 Health Project

Self- Reported Diagnosis of Myocardial Infarction in Male Adults Stratified by Age



C8 Health Project

Self- Reported Diagnosis of Myocardial Infarction in Female Adults Stratified by Age



Ischemic Heart Disease

Conclusion

No epidemiologic study has associated PFOA or PFOS with ischemic heart disease.

Health Endpoints Covered

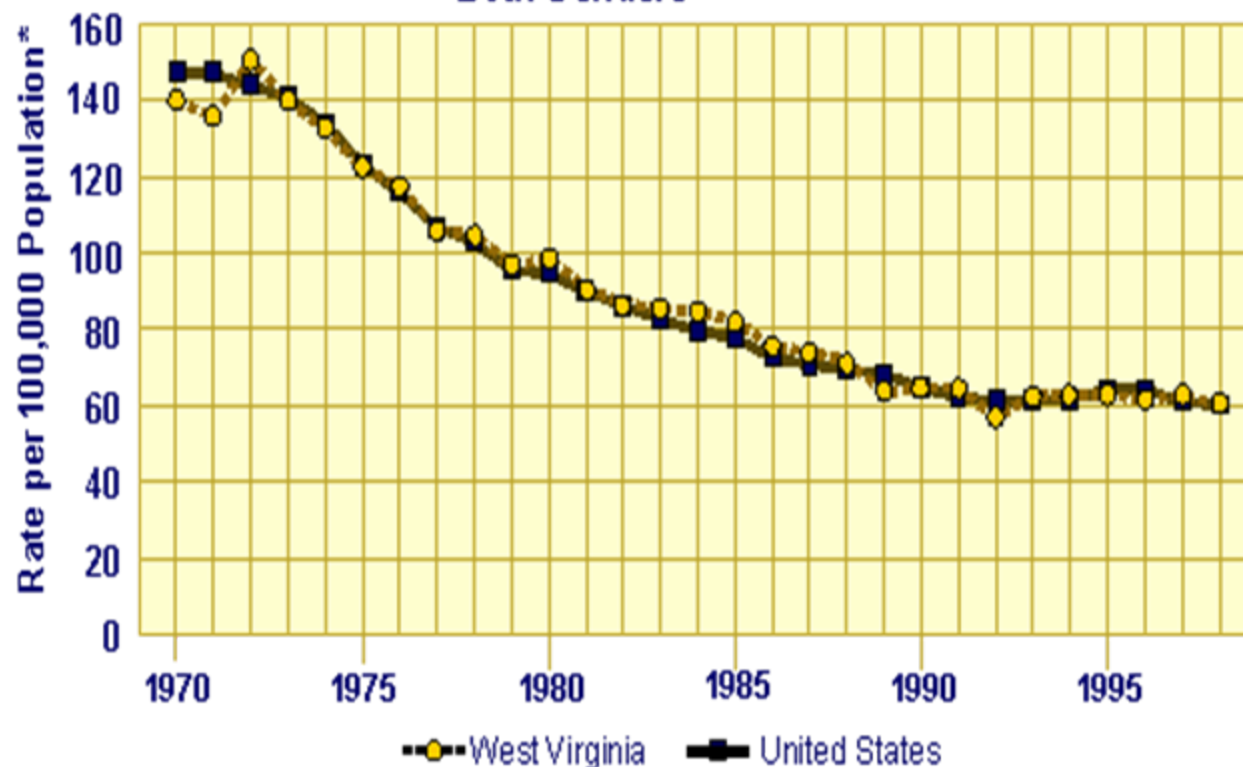
Cerebrovascular Disease

Occupational Studies, Cerebrovascular Disease*

Study	Categorization	Obs	Exp	SMR	95%CI
Alexander et al.	Decatur Facility (AL comparison)	5	7.1	0.7	0.2 - 1.6
	“Not exposed PFOS job”	1	2.6	0.4	0.0 - 2.1
	Ever “Low exposure”	2	1.6	1.3	0.2 - 4.5
	Ever “High exposure”	2	2.8	0.7	0.1 - 2.6
Lundin et al.	Cottage Grove Facility (MN comparison)	35	54.4	0.6	0.5 - 0.9
	“Not exposed PFOA job”	13	27.1	0.5	0.3 - 0.8
	Ever “Probable exposure”	17	24.2	0.7	0.4 - 1.1
	Ever “Definite exposure”	5	3.1	1.6	0.5 - 3.7
Leonard et al.	Washington Works Facility (W.V. comparison)	35	58.6	0.6	0.4 - 0.8
	Washington Works Facility (DuPont comparison)	35	40.6	0.9	0.6 - 1.2

*Decatur facility = All Heart Disease

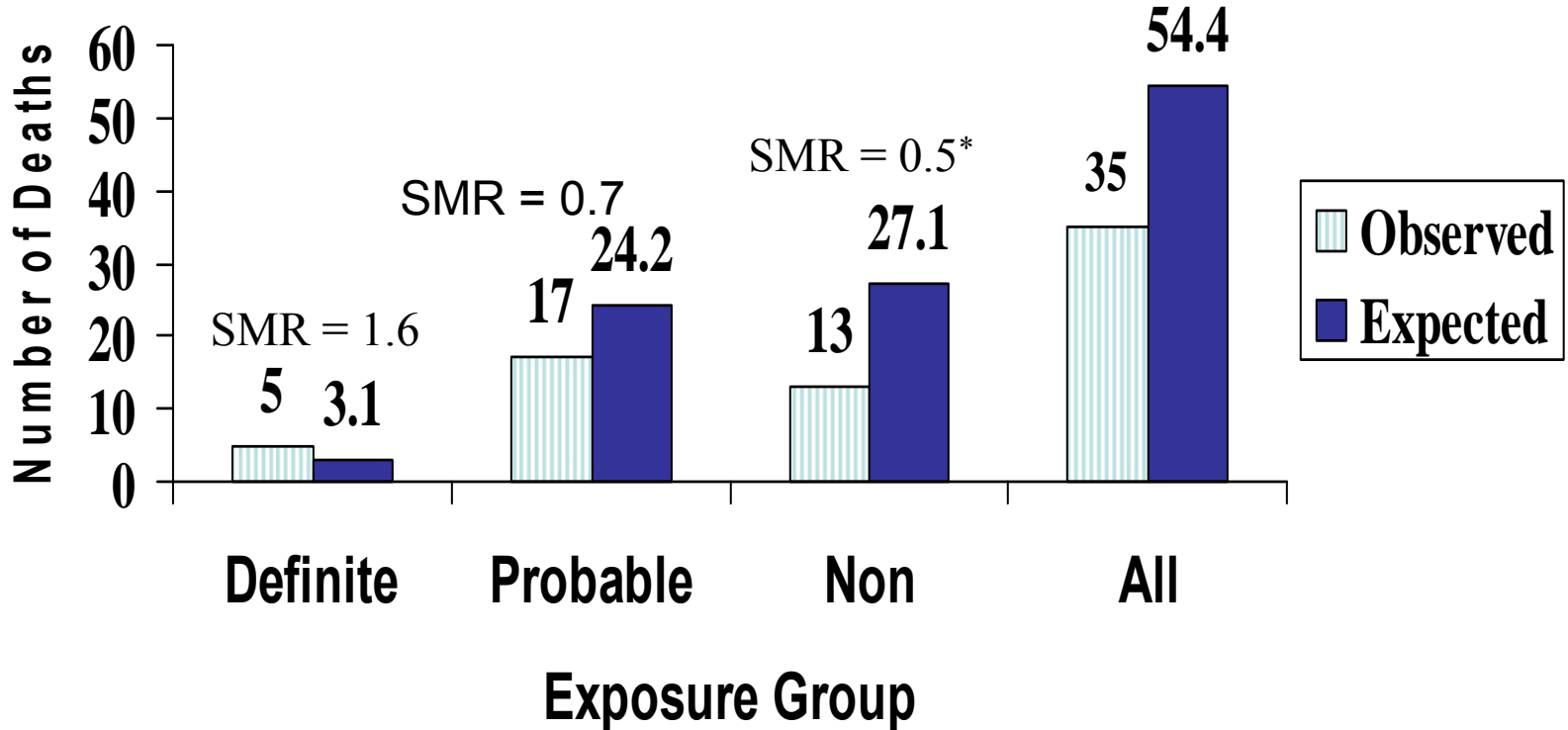
**Figure 4.7. Cerebrovascular Disease Mortality
West Virginia and United States, 1970-1998
Both Genders**



*Rates are adjusted by age to the 2000 U.S. Standard million.

Lundin et al.

3M Cottage Grove Observed and Expected Deaths for Cerebrovascular Disease by Exposure Group



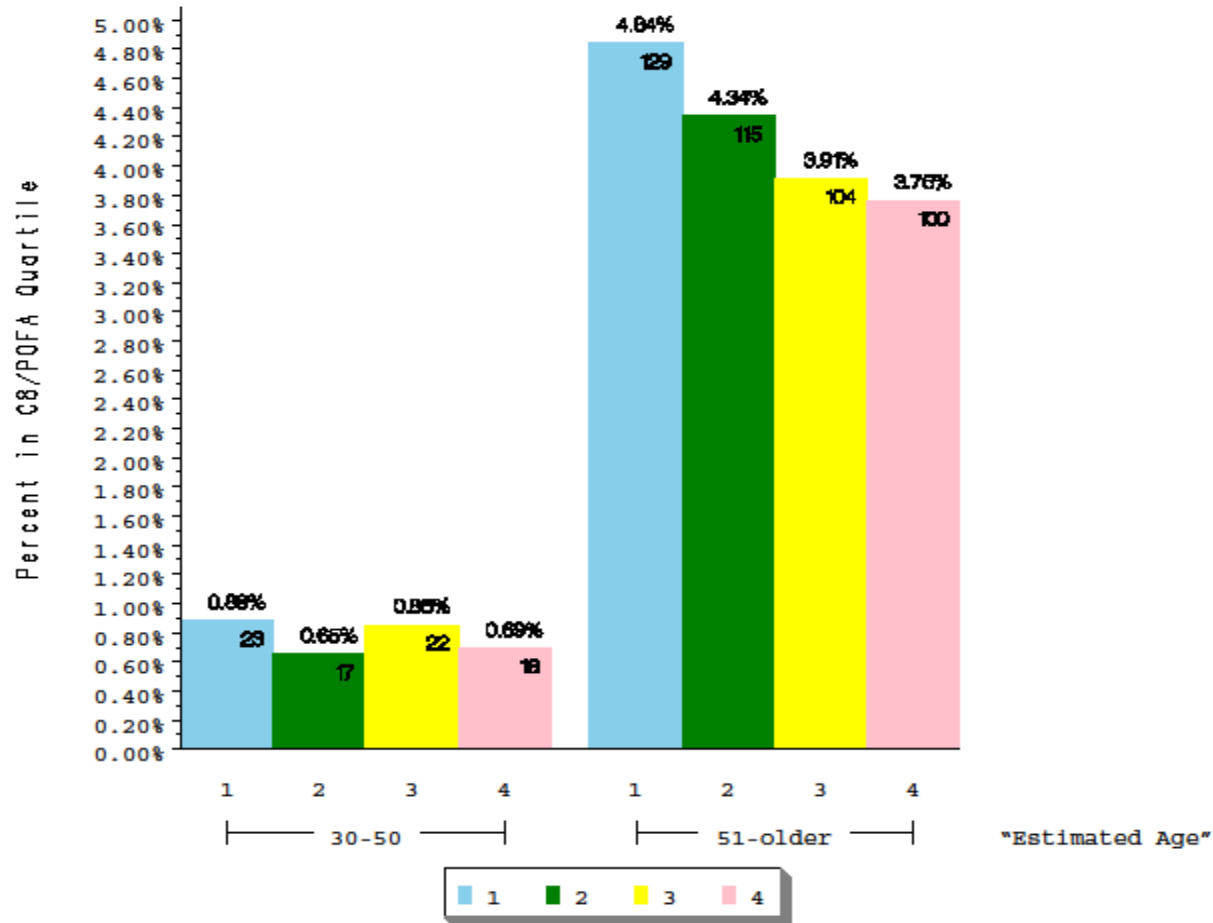
*=Statistically lower than expected compared to the rest of Minnesota

Lundin et al.
Cerebrovascular Disease: Comparing Exposure
within the 3M Cottage Grove Study,
 Results from Cox Proportional Hazard Model

Exposure classification	N	RR	95% CI
Job levels			
High	3	4.6	1.3 - 17.0
Moderate	19	1.8	0.9 - 2.1
Low	13	1.0	-
High exposure job equivalents			
≥5 years	9	2.1	1.0 – 4.6
1-4 years	3	0.6	0.2 - 2.2
<1 Years	23	1.0	-

