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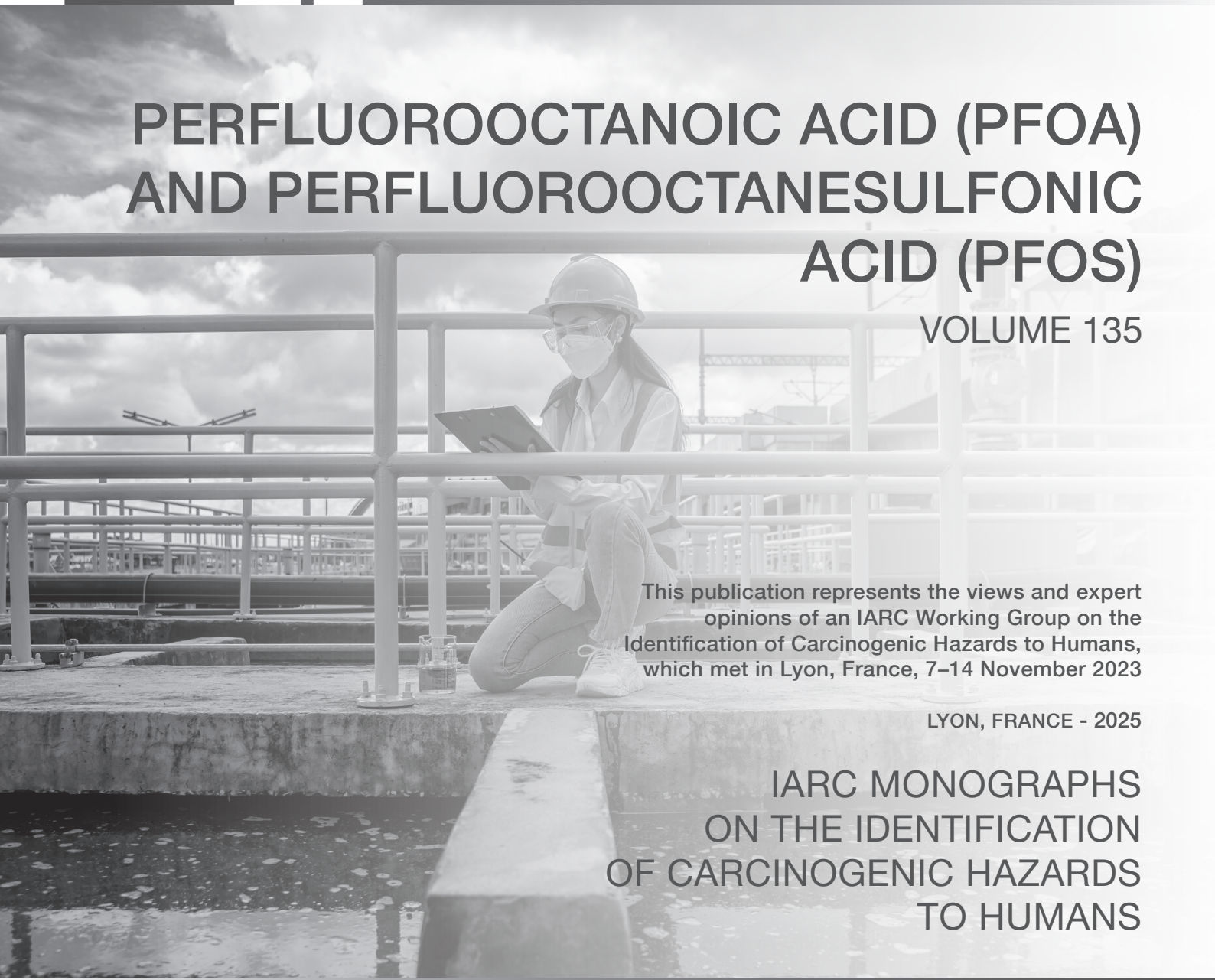

PERFLUOROOCTANOIC ACID (PFOA) AND PERFLUOROOCTANESULFONIC ACID (PFOS)

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International Agency for Research on Cancer

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Table S2.7 Epidemiological studies on exposure to PFOA or PFOS and cancers of all sites combined

