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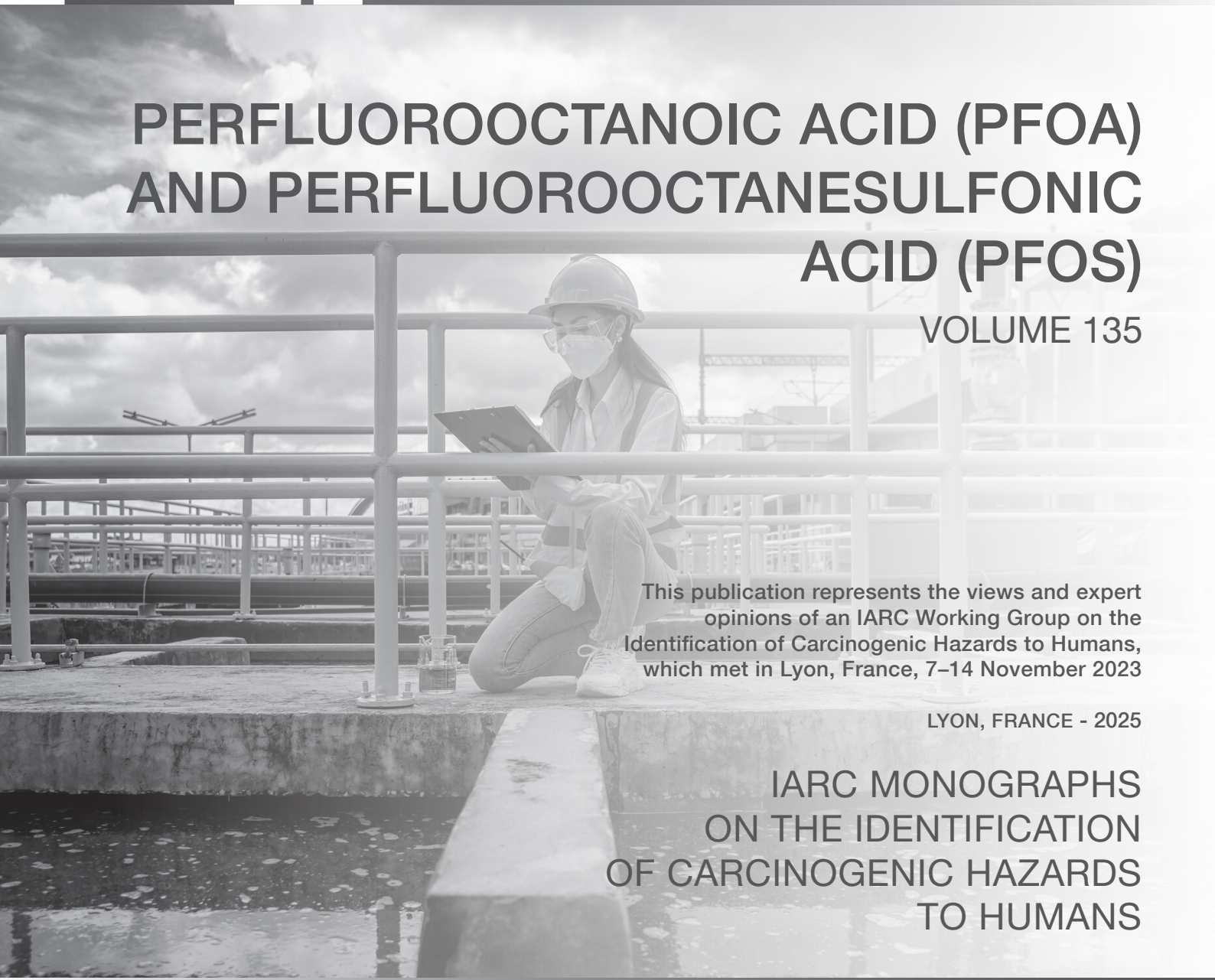

PERFLUOROOCTANOIC ACID (PFOA) AND PERFLUOROOCTANESULFONIC ACID (PFOS)

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International Agency for Research on Cancer

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Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
Lundin et al. (2009) MN, USA Enrolment: 1947–1997/follow-up: 1947–2002 (mortality) Cohort	3993 employees; Cottage Grove (MN) PFOA cohort: Workers employed at a PFOA production plant for at least 365 days before 31 December 1997. Exposure assessment method: See Table 2.1	CNS (central nervous system), mortality	Employed in APFO-exposed job (SMR, MN referent):			Age, sex, calendar period	*Exposure assessment critique*: See Table 2.1 *Other strengths:* Occupational cohort with relatively high exposures. *Other limitations:* Small cohort with few deaths; potential healthy-worker effect due to external comparison of rates from general population; limited information on covariates
			Never	2	0.44 (0.05–1.59)		
			Ever probable/never definite	5	1.16 (0.37–2.70)		
			Ever definite	0	0 (0.00–3.81)		
		Lymphatic and haematopoietic, mortality	Employed in APFO-exposed job (SMR, MN referent):			Age, sex, calendar period	
			Never	14	0.90 (0.49–1.51)		
			Ever probable/never definite	14	0.96 (0.53–1.61)		
			Ever definite	1	0.37 (0.01–2.08)		
		Lymphosarcoma-reticulosarcoma, mortality	Employed in APFO-exposed job (SMR, MN referent):			Age, sex, calendar period	
			Never	1	0.84 (0.02–4.65)		
			Ever probable/never definite	2	1.80 (0.22–6.51)		
			Ever definite	0	0 (0.00–19.45)		
		HL (Hodgkin lymphoma), mortality	Employed in APFO-exposed job (SMR, MN referent):			Age, sex, calendar period	
			Never	1	1.09 (0.03–6.04)		
			Ever probable/never definite	0	0 (0.00–4.21)		
			Ever definite	0	0 (0.00–18.69)		
		Leukaemia, mortality	Employed in APFO-exposed job (SMR, MN referent):			Age, sex, calendar period	
			Never	4	0.68 (0.18–1.73)		
			Ever probable/never definite	7	1.27 (0.51–2.61)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
			Ever definite	1	0.96 (0.02–5.34)		
		Other lymphatic and haematopoietic, mortality	Employed in APFO-exposed job (SMR, MN referent):			Age, sex, calendar period	
			Never	8	1.07 (0.46–2.10)		
			Ever probable/never definite	5	0.71 (0.23–1.66)		
			Ever definite	0	0 (0.00–2.96)		
Alexander et al. (2003) Decatur, Alabama, USA Enrolment: 1961–1997/follow-up: 1961–1998 (mortality) Cohort	2083; Decatur (AL)PFOS occupational cohort Exposure assessment method: See Table 2.1	Lymphatic and haematopoietic, mortality	PFOS exposure group (SMR, Alabama referent)			Sex, age, calendar period	*Exposure assessment critique*: See Table 2.1 *Other strengths:* highly exposed occupational cohort with long follow-up *Other limitations:* few cases do not allow estimation of risk with reasonable precision.