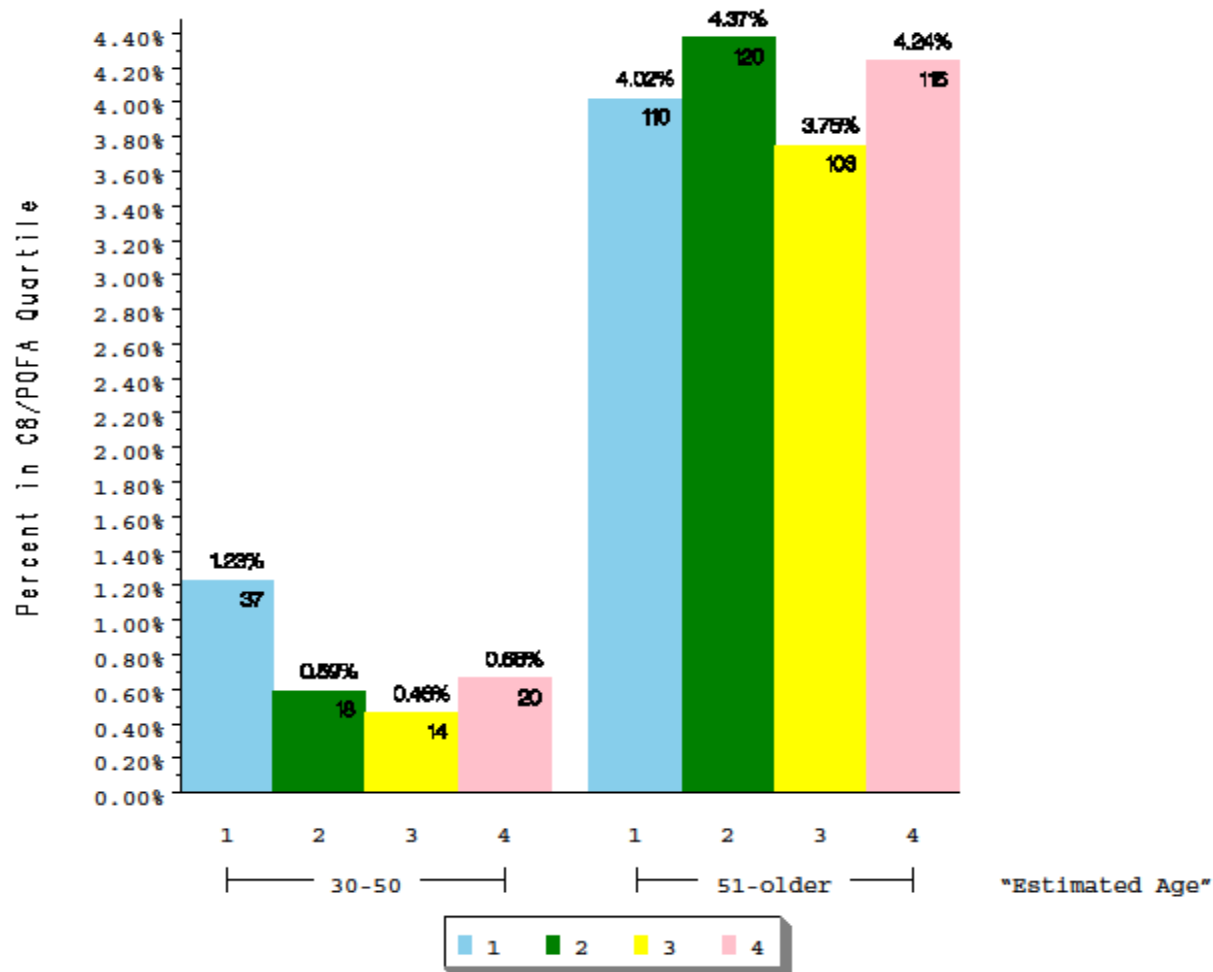
C8 Health Project

*Self- Reported Diagnosis of Stroke in Male Adults
Stratified by Age*



C8 Health Project

*Self- Reported Diagnosis of Stroke in Female Adults
Stratified by Age*



Cerebrovascular Disease

- Conclusion

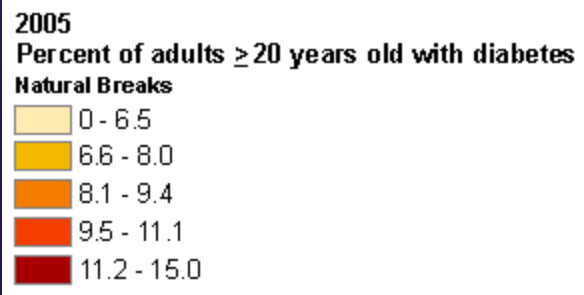
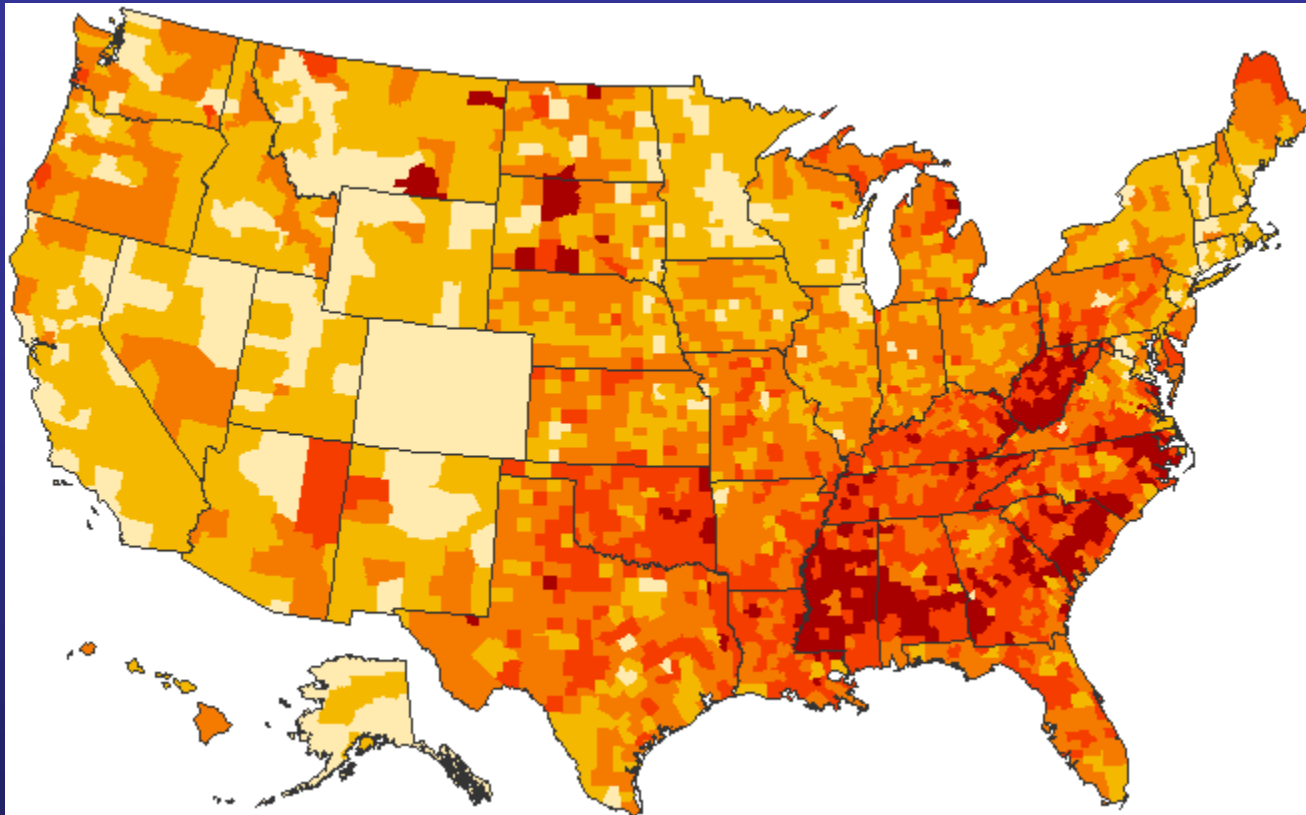
- One epidemiologic report (Lundin et al.) reported an association, albeit inconsistently, with cerebrovascular disease and having exposure to PFOA (ammonium salt).
- The inconsistency was due to the fact that the association was magnified by a large deficit of mortality from cerebrovascular disease among those with less exposure to PFOA.
- No other reports have associated PFOA or PFOS with cerebrovascular disease.

Health Endpoints Covered

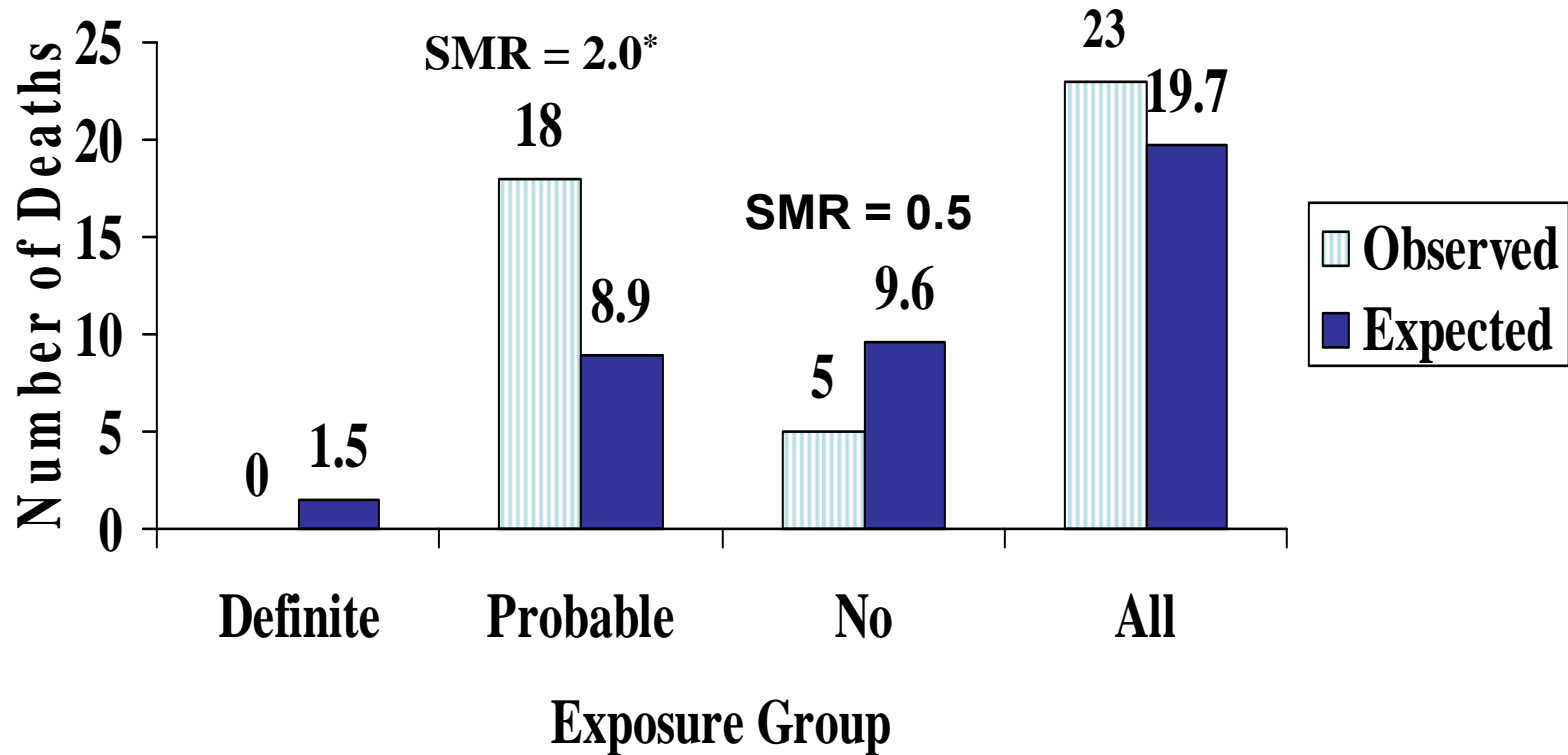
Diabetes

Occupational Studies Diabetes

Study	Categorization	Obs	Exp	SMR	95%CI
Alexander et al.	Decatur Facility (AL comparison)	0	1.5	0.0	-
Lundin et al.	Cottage Grove Facility (MN comparison)	23	20.0	1.2	0.7 – 1.7
	“Not exposed PFOA job”	5	9.6	0.5	0.2 - 1.2
	Ever “Probable exposure”	18	8.9	2.0	1.2 - 3.2
	Ever “Definite exposure”	0	1.5	0.0	0.0 - 2.4
Leonard et al.	Washington Works Facility (W.V. comparison)	22	31.5	0.7	0.4 - 1.1
	Washington Works Facility (DuPont comparison)	22	11.2	2.0	1.2 - 3.0



Observed and Expected Deaths From Diabetes by Exposure Group



*=Statistically higher than expected compared to the rest of Minnesota

Lundin et al.