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (incidence or mortality)	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Raleigh et al. (2014) MN, USA Enrolment: 1947–2002/follow-up: 1947–2008 Cohort	9027 (4668 exposed workers, 4359 reference workers); Cottage Grove (MN) PFOA cohort latest update (previous Gilliland and Mandel (1993) and Lundin et al. (2009)). Workers employed for at least 1 yr 1947–2002 at an ammonium perfluorooctanoate (APFO) facility (n = 4668). Reference workers employed at a tape and abrasives production facility without any exposure to APFO located in the same suburban geographical area and managed by the same company (Saint Paul, MN, n = 4359). Exposure assessment method: See Table 2.1	All cancers combined, mortality	Exposed to APFO (SMR, MN referent):			Age, sex, calendar period	*Exposure assessment critique*: See Table 2.1 *Other strengths:* Unlikely TFE co-exposure; reference population shared similar socioeconomic characteristics. *Other limitations:* Lacking data on workers who left MN or Wisconsin.
			Unexposed (Saint Paul Plant)	514	1.04 (0.95–1.13)		
			Exposed (Cottage Grove Plant)	332	0.87 (0.78–0.97)		
		All cancers combined, mortality	Estimated cumulative airborne APFO exposure quartile (SMR, MN referent):			Age, sex, calendar period	
			1st quartile ($< 2.6 \times 10^{-5}$ μg/m^3-yr)	79	0.70 (0.55–0.87)		
			2nd quartile (2.6×10^{-5} to $< 1.4 \times 10^{-4}$ μg/m^3-yr)	81	0.89 (0.71–1.11)		
			3rd quartile (1.4×10^{-4} to $< 7.3 \times 10^{-4}$ μg/m^3-yr)	103	1.01 (0.82–1.22)		
			4th quartile ($\geq 7.3 \times 10^{-4}$ μg/m^3-yr)	69	0.92 (0.71–1.16)		
Alexander et al. (2003) Decatur, Alabama, USA Enrolment: 1961–1997/follow-up: 1961–1998 (mortality)	2083; Decatur (AL) PFOS cohort. Production workers (83% male) who worked at least 365 days in a plant producing specialty films and fluorochemicals, one of the main ones being perfluorooctanesulfonyl (POSF). Exposure assessment method: See	All cancers combined, mortality	PFOS exposure group (SMR, Alabama referent):			Age, sex, calendar period	*Exposure assessment critique*: See Table 2.1 *Other limitations:* Occupational cohort with few cancer deaths (39 overall, 18 in high exposure group), limited to mortality; limited to few exposure
			All jobs	39	0.72 (0.51–0.98)		
			Only non-exposed	15	0.73 (0.41–1.21)		
			Ever low, never high	6	0.52 (0.19–1.14)		
			Ever high	18	0.84 (0.50–1.32)		
			High for at least 1 yr	14	0.84 (0.46–1.41)		

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Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (incidence or mortality)	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Cohort	Table 2.1						categories (non-exposed, low-exposed, high-exposed); lack of data on smoking; mostly male.
Steenland and Woskie (2012) Parkersburg, WV, USA Enrolment: 1948–2002/follow-up: 1952–2008 Cohort	5791; Parkersburg (WV, USA), polymer production PFOA cohort. Workers (81% male) at a US polymer manufacturing facility who had potential exposure to fluoropolymers with sufficiently detailed work histories. Exposure assessment method: See Table 2.1	All cancers combined, mortality	PFOA-exposed workers (SMR):			Age, sex, calendar period	*Exposure assessment critique*: See Table 2.1 *Other strengths:* Large exposure contrast. *Other limitations:* Did not evaluate incidence of all cancers combined
			Other workers referent (same company and region)	304	0.93 (0.83–1.04)		
			US referent	304	0.74 (0.66–0.83)		
		All cancers combined, mortality	Cumulative serum exposure, no lag (SMR, other workers referent, same company and region):			Age, sex, calendar period	
			1st quartile (0 to < 904 ppm-yrs)	62	0.93 (0.72–1.20)		
			2nd quartile (904 to < 1520 ppm-yrs)	68	0.90 (0.70–1.14)		
			3rd quartile (1520 to < 2700 ppm-yrs)	83	0.95 (0.75–1.76)		
			4th quartile (≥ 2700 ppm-yrs)	91	0.94 (0.76–1.16)		
		All cancers combined, mortality	Cumulative serum exposure, 10-year lag (SMR, other workers referent same company and region):			Age, sex, calendar period	
			1st quartile (0 to < 798 ppm-yrs)	69	0.97 (0.75–1.22)		
			2nd quartile (798 to < 1379 ppm-yrs)	69	0.91 (0.71–1.15)		
			3rd quartile (1379 to < 2384 ppm-yrs)	76	0.95 (0.75–1.19)		
			4th quartile	79	0.92 (0.73–1.15)		

Table S2.7 Epidemiological studies on exposure to PFOA or PFOS and cancers of all sites combined

