Human Epidemiologic Studies of Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS)

Craig Steinmaus, MD, MPH

California Environmental Protection Agency

Office of Environmental Health Hazard Assessment

11/15/2019

CalEPA
California Environmental Protection Agency

OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Primary Health Outcomes

- Immunologic
- Thyroid
- Liver
- Cancer (kidney, liver, testicular, prostate)
- Lipids
- Reproductive
- Other

Literature search

Most recent NTP (2016), US EPA (2016), and A T S D R (2018) reviews

Updated with:

- PubMed
- Google Scholar
- Published review articles
- Bibliographies of all included articles
- Other

Search string: example

From NTP's 2016 review of PFOS/PFOA and Immunotoxicity

(perfluoroalkyl*[tiab] OR perfluorocaprylic[tiab] OR perfluorocarbon*[tiab] OR perfluorocarboxyl*[tiab] OR perfluorochemical*[tiab] OR (perfluorinated[tiab] AND (C8[tiab] OR carboxylic[tiab] OR chemical*[tiab] OR compound*[tiab] OR octanoic[tiab])) OR PFAA*[tiab] OR "fluorinated polymer"[tiab] OR "fluorinated polymers"[tiab] OR (fluorinated[tiab] AND (polymer[tiab] OR polymers[tiab])) OR (fluorocarbon[tiab] AND (polymer[tiab] OR polymers[tiab])) OR Fluoropolymer*[tiab] OR (fluorinated[tiab] AND telomer*[tiab]) OR fluorotelomer*[tiab] OR fluoro-telomer*[tiab] OR fluorosurfactant*[tiab] OR "FC 143"[tiab] OR FC143[tiab] OR 335-67-1 [rn] OR Pentadecafluoroctanoate*[tiab] OR Pentadecafluorooctanoate*[tiab] OR pentadecafluoroctanoic[tiab] OR pentadecafluorooctanoic[tiab] OR "pentadecafluoro-1-octanoic"[tiab] OR "pentadecafluoro-n-octanoic"[tiab] OR "perfluoro-1-heptanecarboxylic"[tiab] OR perfluorocaprylic[tiab] OR perfluoroheptanecarboxylic[tiab] OR perfluoroctanoate[tiab] OR perfluorooctanoate[tiab] OR "perfluoro octanoate"[tiab] OR "perfluorooctanoic acid"[nm] OR perfluoroctanoic[tiab] OR perfluorooctanoic[tiab] OR "perfluoro octanoic"[tiab] OR "perfluoro-n-octanoic"[tiab] OR "perfluorooctanoyl chloride"[tiab] OR PFOA[tiab] OR APFO[tiab] OR 1763-23-1[rn] OR 307-35-7[rn] OR "1-octanesulfonic acid"[tiab] OR "1-perfluorooctanesulfonic"[tiab] OR "1-perfluoroctanesulfonic"[tiab] OR "heptadecafluoro-1-octanesulfonic"[tiab] OR "heptadecafluoro-1-octane sulfonic"[tiab] OR "heptadecafluorooctanesulfonic"[tiab] OR "heptadecafluorooctane sulfonic"[tiab] OR "heptadecafluoroctane sulfonic"[tiab] OR "perfluoroalkyl sulphonate"[tiab] OR perfluoroctanesulfonate[tiab] OR perfluorooctanesulfonate[tiab] OR "perfluoroctane sulfonate"[tiab] OR "perfluorooctane sulfonate"[tiab] OR "perfluoro-n-octanesulfonic"[tiab] OR perfluoroctanesulfonic[tiab] OR perfluorooctanesulfonic[tiab] OR "perfluorooctane sulfonic acid"[nm] OR "perfluoroctane sulfonic"[tiab] OR "perfluorooctane sulfonic"[tiab] OR perfluoroctanesulphonic[tiab] OR perfluorooctanesulphonic[tiab] OR "perfluoroctane sulphonic"[tiab] OR "perfluorooctane sulphonic"[tiab] OR perfluoroctylsulfonic[tiab] OR PFOS [tiab]) **AND [Health effect]**

Inclusion-exclusion criteria

Inclusion

- Human epidemiologic studies
- PFOA or PFOS
- Exposure: water, blood or urine
- Outcomes expressed as relative risk, mean differences, correlations, regressions, other
- Cohort, case-control, cross-sectional, and ecologic designs

Exclusion

- Case-reports
- No comparison group
- Abstracts and studies without original data (e.g. reviews or editorials)
- Results only for multiple perfluoroalkylate substances (PFAS) combined

Evaluating study quality

Selection: Were all eligible people, or a random selection of all eligible people, invited to participate?

Participation: Of those who were invited to participate, what was the percentage of people who actually agreed to participate and for whom there were sufficient data to be included in the final study analyses?

Equal groups: Were there any major socioeconomic or other relevant differences between people with higher or lower PFOA or PFOS levels or between people with or without the outcome of interest?

Blinding: Were the researchers measuring the exposure blinded to the outcome status of the participants?