**Diabetes Mortality: Comparing Exposure
within the 3M Cottage Grove Study,
Results from Cox Proportional Hazard Model**

Exposure classification	N	RR	95% CI
Job levels			
High	0	0.0	-
Moderate	18	3.7	1.4 - 10.1
Low	5	1.0	-
High exposure job equivalents			
≥5 years	4	1.3	0.4 - 4.1
1-4 years	5	1.3	0.5 - 3.7
<1 Years	14	1.0	-

Adjusted Odds Ratios for Validated Type II Diabetes, C8 Health Project, MacNeil et al. Am J Epidemiol 2009

PFOA Decile (ng/mL)	Adjusted Odds Ratio (95% CI)
<7.9 ng/mL	1.00 (Reference)
8.0 – 11.6	0.74 (0.62, 0.88)
11.7 – 15.6	0.67 (0.56, 0.80)
15.7 – 20.8	0.62 (0.52,0.74)
20.9 – 28.0	0.66 (0.56,0.79)
28.1 – 39.4	0.69 (0.58,0.82)
39.5 – 57.5	0.73 (0.61,0.86)
57.6 – 89.7	0.68 (0.58,0.81)
89.8 – 191.2	0.64 (0.54,0.76)
>191.2	0.62 (0.53,0.74)

Diabetes

•Conclusion

- Inconsistent associations reported in the occupational epidemiology studies.
- No association with diabetes in the C8 Health project cross-sectional study.
- Blood glucose has not been associated with serum PFOA or PFOS concentrations in epidemiology or toxicology studies.

Health Endpoints Covered Here

Clinical Chemistries

Clinical Chemistries

- Hepatic
- Lipids
- Blood Glucose
- Uric Acid
- Thyroid

Clinical Chemistries

Occupational Studies

PFOS and PFOA

Olsen et al. (JOEM 2003)

- N = 451 (cross sectional) N = 174 (longitudinal)

PFOA

Olsen and Zobel (Int Arch Occup Environ Health 2007)

- N = 508

Sakr et al. (JOEM 2007 two papers)

- N = 1,016 (cross sectional); N = 454 (longitudinal)

Costa et al. (JOEM 2009)

- N = 160

Community Studies

PFOA

Emmett et al. (JOEM 2006)

- N = 371

C8 Health Project (website)

- N = 69,030

C8 Science Panel (website)

- N = 69,030

General Population Studies

PFOS

Inoue et al. (EHP 2004)

N = 15

Bloom et al. (Physiol Behav 2009)

N = 31

Dallaire et al. (EHP 2009)

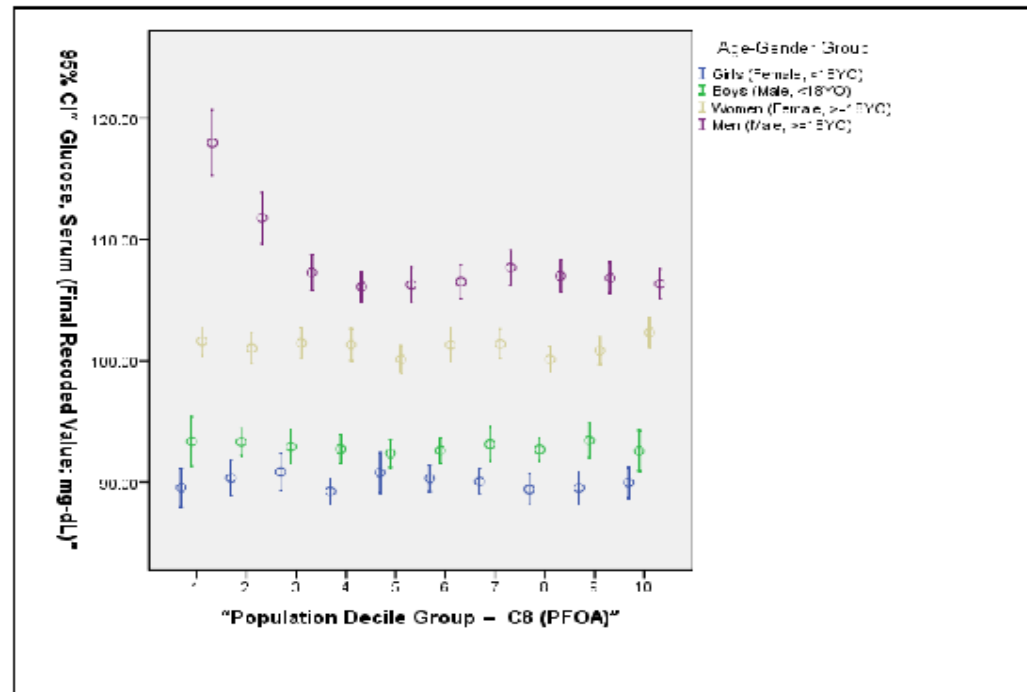
N = 623

Adjusted Odds Ratios for Validated Type II Diabetes, C8 Health Project, MacNeil et al. Am J Epidemiol 2009

PFOA Decile (ng/mL)	Adjusted Odds Ratio (95% CI)
<7.9 ng/mL	1.00 (Reference)
8.0 – 11.6	0.74 (0.62, 0.88)
11.7 – 15.6	0.67 (0.56,0.80)
15.7 – 20.8	0.62 (0.52,0.74)
20.9 – 28.0	0.66 (0.56,0.79)
28.1 – 39.4	0.69 (0.58,0.82)
39.5 – 57.5	0.73 (0.61,0.86)
57.6 – 89.7	0.68 (0.58,0.81)
89.8 – 191.2	0.64 (0.54,0.76)
>191.2	0.62 (0.53,0.74)

Association Between C8 Deciles and Glucose, Serum (mg-dL) Stratified by Age & Gender

NOTE: The graph below depicts the association between the blood concentration of a "standard" clinical laboratory test for the corresponding population serum PFOA (C8) decile. The results are stratified by age and gender categories. The association, if any, is univariate and therefore unadjusted for potential confounding variables or other mediating factors. Associations require further complex, multivariate analysis in order to ascertain the statistical and clinical meaning, if any.

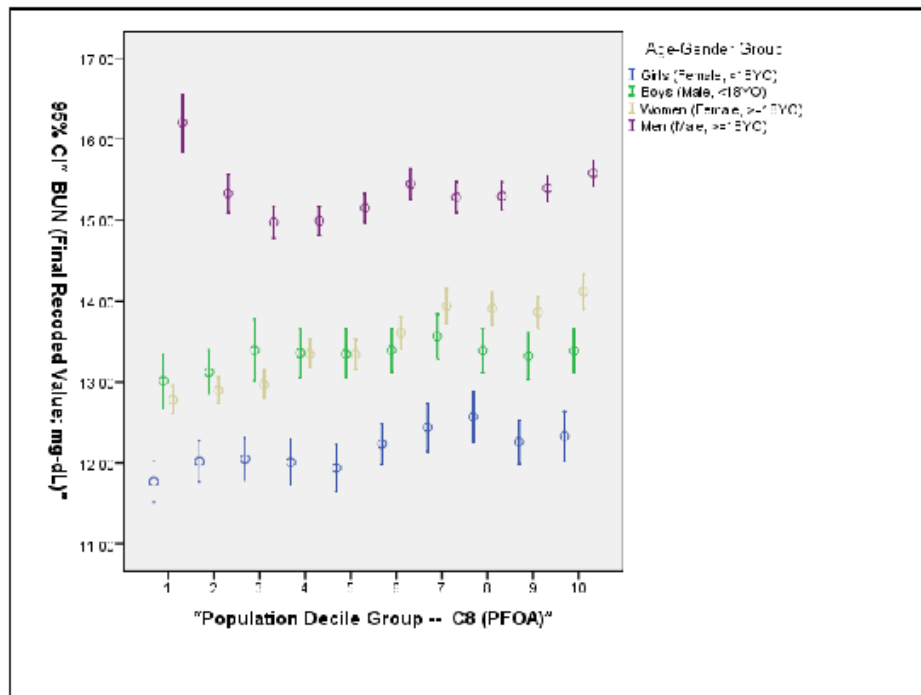


Analytic Note: Deciles were established using the entire population, not for specific age and / or gender sub-strata.

C8 Health Project

Association Between C8 Deciles and BUN (mg-dL) Stratified by Age & Gender

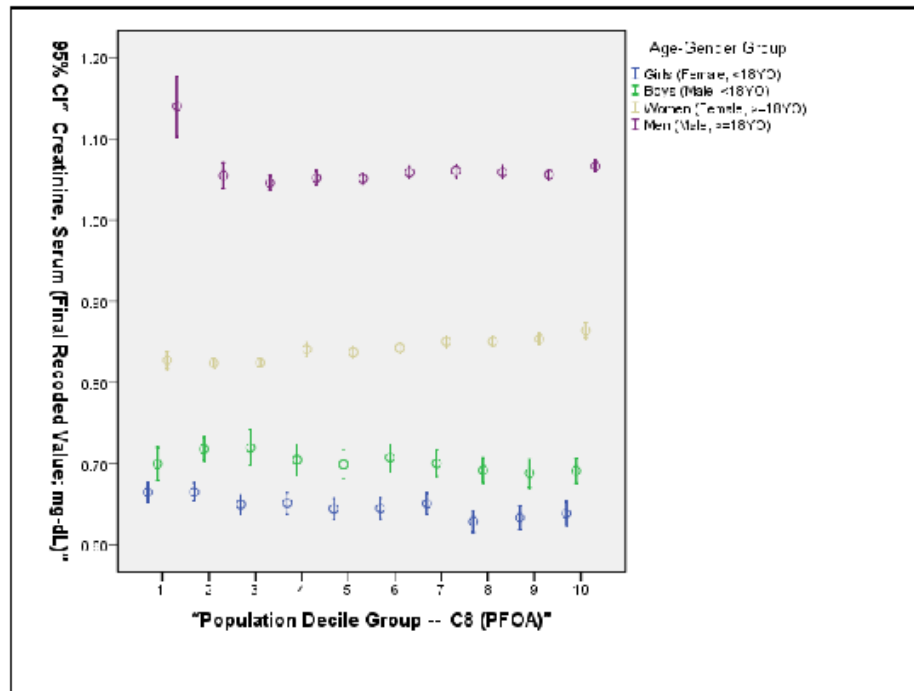
NOTE: The graph below depicts the association between the blood concentration of a "standard" clinical laboratory test for the corresponding population serum PFOA (C8) decile. The results are stratified by age and gender categories. The association, if any, is univariate and therefore unadjusted for potential confounding variables or other mediating factors. Associations require further complex, multivariate analysis in order to ascertain the statistical and clinical meaning, if any.



Analytic Note: Deciles were established using the entire population, not for specific age and / or gender sub-strata.