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (incidence or mortality)	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
			(≥ 2384 ppm-yrs)				
Consonni et al. (2013) USA, United Kingdom, Italy, Germany, the Netherlands Enrolment: 1950–2002/follow-up: 1950–2008 Cohort	5879 male workers (4205 APFO-exposed); The pooled international TFE (tetrafluoroethylene) cohort includes male workers who for at least 0–12 mo were employed at one or more of 6 TFE production sites in North America and Europe from 1950–2002. The principal occupational exposures were TFE and ammonium perfluorooctanoic acid (aiding production of PTFE) Exposure assessment method: See Table 2.1	All cancers combined, mortality	Cumulative APFO exposure (SMR, national referent):			Age, calendar period, country	*Exposure assessment critique*: See Table 2.1 *Other strengths:* The cohort includes all TFE production sites worldwide during the entire period of production and benefits from almost complete enrolment and follow-up data. *Other limitations:* Low statistical power to detect risk of rare cancers; high correlations between exposure to TFE monomer (IARC Group 2A) and PFOA which precludes evaluation of effects of the individual compounds.
			Ever APFO-exposed	159	0.79 (0.67–0.92)		
			< 16 unit-yr	51	0.78 (0.58–1.02)		
			16–138 unit-yr	53	0.81 (0.61–1.06)		
			139+ unit-yr	55	0.78 (0.59–1.02)		
			Trend-test *P*-value, 0.70				
		All cancers combined, mortality	Cumulative APFO exposure by cumulative TFE exposure (SMR, national referent):			Age, calendar period, country	
			Low APFO and low TFE	42	0.78 (0.56–1.05)		
			Low APFO and medium TFE	9	0.85 (0.39–1.61)		
			Low APFO and high TFE	0	0		
			Medium APFO and low TFE	3	0.50 (0.10–1.46)		
			Medium APFO and medium TFE	44	0.94 (0.68–1.27)		
			Medium APFO and high TFE	6	0.47 (0.17–1.02)		
			High APFO and low TFE	0	0		
			High APFO and medium TFE	4	0.58 (0.16–1.48)		

Table S2.7 Epidemiological studies on exposure to PFOA or PFOS and cancers of all sites combined

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (incidence or mortality)	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
			High APFO and high TFE	51	0.81 (0.60–1.06)		
Girardi and Merler (2019) Vicenza province, Veneto Region, Italy Enrolment: 1960–2008/follow-up: 1970–2018 (mortality) Cohort	462 (PFAS workers); 1383 (railroad workers); Workers in perfluorocarbon production facility manufacturing PFOA, PFOS, other perfluorinated compounds and other chemicals in Trissino (Veneto, Italy). Comparison populations included regional general population and workers in a local railroad industry not exposed to chemicals. For both occupational cohorts, workers included were men employed ≥ 6 mo Exposure assessment method: See Table 2.1	All cancers combined, mortality	SMR (regional referent):			Age, calendar period	Exposure assessment critique: See Table 2.1 *Other strengths:* Highly exposed occupational cohort; internal comparisons with non-exposed workers *Other limitations:* Small occupational cohort with relatively few deaths (n = 42 cancer-related deaths); limited to men; no data on confounders
			All Trissino plant workers	42	1.00 (0.74–1.36)		
			Offices	10	0.79 (0.43–1.47)		
			Never at PFAS department	19	0.94 (0.60–1.47)		
			Ever at PFAS department	13	1.46 (0.85–2.51)		
		All cancers combined, mortality	Cumulative PFOA concentration (SMR, regional referent):			Age, calendar period	
			1st tertile (≤ 4034 ng/mL-yr)	11	0.78 (0.43–1.41)		
			2nd tertile (4034–16 956 ng/mL-yr)	10	0.95 (0.51–1.76)		
			3rd tertile (> 16 956 ng/mL-yr)	21	1.22 (0.79–1.87)		
		All cancers combined, mortality	RR (relative to railroad workers):			Age, calendar period	
			Railroad workers	92	1		
			All Trissino plant workers	42	1.32 (0.91–1.91)		
			Offices	10	0.99 (0.51–1.92)		
			Never at PFAS	19	1.25 (0.76–2.06)		

Table S2.7 Epidemiological studies on exposure to PFOA or PFOS and cancers of all sites combined