Exposure levels: What was the distribution of PFOA or PFOS levels among the study participants? Were exposure levels too low to identify true associations?

Exposure and outcome methods: Were validated, generally accepted, or otherwise reasonable methods for assessing exposure and outcome used?

Confounding: Is the factor associated with both exposure and outcome, strength of these associations, prevalence of the risk factor?

Example: Identifying potential confounders for human studies of PFOS/PFOA and cancer

Kidney cancer	Testicular cancer	Prostate cancer
• Older age • Gender (males) • Race (African Americans and American Indians/Alaska Natives) • Smoking • Obesity • Hypertension • Dialysis • Inherited diseases: von Hippel-Lindau disease, Birt-Hogg-Dube syndrome, tuberous sclerosis complex, hereditary papillary renal cell carcinoma or familial renal cancer. • Occupational exposures: cadmium, pesticides, TCE • Medications: phenacetin, diuretics • Exercise and diet (low fruit and vegetable intake, acrylamide, lower alcohol)	• Age • Race/ethnicity (Caucasian) • Undescended testicle • Family history • HIV infection • Carcinoma in situ • Occupations: firefighting and aircraft maintenance • Organochloride pesticides	• Age • Race/ethnicity (African American). • Family history • Hereditary • Agent Orange • Possibly diet • Geography: North America, northwestern Europe, Australia, and Caribbean islands • PSA testing
References: • American Cancer Society, https://www.cancer.org/cancer/kidney-cancer/causes-risks-prevention/risk-factors.html • Mayo Clinic, https://www.mayoclinic.org/diseases-conditions/kidney-cancer/symptoms-causes/syc-20352664 • Chow, W. H., Dong, L. M., & Devesa, S. S. (2010). Epidemiology and risk factors for kidney cancer. Nature reviews. Urology, 7(5), 245–257	References: • American Cancer Society, https://www.cancer.org/cancer/testicular-cancer/causes-risks-prevention/risk-factors.html • McGlynn, K. A., & Trabert, B. (2012). Adolescent and adult risk factors for testicular cancer. Nature reviews. Urology, 9(6), 339–49.	References: • American Cancer Society, https://www.cancer.org/cancer/prostate-cancer/causes-risks-prevention/risk-factors.html • Centers for Disease Control and Prevention, https://www.cdc.gov/cancer/prostate/basic_info/risk_factors.htm • UpToDate. Risk factors for prostate cancer. Sartor, OA. Sept 2019, https://www-uptodate-com.ucsf.idm.oclc.org/contents/risk-factors-for-prostate-cancer?search=prostate%20cancer%20epidemiology&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1

Other aspects of causal inference

Modified version of the Bradford Hill criteria

- Precision (e.g. statistical significance)
- Magnitude of the association
- Dose-response
- Temporality
- Consistency
- Subgroups and susceptibility
- Plausibility

Example of the format used to describe each study

Study details	Factors related to bias	Exposure method	Outcome method	Results	Comparison group	Confounding	Other aspects of causal inference	Notes
Grandjean et al., 2017a Faroe Islands 2007-09 Prospective cohort and cross-sectional Children ages 5 and under N=275-349 PFOA	**Selection**: unclear **Participation:** unclear **Equal groups:** unclear **Blinded:** unclear **Above detection:** unclear **Exposure levels:** median (IQR) = 2.8 (2.0-4.5) ng/ml at age 18 months	Serum near birth, 18 months, age 5	Antibody response: diphtheria Serum IgG age 5	**2007-09 cohort:** PFOA IgG %change Birth -18.9 (p=0.03) 18 mo. 4.1 (p=0.63) 5 yr. 18.3 (p=0.24) **Combined cohort:** PFOA IgG %change Birth -17.8 (p=0.009) 18 mo. 5.4 (p=0.52) 5 yr. 3.4 (p=0.73) No major differences between 1997-2000 and 2007-09 cohorts	Percent change for a 2-fold increase in PFAS concen-tration	Age, sex, PCB con-centrations and Cesarean section	**Magnitude** (O R>1.2): yes **Statistical significance:** yes **Dose-response:** linear **Temporal association:** yes **Subgroup only:** no **Adjustments:** unclear	PFAS concentrations highly correlated with breastfeeding duration Correlation coefficients up to 0.7 for PFAS levels at age 18 months and age 5 years Correlations between the different PFAS were up to 0.8 to 0.9 44 and 36% had IgG below protective levels for diphtheria and tetanus at age 5, respectively

Epidemiologic studies of PFOA and vaccine response: summary

	Diphtheria Ig age ↓					Tetanus Ig age ↓				
PFOA Age ↓	**5 years pre**	**5 years post**	**7 years**	**13 years**	**Adult**	**5 years pre**	**5 years post**	**7 years**	**13 years**	**Adult**
Birth	-16.2 **-18.9[a]***	-6.2	**-22.8**			-10.5 **-22.2[a]***	14.5	7.4		
1.5 years	4.2*					**-16.3***				
5 years	-6.8 18.3[a]*	-6.1	**-25.2**			-13.3 **-25.3[a]***	-9.7	**-35.8**		
7 years			**-25.4**	-9.2*				-20.5	2.9*	
13 years				**-25.3***					-5.6*	
Adult					-8.2[b]					0.23[b]