Association Between C8 Deciles and Creatinine, Serum (mg-dL) Stratified by Age & Gender

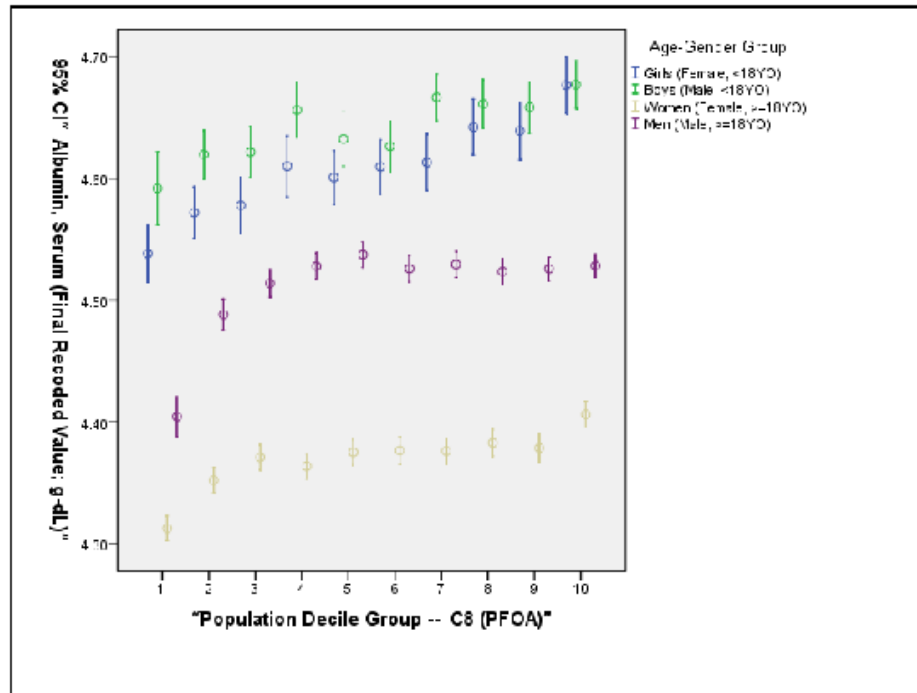
NOTE: The graph below depicts the association between the blood concentration of a "standard" clinical laboratory test for the corresponding population serum PFOA (C8) decile. The results are stratified by age and gender categories. The association, if any, is univariate and therefore unadjusted for potential confounding variables or other mediating factors. Associations require further complex, multivariate analysis in order to ascertain the statistical and clinical meaning, if any.



Analytic Note: Deciles were established using the entire population, not for specific age and / or gender sub-strata.

Association Between C8 Deciles and Albumin, Serum (g-dL) Stratified by Age & Gender

NOTE: The graph below depicts the association between the blood concentration of a "standard" clinical laboratory test for the corresponding population serum PFOA (C8) decile. The results are stratified by age and gender categories. The association, if any, is univariate and therefore unadjusted for potential confounding variables or other mediating factors. Associations require further complex, multivariate analysis in order to ascertain the statistical and clinical meaning, if any.



Analytic Note: Deciles were established using the entire population, not for specific age and / or gender sub-strata.

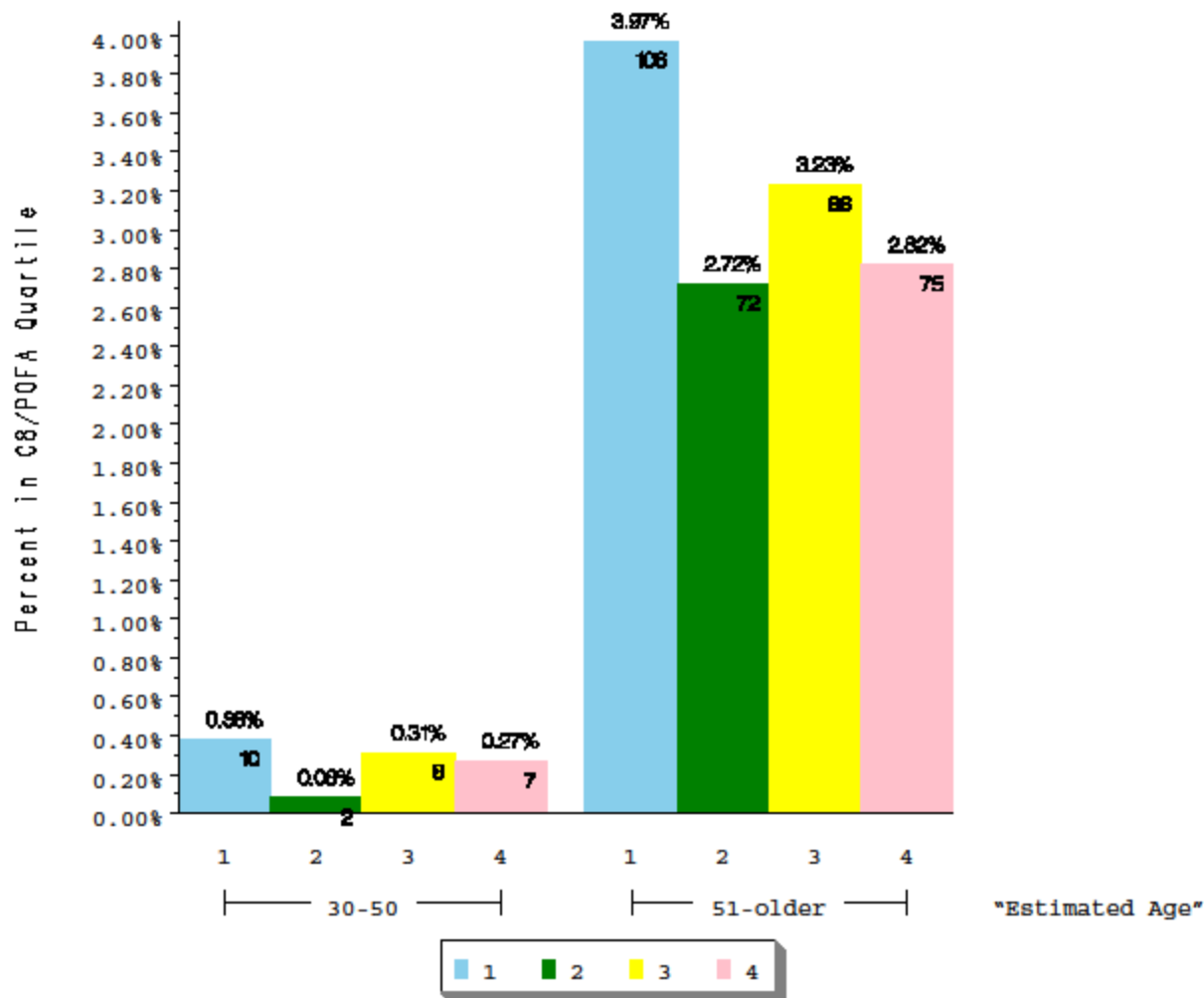
Other clinical chemistry associations with 1st decile from C8 Health Project

- Increased triglycerides
- Decreased sodium
- Increased potassium
- Decreased RBCs, Hemoglobin, Hematocrit, increased RBC diameter
- Decreased iron
- Increased Vitamin B12

Are there other health outcomes,
associated with type II diabetes,
seen with the 1st decile of the
C8 Health Project?