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (incidence or mortality)	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
			department				
			Ever at PFAS department	13	1.97 (1.10–3.54)		
		All cancers combined, mortality	Cumulative PFOA concentration (RR, relative to railroad workers):			Age, calendar period	
			Railroad workers	92	1		
			1st tertile (≤ 4034 ng/mL-yr)	11	1.00 (0.53–1.87)		
			2nd tertile (4034–16 956 ng/mL-yr)	10	1.23 (0.64–2.37)		
			3rd tertile (> 16 956 ng/mL-yr)	21	1.65 (1.02–2.65)		
Li et al. (2022a) Ronneby, southern Sweden Enrolment:1985–2013/follow-up: 1985–2016 (incidence) Cohort	60 507; The Ronneby Register Cohort includes all individuals who ever lived in Ronneby municipality 1985–2013. One third of the households received PFAS-contaminated drinking-water from a waterworks situated near a military airfield where PFAS containing firefighting foam was used 1985–2013 (*n* = 15 811 individuals considered "ever high"). Subsets with long-term exposure (11 yr or more) in the latest part of the follow-up period (2005–2013) were considered more highly exposed. Exposure assessment method: See Table 2.1	All cancers combined, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	*Exposure assessment critique*: See Table 2.1 *Other strengths:* Large study population; data on cancer incidence; strong exposure contrast; unbiased inclusion; complete follow-up; long follow-up for part of the population; reference group from same municipality. *Other limitations:* Mixed exposure to multiple PFAS limits ability to single out effects due to specific compounds; limited information on potential
			Males: Never	2368	1.00 (0.96–1.05)		
			Ever	725	1.04 (0.96–1.12)		
		All cancers combined, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar period	
			Females: Never	1949	0.89 (0.85–0.93)		
			Ever	600	0.89 (0.82–0.96)		
		All cancers combined, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	4320	1		
			Ever	1325	1.02 (0.96–1.09)		

Table S2.7 Epidemiological studies on exposure to PFOA or PFOS and cancers of all sites combined

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (incidence or mortality)	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
							confounders
		All cancers combined, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex, highest education	
			Never	4042	1		
			Ever	1247	1.01 (0.95–1.08)		
		All cancers combined, incidence	Time period of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	4320	1		
			Early (1985–2004)	832	0.99 (0.91–1.06)		
			Late (2005–2013)	493	1.09 (0.99–1.20)		
		All cancers combined, incidence	Time period of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex, highest education	
			Never	4042	1		
			Early (1985–2004)	754	0.96 (0.88–1.04)		
			Late (2005–2013)	493	1.11 (1.01–1.22)		
		All cancers combined, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	4320	1		
			Short (1–10 yr)	704	1.03 (0.95–1.11)		
			Long (≥ 11 yr)	621	1.02 (0.93–1.11)		
		All cancers combined, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex, highest education	
			Never	4042	1		
			Short (1–10 yr)	627	1 (0.92–1.09)		
			Long (≥ 11 yr)	620	1.02 (0.93–1.11)		

Table S2.7 Epidemiological studies on exposure to PFOA or PFOS and cancers of all sites combined

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Organ site (incidence or mortality)	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wen et al. (2022) USA Enrolment: 1999–2014/follow-up: 1999–2015 (mortality) Cohort	11 747; NHANES cohort: nationally representative cross-sectional survey of adults (age ≥ 18 yr) followed for mortality through 2015. Exposure assessment method: See Table 2.1	All cancers combined, mortality	Serum PFOA concentration (HR):			Age, sex, race/ethnicity, smoking status, alcohol intake, physical activities, hypertension, diabetes, healthy eating index, creatinine clearance rate, serum total cholesterol, serum cotinine, PFAS excluding PFOA, time on study	*Exposure assessment critique:* See Table 2.1 *Other strengths:* Nationally representative of the USA; considered mixtures of PFAS *Other limitations:* Short follow-up time (median 81 mo); heterogeneous outcome; representative of incidence only in the case of high fatality of cancers.
			1st tertile (< 2.4 ng/mL)	59	1		
			2nd tertile (2.4–4.3 ng/mL)	74	0.99 (0.60–1.62)		
			3rd tertile (≥ 4.3 ng/mL)	115	1.06 (0.68–1.71)		
		All cancers combined, mortality	Serum PFOS concentration (HR):			Sex, age, race/ethnicity, education, smoking status, physical activity, hypertension, healthy eating index, creatinine clearance rate, serum total cholesterol, serum cotinine, PFAS excluding PFOS, time on study	
			1st tertile (< 7.9 ng/mL)	39	1		
			2nd tertile (7.9–17.1 ng/mL)	79	1.26 (0.75–2.06)		
			3rd tertile (≥ 17.1 ng/mL)	130	1.75 (1.10–2.83)		

AL, Alabama; APFO, ammonium perfluorooctanoate; BMI, body mass index; CI, confidence interval; HR, hazard ratio; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; MN, Minnesota; mo, month(s); NR, not reported; OH, Ohio; OR, odds ratio; ppm, parts per million; PFAS, perfluoroalkyl and polyfluoroalkyl substance(s); PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; POSF, perfluorooctanesulfonyl; PTFE, polytetrafluoroethylene; RR, rate ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SES, socioeconomic status; TFE, tetrafluoroethylene; US, United States; USA, United States of America; WV, West Virginia; yr, year(s).

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