Results codes:

- Negative numbers = PFOA associated with decreased vaccine response
- All results are from the 1997-2000 Faroe Islands cohort except:
  - [a] 2007-09 Faroe Islands cohort
  - [b] Kielsen et al., 2016
- Bolded: statistically significant
- Light orange: cross-sectional analyses (all others are prospective)

Epidemiologic studies of PFOS and vaccine response: summary

	Diphtheria Ig age ↓					Tetanus Ig age ↓				
PFOS Age ↓	5 years pre	5 years post	7 years	13 years	Adult	5 years pre	5 years post	7 years	13 years	Adult
0	**-38.6** -14.0[a]	-20.6	-10.0			-10.1 -10.8[a]	-2.3	35.3		
1.5 years	17.5					-7.0				
5 years	-16.0 17.1[a]	-15.5	**-27.6**			-11.9 -9.1[a]	**-28.5**	-23.8		
7 years			**-30.3**	-25.6				-9.1	**45.4**	
13 years				-10.5					23.4	
Adult					**-11.9**[b]					-3.6[b]

Thyroid hormone levels

33 human studies

16 new studies since the 2016 US EPA review

54 different results categorized by age (infants, children, adults), gender, and pregnancy status

Outcomes: serum total T4, free T4, TSH

Overall: mixed results

Thyroid diseases Fewer studies

Some suggestive evidence (e.g. hypothyroidism, “all thyroid diseases”)

Limited by small sample sizes, potential confounding, lack of replication by outcome…

Still updating literature searches and detailed evaluations of study quality

Example: Epidemiologic studies of PFOS/PFOA and thyroid hormones in pregnant women

Study	Source	Location	Design	N	Exp	Group	Sex	PFAS	TH	PFOA			PFOS			Adjustments
										TSH	T4	fT4	TSH	T4	fT4	
Wang et al., 2013	USEPA	Norway	CS	903	Low	Pregnant	Female	Preg	Preg	↓	0	0	↑↑	0	0	Age, HDL chol, diet, parity, gest age
Wang et al., 2014	USEPA	Taiwan	CS	283	Low	Pregnant	Female	Preg	Preg	↑	↑	↓	↓	↑	↑	Age, educ, parity
Webster et al., 2014	USEPA	Vancouver	CS	151	Low	Pregnant	Female	Preg	Preg	↑	↓	↓	↑	↓	↑	Age, sampling time, anti-TPO
Berg et al., 2015	USEPA	Norway	CS	375	Low	Pregnant	Female	Preg	Preg	↑	0	0	↑↑	0	0	Age, parity, BMI, thyroxine binding
Kato et al., 2016	New	Japan	CS	392	Low	Pregnant	Female	Preg	Preg	↑	0	↑	↓↓	0	↑	Age, parity, educ, anti-TPO, diet, sampling
Yang et al., 2016	New	China	CS	157	Low	Pregnant	Female	Preg	Preg	↓	↑	↑↓	↓↓	↑	↓	Age, BMI, income, delivery
Preston et al., 2018	New	Boston	CS	718	Low	Pregnant	Female	Preg	Preg	↑	↑	↓↓	↓	↑	↓	Age, race, smok, diet, parity, gest

Results coding:

↑↑, statistically significant positive association
↓↓, statistically significant inverse association
Single arrow, not statistically significant
0, data not provided; ↑↓, no association

Study of PFOA and kidney and testicular cancer by Vieira et al 2013

Exposure		Kidney cancer			Testicular cancer		
Category	**ug/L**	**N**	**OR**	**95%CI**	**N**	**OR**	**95%CI**
Reference	<3.7	187	1.0	ref	50	1.0	ref
Low	3.7-12.8	11	0.8	0.4-1.5	1	0.2	0.0-1.6
Medium	12.9-30.7	17	1.2	0.7-2.0	3	0.6	0.2-2.2
High	30.8-109	22	2.0	1.3-3.2	1	0.3	0.0-2.7
Very high	110-655	9	2.0	1.0-3.9	6	2.8	0.8-9.2

Study details

- Study area: 13 counties in Ohio and West Virginia, near a Teflon manufacturing plant
- Incident cancers diagnosed from 1996 to 2005 from the state cancer registries
- Exposure based on residential address at diagnosis and modeled serum levels for 1995 (C8 Health Project)
- Controls are cancers other than kidney, pancreas, prostate, and liver
- Adjusted for age, sex, diagnosis year, smoking, insurance type (e.g. Medicaid)

Human epidemiologic evidence

Next Steps:

- ✓ Updated literature searches
- ✓ Detailed evaluations of bias and confounding
- ✓ Other health effects