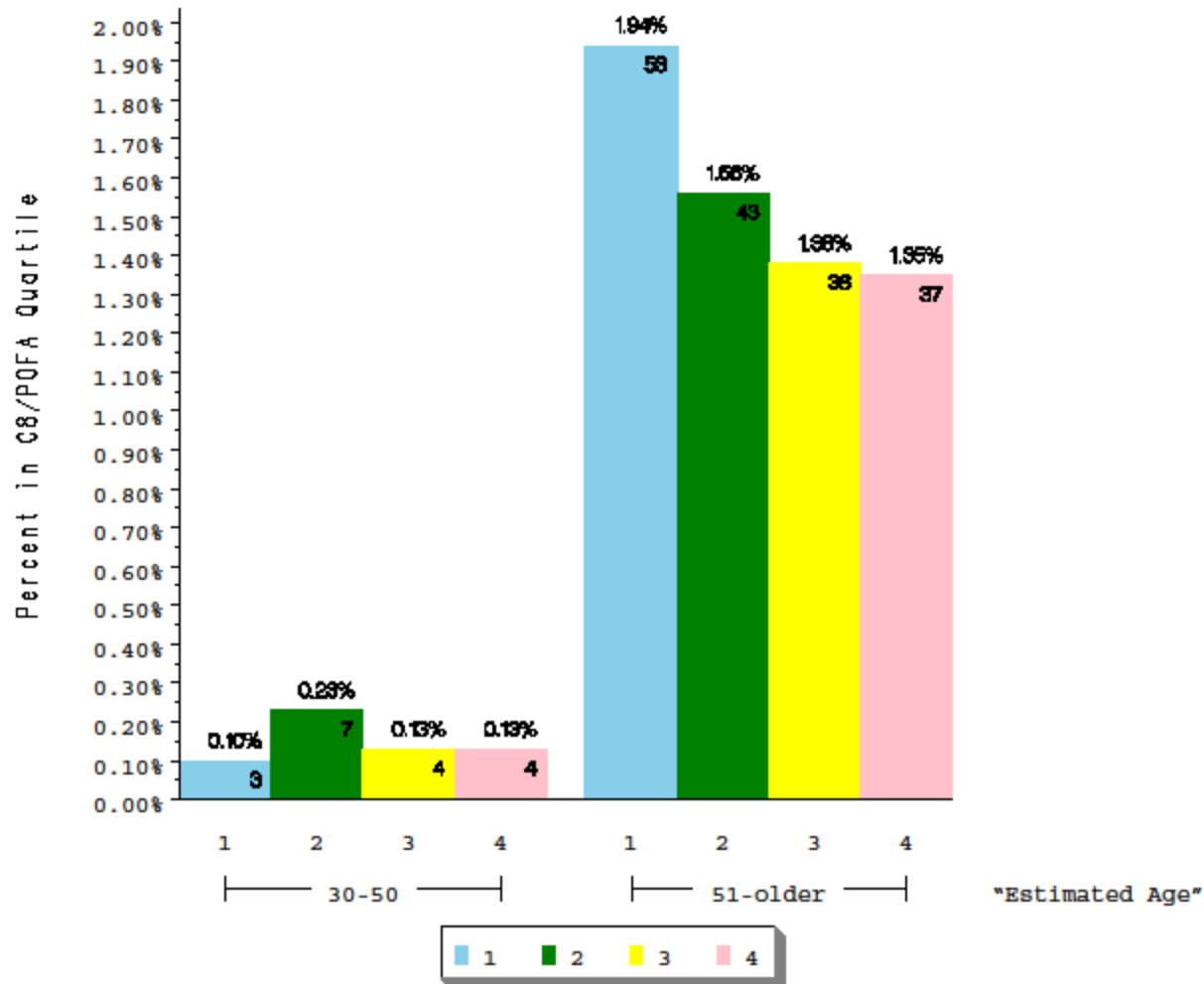
C8 Health Project

*Self- Reported Diagnosis of Arteriosclerosis in Male Adults
Stratified by Age*



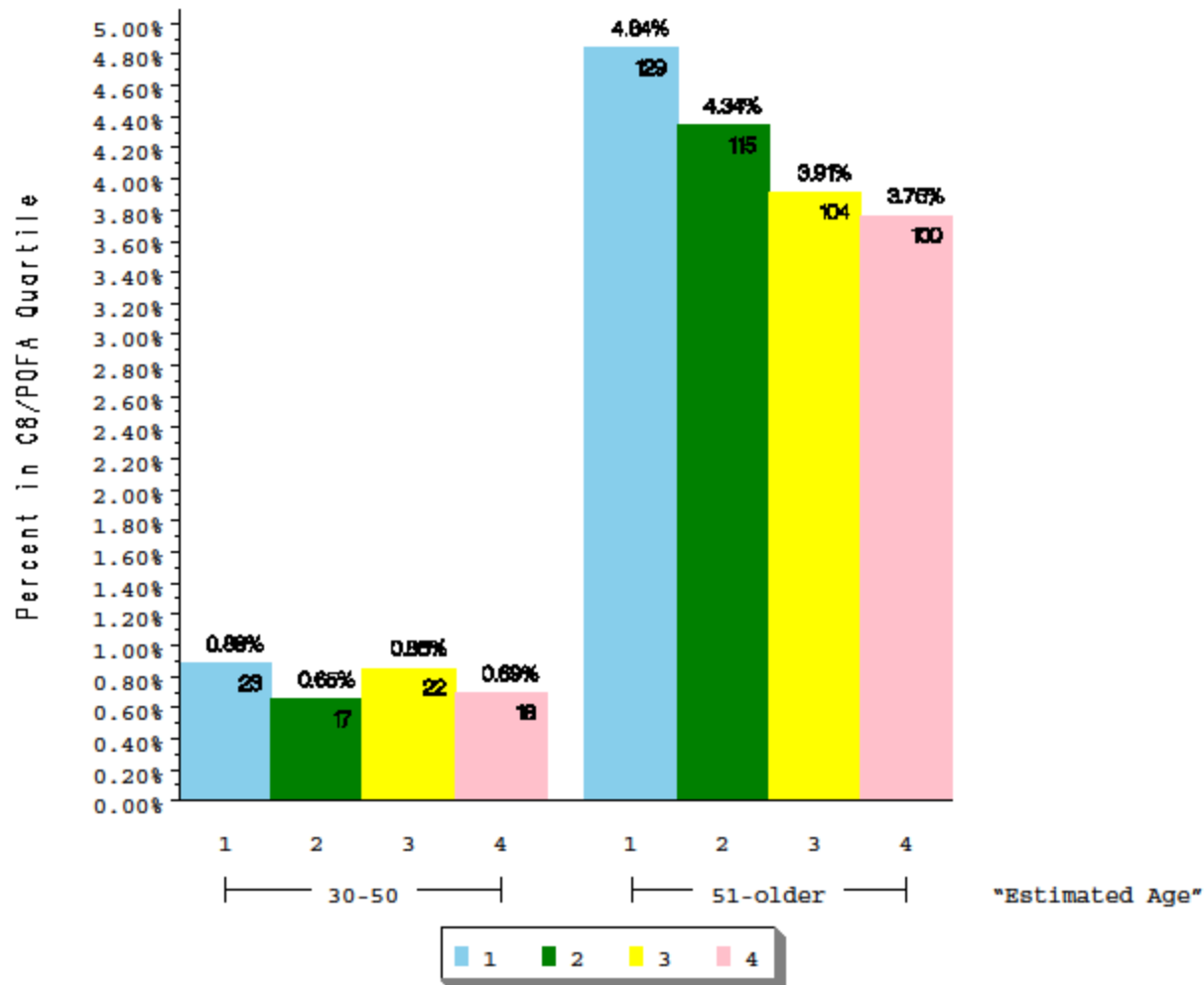
C8 Health Project

Self- Reported Diagnosis of Arteriosclerosis in Female Adults Stratified by Age



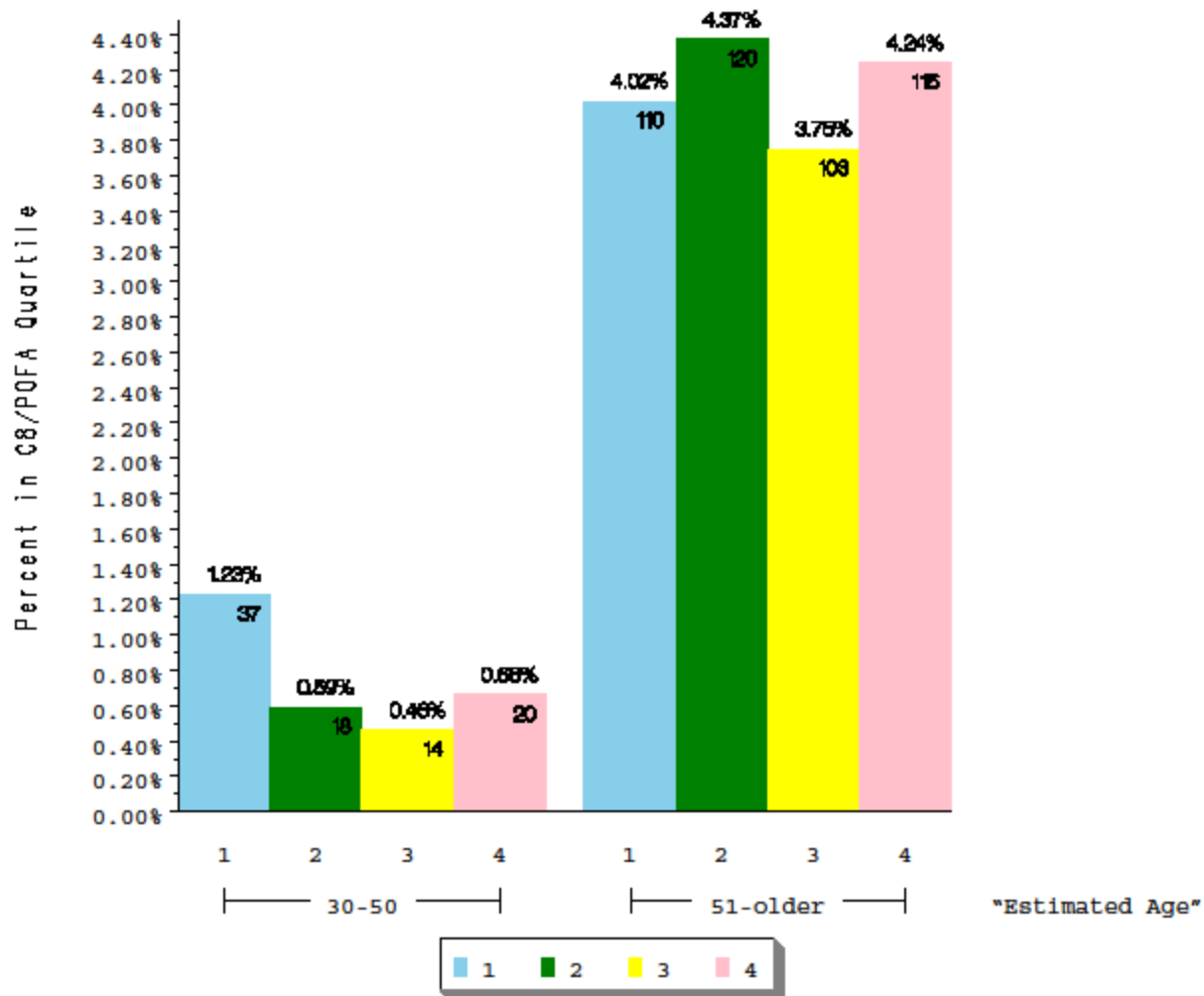
C8 Health Project

*Self- Reported Diagnosis of Stroke in Male Adults
Stratified by Age*



C8 Health Project

*Self- Reported Diagnosis of Stroke in Female Adults
Stratified by Age*



First decile of the **C8 Health Project** has higher self-reported prevalence of . . .

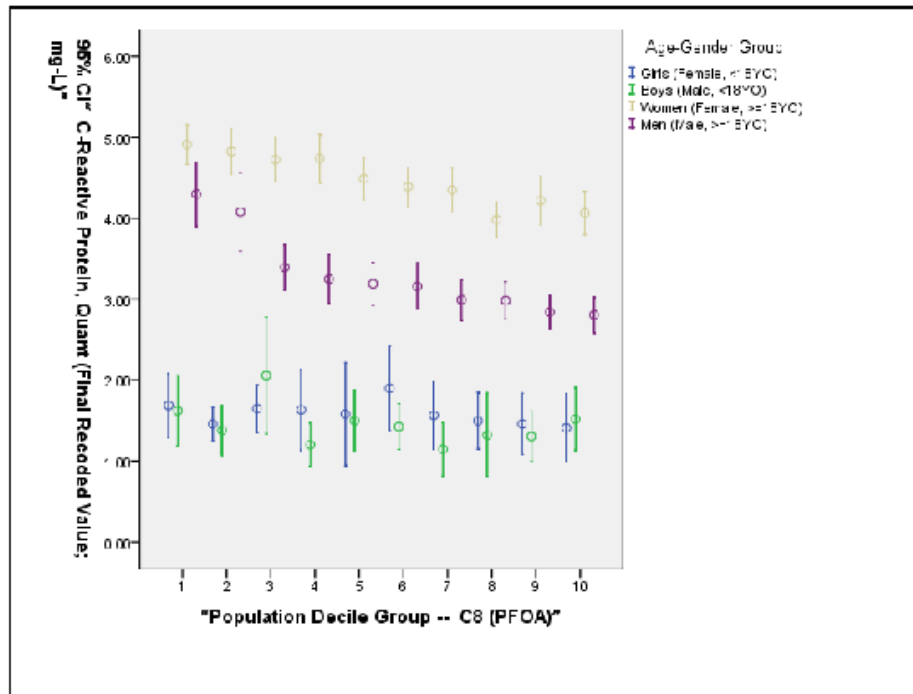
- Type II diabetes (includes validated cases)
- Cardiovascular disease
- Cerebrovascular disease (stroke)

Should expect to see increase in C-reactive protein . . .

C8 Health Project

Association Between C8 Deciles and C-Reactive Protein, Quant (mg-L) Stratified by Age & Gender

NOTE: The graph below depicts the association between the blood concentration of a "standard" clinical laboratory test for the corresponding population serum PFOA (C8) decile. The results are stratified by age and gender categories. The association, if any, is univariate and therefore unadjusted for potential confounding variables or other mediating factors. Associations require further complex, multivariate analysis in order to ascertain the statistical and clinical meaning, if any.



Analytic Note: Deciles were established using the entire population, not for specific age and / or gender sub-strata.

Conclusion regarding 1st decile of the **C8 Health Project**

- The 1st decile for PFOA in the **C8 Health Project** is considerably different than the other deciles regarding a variety of clinical and disease outcomes.
- Use of the 1st decile as the 'referent' group can result in erroneous conclusions.
- Review of individual endpoints in isolation can result in erroneous conclusions.
- C8 Science Panel urges caution in the interpretation of these cross-sectional data

Health Endpoints Covered

Hepatic Clinical Chemistries

Caveats in Reviewing Clinical Chemistry Results

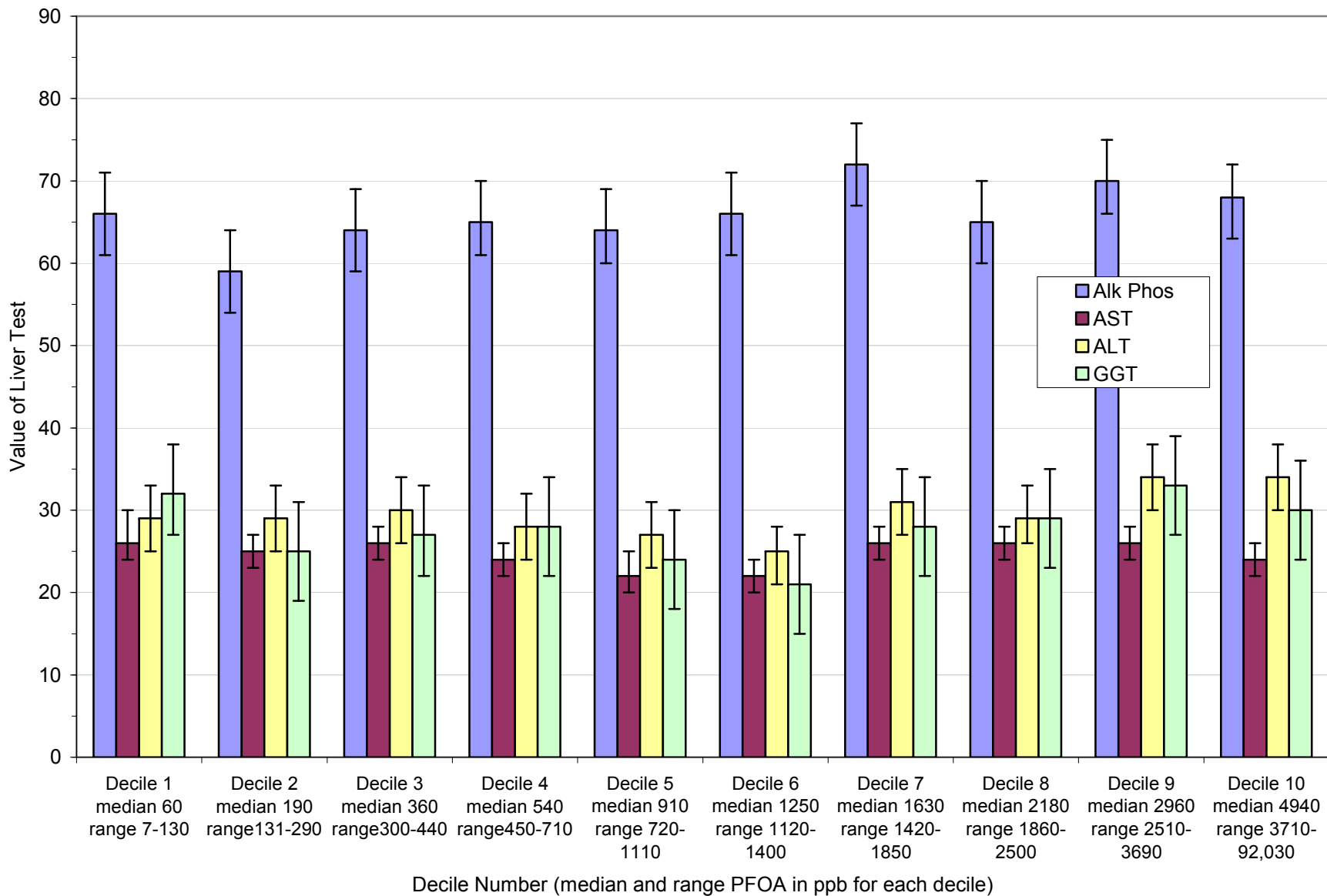
- Reference Ranges
 - within 2 standard deviations
 - laboratory-specific with few exceptions
 - inside reference range
 - outside reference range
 - cut-off points (e.g., < 200 mg/dl cholesterol)
 - statistical variability
 - multiple comparisons
 - regression analysis through reference ranges
 - estimates of risk above reference range
 - confounders
 - biological variability

Potential Confounding Factors with Hepatic Clinical Chemistry Tests

- Age
- Alcohol
- BMI
- Lipids
- Medications
- Nonalcoholic fatty liver disease
- Metabolic syndrome

Adjusted Mean Liver Clinical Chemistry Values by PFOA Deciles

Olsen and Zobel (Int Arch Occup Environ Health 2007)



	Sakr et al. Cross Sectional	N = 1016		Sakr et al. Cross Sectional	N = 840 Excl chol meds		Sakr et al. Longitudinal	N = 454
Model	PFOA Reg Coef	P value		PFOA Reg Coef	P value		PFOA Reg Coef	95% CI
AST	0.012	0.32		0.023	0.08		0.35*	0.10, 0.60
ALT	0.023	0.12		0.031	0.07		0.54	-0.46, 1.54
GGT	0.048*	0.02		0.050*	0.03		1.24	-1.09, 3.57
Bilirubin	0.008	0.59		0.008	-0.64		-0.008	-0.014, 0.002
Alk Phos	No data			No data			-0.21	-0.60, 0.18

	Costa et al. Cross Sectional	N = 141		Costa et al. Longitudinal	N = 56
Model	PFOA Reg Coef	95% CI		PFOA Reg Coef	95% CI
AST	1.35	-2.72, 5.41		0.038	-0.003, 0.080
ALT	-5.18	-13.7, 3.32		0.116*	0.054, 0.177
GGT	0.32	-17.5, 18.1		0.177*	0.076, 0.278
Alk Phos	-0.78	-8.51, 6.95		0.057	0.007, 0.107

Emmett et al.