			All jobs	4	0.70 (0.19–1.80)		
			Only non-exposed	3	1.37 (0.28–4.00)		
			Ever low, never high	0	0		
			Ever high	1	0.43 (0.01–2.40)		
			High for at least 1 yr	1	0.56 (0.01–3.08)		
		Melanoma, mortality	PFOS exposure group (SMR, Alabama referent):			Sex, age, calendar period	
			All jobs	3	1.67 (0.34–4.88)		
			Only non-exposed	1	1.38 (0.03–7.67)		
			Ever low, never high	0	0		
			Ever high	2	2.62 (0.32–9.46)		
			High for at least 1 yr	1	1.67 (0.04–9.25)		
		Respiratory system, mortality	PFOS exposure group (SMR, Alabama referent):			Sex, age, calendar period	
			All jobs	15	0.71 (0.40–1.18)		
			Only non-exposed	4	0.51 (0.14–1.30)		
			Ever low, never high	4	0.87 (0.24–2.22)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
			Ever high	7	0.85 (0.34–1.75)		
			High for at least 1 yr	6	0.93 (0.34–2.03)		
		Bronchus, trachea, lung, mortality	PFOS exposure group (SMR, Alabama referent):			Sex, age, calendar period	
			All jobs	15	0.74 (0.41–1.22)		
			Only non-exposed	4	0.52 (0.14–1.34)		
			Ever low, never high	4	0.90 (0.24–2.29)		
			Ever high	7	0.88 (0.35–1.81)		
			High for at least 1 yr	6	0.96 (0.35–2.09)		
Leonard et al. (2008) Parkersburg, WV, USA Enrolment: 1948–2002/follow-up: 1948–2002 (mortality) Cohort	6027; Parkersburg (WV, USA), polymer production occupational PFOA cohort. Workers (81% male) at a US polymer manufacturing facility who had potential exposure to fluoropolymers with sufficiently detailed work histories. Most recent follow-up for some cancer sites (see those listed here), later follow-up by Steenland and Woskie (2012). The latest update of the cohort by Steenland and Woskie (2012) extends the follow-up from 2002 until and including 2008 and adds 5 cases of NHL (from 9 to 14) and 1 case of leukaemia (from 13 to 14 cases). Exposure assessment method: See Table 2.1	Melanoma, mortality	Plymer-production cohort (SMR):			Sex, age, calendar period	*Strengths:* Occupational cohort with relatively high exposures; complete cohort ascertainment and follow-up; local reference groups increase comparability with respect to socioeconomic factors and health behaviours. *Limitations:* No assessment of exposure to specific chemicals (the company utilizes a wide variety of chemicals including PFOA); small numbers. *Other comments*: The Parkersburg (WV, USA) facility manufactured a broad range of commercial products including fluoropolymers, nylon filaments, and acrylic polymers; all study participants, regardless of work area, had detectable levels of serum PFOA.