Hepatic Clinical Chemistries

Clinical Chemistry	Median	PFOA	
		Slope	P value
AST (IU/L)	21.0	-0.00076	0.76
ALT (IU/L)	21.0	-0.00183	0.65
GGT (IU/L)	20.0	-0.00058	0.89
Alkaline Phos (IU/L)	82.0	-0.00416	0.65

Hepatic Clinical Chemistries

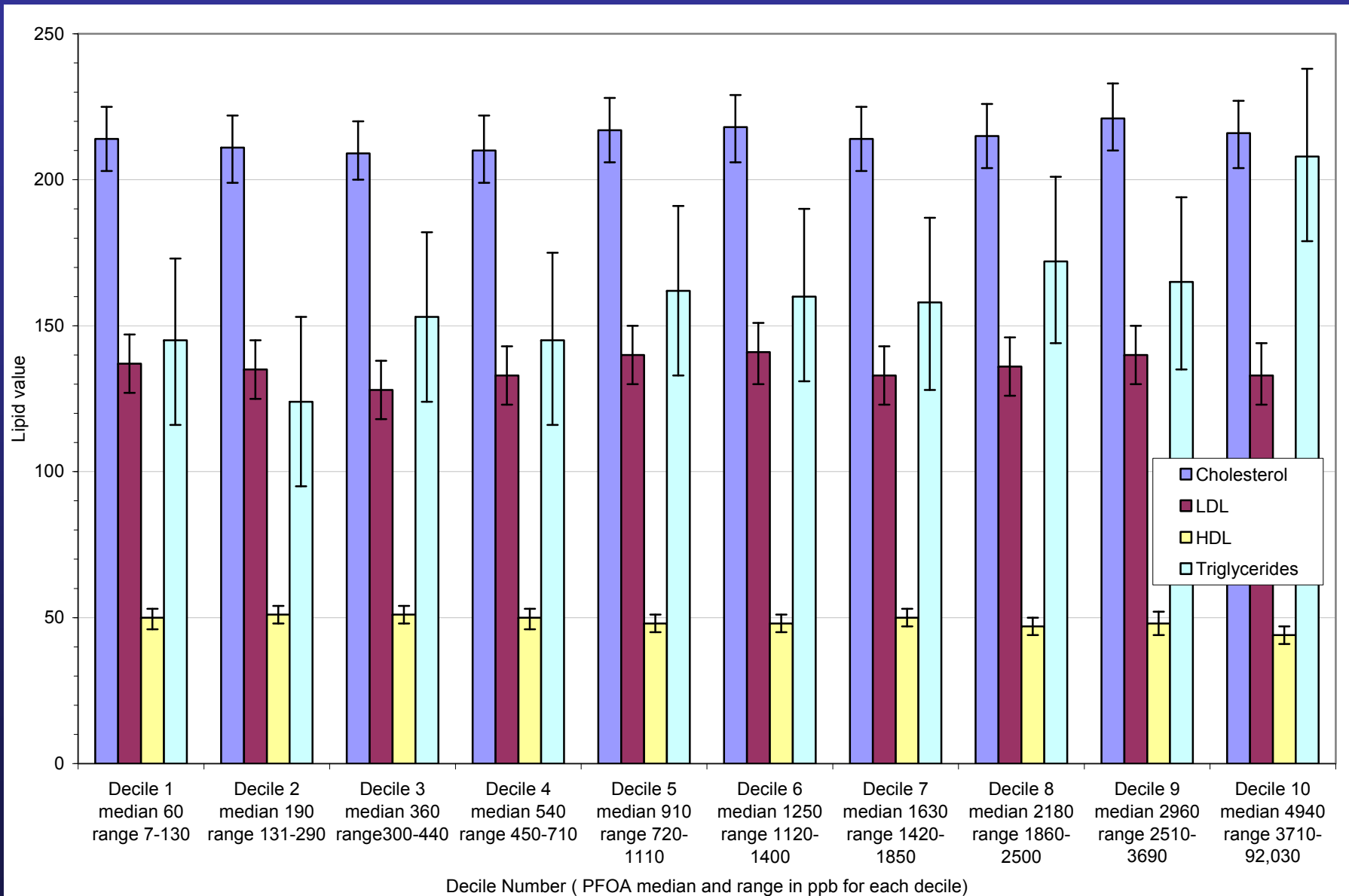
- Conclusions
 - Need to adjust for potential confounding factors.
 - Individual out-of-reference values are to be expected.
 - Depending upon the unit of change, a statistically significant regression coefficient within a reference distribution may have no clinical relevance.
 - In the studies reviewed, there were no consistent statistical associations with hepatic clinical chemistries.

Health Endpoints Covered

Lipid
Clinical Chemistries

Adjusted Mean Lipid Values by PFOA Deciles

Olsen and Zobel (Int Arch Occup Environ Health 2007)



	Sakr et al. Cross Sectional	N = 1016		Sakr et al. Cross Sectional	N = 840 Excl chol meds		Sakr et al. Longitudinal	N = 454
Model	Adj PFOA Reg Coef	P value		Adj PFOA Reg Coef	P value		Adj PFOA Reg Coef	95% CI
Total Chol	4.036*	0.002		5.519*	<0.001		1.06*	0.24, 1.88
LDL	2.834*	0.008		3.561*	0.003		0.46	-0.87, 1.79
VLDL	0.045*	0.03		0.050*	0.03		No data	
HDL	-0.178	0.68		0.023	0.96		0.16	-0.039, 0.71
Trig	0.018	0.38		0.030	0.21		0.79	-5.99, 7.57

	Costa et al. Cross Sectional	N = 141		Costa et al. Longitudinal	N = 56
Model	Adj PFOA Reg Coef	95% CI		Adj PFOA Reg Coef	95% CI
Total Chol	21.7*	6.8, 36.6		0.028*	0.002, 0.055
HDL	2.42	-2.3, 7.13		-0.018	-0.047, 0.012
Trig	-0.15	-34.6, 34.3		0.055	-0.036, 0.147

Emmett et al.

Lipids

<u>Clinical Chemistry</u>	Median	PFOA	
		Slope	P value
Cholesterol (mg/dL)	194.0	0.00551	0.27

C8 Science Panel Website

“The predicted increase in cholesterol from lowest to highest decile of either PFOA or PFOS was 11 – 12 mg/dl.”

Adjusted odds ratios, by quartile of exposure for total cholesterol \geq 240 mg/dl.

Quartile	PFOA (95% CI)	PFOS (95% CI)
Q1	1.00	1.00
Q2	1.21 (1.12, 1.31)	1.13 (1.04, 1.22)
Q3	1.33 (1.23, 1.43)	1.28 (1.19, 1.39)
Q4	1.40 (1.29, 1.51)	1.51 (1.40, 1.64)

Lipid Clinical Chemistries

- **Conclusions**

- Positive associations have been observed with total cholesterol and LDL, but not with HDL.
- There are inconsistent trends within the positive associations.
 - Example: 5 mg/dL increase for total cholesterol with 1,000 ppb PFOA (Sakr et al.) compared with approx 10 mg/dL increase with \approx 200 ppb PFOA (C8 Science panel reports).
- Could these be non-causal associations related to binding of beta-lipoproteins?
- There is a lack of association with related health outcomes (e.g., Ischemic heart disease mortality).

Health Endpoints Covered

Blood Glucose

Blood Glucose

No occupational study has reported an association with PFOA or PFOS and blood glucose.

MacNeil et al. (C8 Science Panel) reported among fasting serum glucose levels in the C8 Health Project population, that excluded type II diabetics, “there was no consistent pattern between fasting serum glucose and serum PFOA and blood glucose by decile.”

(blood glucose by decile = 94, 95, 95, 93, 94, 92, 92, 92, 92, 93).

Health Endpoints Covered

Uric Acid

Uric Acid Occupational Studies

- Sakr et al. in a cross-sectional study 'showed statistically significant association with serum PFOA in linear regression model.'
- Costa et al. (34 current workers)

Mean	PFOA Exposure		P value
	<u>Exposed</u>	<u>Nonexposed</u>	
Uric Acid (mg/dL)	<u>6.29</u>	<u>5.73</u>	<u>0.04</u>

C8 Science Panel Website

“Both PFOA and PFOS were significantly associated with increases in uric acid levels, with an increase of 0.2-0.3 mg/dl in uric acid associated with an increase from the lowest to highest decile of either PFOA or PFOS.”

“The risk of excessive uric acid (defined as >6 mg/dl in women, >6.8mg/dl in men) increased modestly with increasing quartile of each of the two chemicals.”

	<u>PFOA (95% CI)</u>	<u>PFOS (95% CI)</u>
Q1	1.00 -	1.00 -
Q2	1.24 (1.16 – 1.32)	1.06 (0.99 – 1.12)
Q3	1.34 (1.26 -1.43)	1.17 (1.10 – 1.24)
Q4	1.38 (1.30 – 1.47)	1.25 (1.17 – 1.33)

Uric acid

- Conclusion

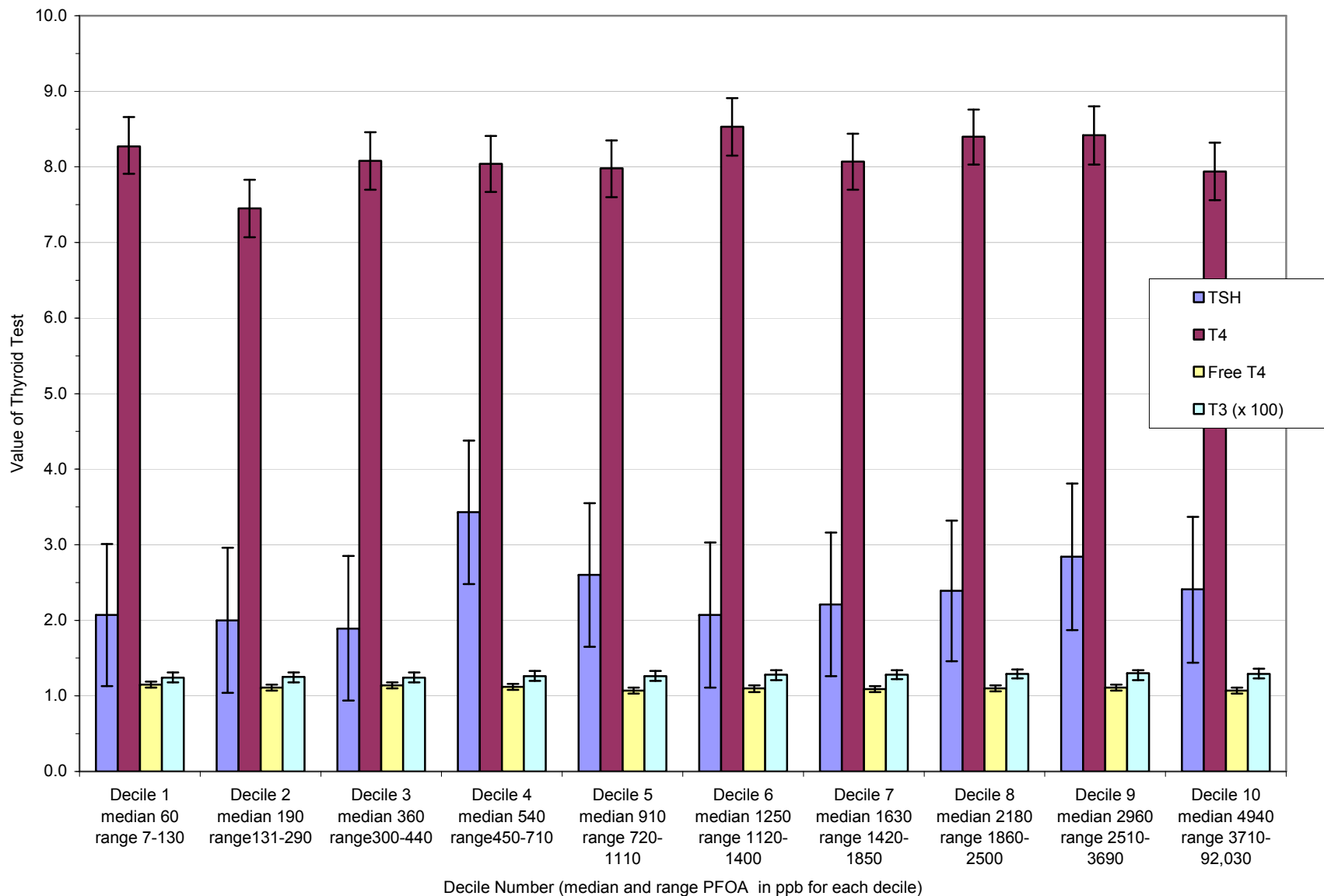
- Associations reported in occupational and community studies with PFOA.
- Lack of evidence of hyperuricemia-related conditions such as gout in APFO production workers.
- In humans, same organic anion transporters for both urate and PFCs.

Health Endpoints Covered

Thyroid
Hormones

Adjusted Mean Thyroid Values by PFOA Deciles

Olsen and Zobel (Int Arch Occup Environ Health 2007)



Emmett et al.

Serum Chemistries

<u>Clinical Chemistry</u>	Median	PFOA	
		<u>Slope</u>	<u>P value</u>
TSH	1.7	0.00021	0.38

PFOS and Thyroid Assessments, Occupational and General Population Studies

Study	Sample Size	Ave Serum PFOS (ng/mL)	TSH	T4	FT4	T3
Olsen et al. 2003	263 U.S 3M Decatur plant workers	910	N	N	N	N
Olsen et al. 2003	255 3M Antwerp plant workers	440	N	N	N	N
Inoue et al. 2004	15 (cord blood – Japan)	1.6 – 5.2 (range)	N		N	
Bloom et al. 2009	31 anglers from N.Y.	19.6	N		N	
Dallaire et al. 2009	623 Inuits	18.3	N		N	N

N = normal
(within
reference ranges)

Dallaire et al.

Environ Health Perspect 2009;117:1380-1386

Thyroid Parameter	Adj β	Based on study model, change in thyroid parameter from study range of PFOS**	Reference Range of Thyroid Parameter
TSH	-0.102***	-0.27 mIU/L	0.27 – 4.20 mIU/L
fT4	0.014***	0.11 pmol/L	12 – 22 pmol/L
T3	-0.017***	-0.10 nmol/L	1.3 – 3.1 nmol/L

Study model: $\log(\text{thyroid parameter}) = \beta \log \text{PFOA} + \sum \beta X_i$

** range 0.48 ng/mL to 470 ng/mL

*** $p \leq 0.05$

Thyroid

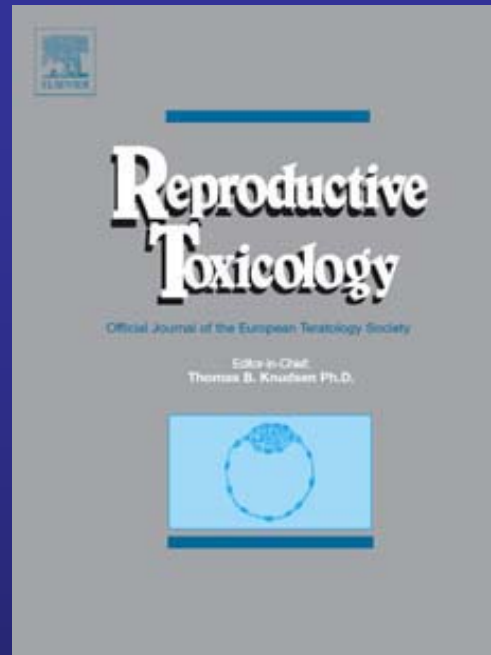
- **Conclusion**

- No evidence of perturbations in thyroid hormones from normal reference ranges in occupational or general population studies.

Health Endpoints Covered

Developmental

Author	Type	Journal	Year	Location
Olsen et al.	Occupational	JOEM	2004	3M Decatur, AL
Grice et al.	Occupational	JOEM	2007	3M Decatur, AL
Apelberg et al. (2 papers)	General population	ES&T and EHP	2006, 2007	Baltimore, MD
Fei et al. (4 papers)	General population	EHP (2), Am J Epi (1), Human Repro (1)	2007, 2008, 2008, 2009	Denmark
Inoue et al.	General population	EHP	2004	Hoikado, Japan
Monroy et al.	General population	Environmental Research	2008	Ontario, Canada
Nolan et al.	Community	Reproductive Toxicology	2008	Washington County, Ohio (C8 Health Project)
Stein et al.	Community	Am J Epidemiology	2009	“6 water districts” C8 Health Project



Olsen GW, Butenhoff JL, Zobel LR. Perfluoroalkyl chemicals and human fetal development: An epidemiologic review with clinical and toxicological perspectives. *Reproductive Toxicology* 2009;27:212-230.

Endpoint	PFC	Olsen	Grice	Inoue	Apelberg	Fei	Monroy	Washino	Nolan	Stein
Gestational age	PFOS				N.S.	N.S.	N.S.			N.S.
	PFOA				N.S.	N.S.	N.S.		N.S.	N.S.
Birth Weight (g)	PFOS		N.S.	N.S.	N.S.*	N.S.	N.S.	S.S. ^{females}		S.S.
	PFOA		N.S		N.S.*	S.S.	N.S.	N.S.	N.S.	N.S.
Birth Length (cm)	PFOS				N.S.	N.S.		N.S.		
	PFOA				N.S.	S.S.		N.S.		
Head Circumference (cm)	PFOS				S.S.	N.S.		N.S.		
	PFOA				S.S.	N.S.		N.S.		
Abd/chest Circumference (cm)	PFOS					N.S.		N.S.		
	PFOA					S.S.		N.S.		
Apgar Score	PFOS					N.S.				
	PFOA					N.S.				
Ponderal Index	PFOS				S.S.	N.S.				
	PFOA				S.S.	N.S.				
Placental Weight (g)	PFOS					N.S.				
	PFOA					N.S.				
Miscarriage	PFOS	N.S.	N.S.							N.S.
	PFOA	N.S.	N.S.							N.S.
Birth defects (non-specific)	PFOS	N.S.								N.S.
	PFOA	N.S.								N.S.
Preeclampsia	PFOS									S.S.
	PFOA									N.S.
Developmental milestones	PFOS					N.S.				
	PFOA					N.S.				

Covariates included in statistical models of birth weight and PFOS or PFOA, by study investigator

Adjusted For:	Olsen	Grice	Inoue	Apelberg	Fei	Monroy	Washino	Nolan	Stein
Maternal age		Yes		Yes	Yes		Yes	Yes	Yes
Maternal BMI				Yes	Yes	Yes	Yes		
Maternal net wt gain				Yes					
Maternal height				Yes					
Maternal race				Yes				Yes	
Maternal smoking		Yes		Yes	Yes	Yes	Yes		Yes
Education							Yes		Yes
SES					Yes			Yes	
Gestational age				Yes	Yes	Yes	Yes	Yes	
Getational age at blood draw					Yes		Yes		
Parity		Yes		Yes	Yes	Yes	Yes		Yes
Infant sex				Yes	Yes	Yes	Yes	Yes	
Diabetes				Yes					
Hypertension				Yes					

Developmental

- **Conclusions**

- Inconsistent associations reported across many studies.
- Differences may be partially due to measured and unmeasured confounders.
- Serum concentrations (umbilical cord, 1st or 2nd trimester) were orders of magnitude below benchmark lower concentration measurements reported in the reproductive toxicology literature.

Do PFCs result in human infertility?

1) Delayed time to pregnancy

Fei et al. Human Repro 2009

2) Lowered sperm counts

Joensen et al. EHP 2009

Parity

CONFOUNDER

EXPOSURE

RESPONSE

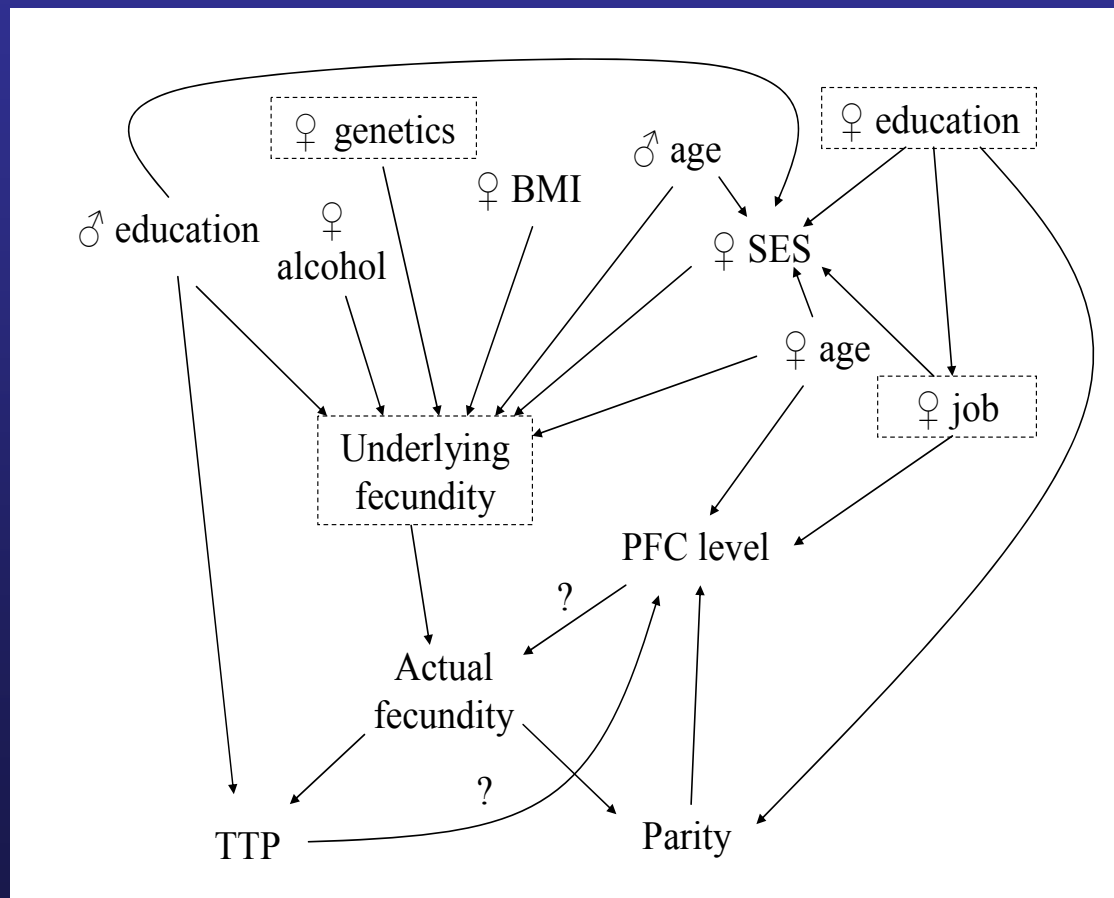
PFOS, PFOA

Delayed TTP

Assumed "Time-to-Pregnancy" Causal Model" by Fei et al. Human Reproduction 2009

Suggested Causal Diagram of Maternal Perfluorochemical Concentrations (PFC) and Time to Pregnancy (TTP)

Olsen et al. *Repro Toxicol* 2009;27:212-230



Concept of “Backward (Reverse) Causation”