			Referent US population	3	[0.559 (0.115–1.632)]		
			Referent WV population	3	[0.518 (0.107–1.514)]		
			Referent other workers (same region and company)	3	[0.675 (0.139–1.974)]		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
Steenland and Woskie (2012) Parkersburg, WV, USA Enrolment: 1948–2002/follow-up: 1952–2008 (mortality) Cohort	5791; Parkersburg (WV, USA), polymer production occupational PFOA cohort. Polymer production workers (81% male), who had potential exposure to fluoropolymers. Earlier follow-up by Leonard et al. (2008). Steenland et al. (2015) presents incidence follow-up for some malignancies in a subset of this cohort. Exposure assessment method: See Table 2.1	NHL, mortality	PFOA-exposed workers (SMR):			Age, sex, calendar period	*Exposure assessment critique*: See Table 2.1 *Other strengths:* Ability to evaluate associations with PFOA in a population exposed to levels much higher than in the general population. *Limitations:* Limited ability to evaluate mortality for some cancers due to small numbers of deaths, particularly for cancers among women and cancers that are relatively rare or less likely to be fatal. Other comments: The Working Group noted that the paper reported an erroneous upper confidence limit for leukaemia, US referent. Exact CI was recalculated by the Working Group, using the observed number and the SMR to calculate the expected number of deaths.
			Other workers referent (same region and company)	14	1.05 (0.57–1.76)		
			US referent	14	0.79 (0.42–1.35)		
		NHL, mortality	Cumulative serum exposure, no lag (SMR, other workers referent, same region and company):			Age, sex, calendar period	
			1st quartile (0 to < 904 ppm-yr)	4	1.54 (0.42–3.95)		
			2nd quartile (904 to < 1520 ppm-yr)	3	0.99 (0.20–2.88)		
			3rd quartile (1520 to < 2700 ppm-yr)	3	0.85 (0.17–2.48)		
			4th quartile (≥ 2700 ppm-yr)	4	0.96 (0.26–2.46)		
		Leukaemia, mortality	PFOA-exposed workers (SMR):			Age, sex, calendar period	
			Other workers referent (same region and company)	14	1.05 (0.57–1.76)		
			US referent	14	[0.88 (0.48–1.48)]		
		Leukaemia, mortality	Cumulative serum exposure, no lag (SMR, other workers referent, same region and company):			Age, sex, calendar period	
			1st quartile (0 to < 904 ppm-yr)	1	0.28 (0.01–1.59)		
			2nd quartile (904 to < 1520 ppm-yr)	7	2.34 (0.94–4.81)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
			3rd quartile (1520 to < 2700 ppm-yr)	2	0.57 (0.07–2.05)		
			4th quartile (≥ 2700 ppm-yr)	4	1.03 (0.28–2.63)		
		Lung, mortality	PFOA-exposed workers (SMR):			Age, sex, calendar period	
			Other workers referent (same region and company)	84	0.78 (0.62–1.64)		
			US referent	84	0.60 (0.48–0.74)		
		Lung, mortality	Cumulative serum exposure, no lag (SMR, other workers referent, same region and company):			Age, sex, calendar period	
			1st quartile (0 to < 904 ppm-yr)	12	0.58 (0.30–1.02)		
			2nd quartile (904 to < 1520 ppm-yr)	16	0.63 (0.36–1.02)		
			3rd quartile (1520 to < 2700 ppm-yr)	32	1.09 (0.35–2.54)		
			4th quartile (≥ 2700 ppm-yr)	24	0.75 (0.48–1.11)		
		Mesothelioma, mortality	PFOA-exposed workers (SMR):			Age, sex, calendar period	
			Other workers referent (same region and company)	6	2.85 (1.05–6.20)		
			US referent	6	4.83 (1.77–10.52)		
		Mesothelioma, mortality	Cumulative serum exposure, no lag (SMR, other workers referent, same region and company):			Age, sex, calendar period	

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
			1st quartile (0 to < 904 ppm-yr)	0	0 (0.00–15.40)		