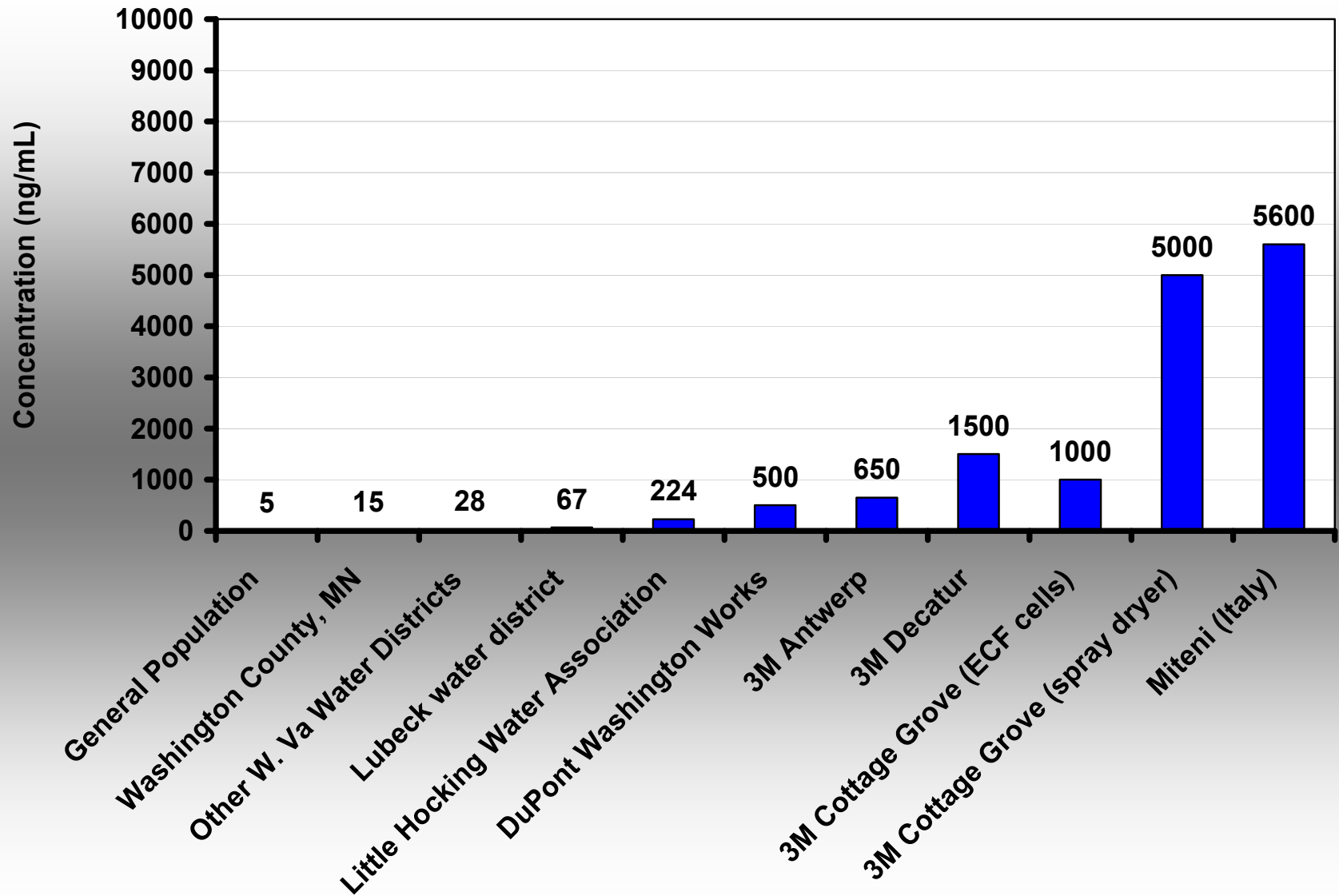
Conclusions

- Many epidemiologic studies have been published, covering numerous endpoints in workforces exposed since the 1950s
- Among the outcomes reviewed, there are no causal associations.
- Statistical associations undergoing further inquiry include:
 - prostate cancer (study incidence data)
 - lipids (role of PFCs binding to beta-lipoproteins?)
 - uric acid (role of shared organic anion transporters?)

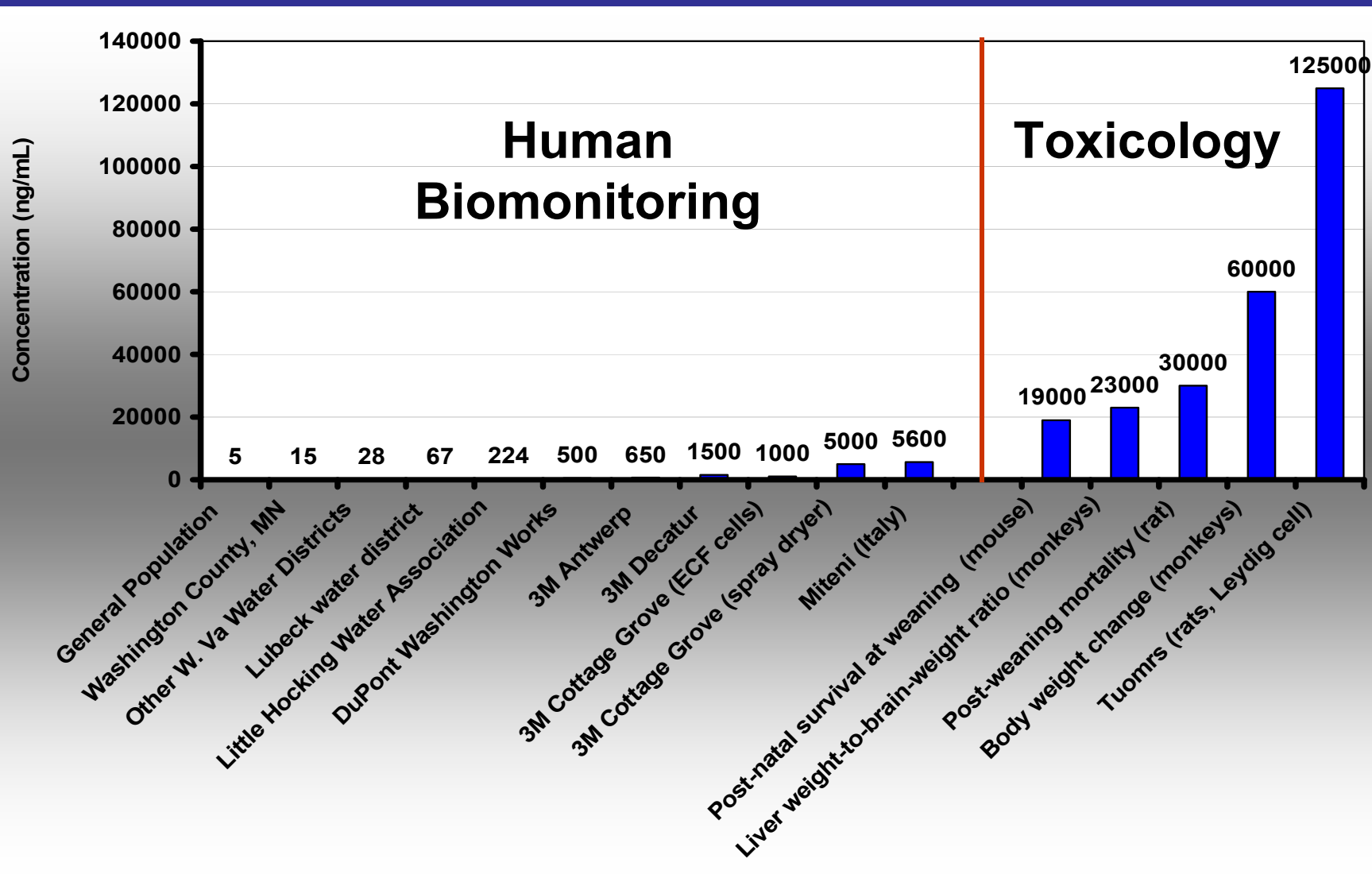
Conclusions

- Because of its sample size (> 69,000 participants), it is to be expected that many statistical associations will be reported by the **C8 Science Panel**.
 - These associations need to be evaluated with respect to:
 - reference groups
 - multiple endpoints
 - measured concentrations
 - plausible modes of action
 - and the toxicological findings.

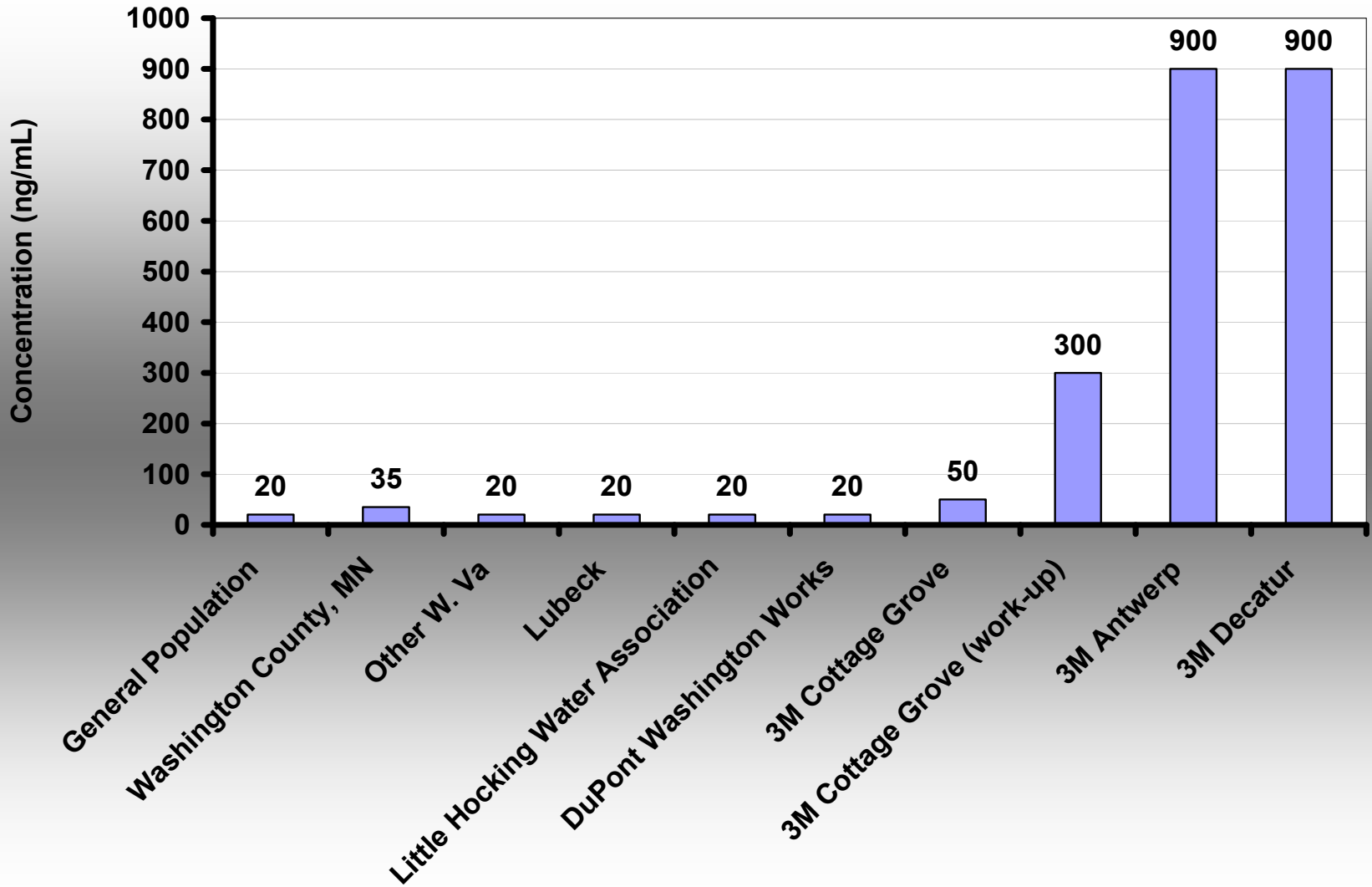
Approximate Average PFOA Concentrations (ng/mL)



Comparison of Human PFOA Biomonitoring Data to Benchmark Lower Bound Internal Concentrations from Toxicological Study Endpoints



Approximate Average PFOS Concentrations (ng/mL)



Comparison of Human PFOS Biomonitoring Data to Benchmark Lower Bound Internal Concentrations from Toxicology Study Endpoints