			2nd quartile (904 to < 1520 ppm-yr)	0	0 (0.00–7.51)		
			3rd quartile (1520 to < 2700 ppm-yr)	1	1.73 (0.04–9.65)		
			4th quartile (≥ 2700 ppm-yr)	5	6.27 (2.04–14.63)		
			Trend-test *P*-value, 0.02				
Steenland et al. (2015) Parkersburg, WV, USA Enrolment: 1948–2002/follow-up: 1951-interview date in 2008–2011 (incidence) Cohort	3713; Parkersburg (WV, USA), polymer production occupational PFOA cohort. This is a subset of the workers described in Steenland and Woskie (2012). Polymer production workers (80% male) who responded (self or next-of-kin) to a questionnaire about health outcomes and who had measured or estimated occupational and residential exposure estimates. 41 incident cases of melanoma. Exposure assessment method: See Table 2.1	Melanoma, incidence	Cumulative PFOA exposure, no lag (RR):			Age, sex, race, education, BMI, time-varying smoking, time-varying alcohol consumption, year of birth	*Exposure assessment critique*: See Table 2.1 *Other strengths:* Ability to evaluate associations between PFOA and cancer incidence in a population exposed to levels much higher than in the general population. *Limitations:* Possibility of selection bias, as the investigation included only 62% of the target population; relatively small numbers of validated cancer cases and inability to evaluate less common malignancies.
			1st quartile (< 3.03 µg/mL-yr)	NR	1		
			2nd quartile (3.03 to < 6.16 µg/mL-yr)	NR	1.16 (0.38–3.54)		
			3rd quartile (6.16 to < 11.42 µg/mL-yr)	NR	1.45 (0.47–4.45)		
			4th quartile (≥ 11.42 µg/mL-yr)	NR	0.88 (0.26–2.95)		
			Trend-test *P*-value, 0.72				
		Melanoma, incidence	Cumulative PFOA exposure, 10-yr lag (RR):			Age, sex, race, education, BMI, time-varying smoking, time-varying alcohol consumption, year of birth	
			1st quartile (< 0.8 µg/mL-yr)	NR	1		
			2nd quartile (0.8 to < 3.44 µg/mL-yr)	NR	0.85 (0.27–2.71)		
			3rd quartile (3.44 to < 7.04 µg/mL-yr)	NR	1.10 (0.34–3.58)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
			4th quartile (≥ 7.04 μg/mL-yr)	NR	0.75 (0.21–2.67)		
			Trend-test *P*-value, 0.33				
Barry et al. (2013) Mid-Ohio Valley (Ohio and WV) Enrolment: August 2005-August 2006/follow-up: 1952 to 2011 (incidence) Cohort	32 254 (28 541 community members and 3713 workers); C8 Science Panel Study. Includes persons enrolled in the C8 Health Project who lived, worked, or attended school for at least 1 yr between 1950 and 3 December 2004 in a contaminated water district in the vicinity of a chemical plant (Parkersburg (WV, USA), polymer production) using PFOA in manufacturing, as well as a subset of those from the original Parkersburg (WV, USA), polymer production occupational cohort who worked at the plant between 1948 and 2002. Exposure assessment method: See Table 2.1	Brain, incidence	Group (HR, per unit increase in the estimated cumulative PFOA serum concentration (ng/mL) on the natural log scale, no lag):			Age, time-varying smoking, time-varying alcohol consumption, sex, education, birth year (5-yr calendar intervals)	Exposure assessment critique: See Table 2.1 *Other strengths:* Large cohort and strong exposure contrast; lagged analyses; adjustment for several covariates. *Other limitations:* Self-reported cancer cases (but with individual validation); co-exposure to other PFAS in residents not evaluated.
			Entire cohort	17	1.13 (0.84–1.51)		
			- Community residents	13	1.14 (0.78–1.65)		
			- Occupational workers	4	0.82 (0.26–2.59)		
		Brain, incidence	Group (HR, per unit increase in the estimated cumulative PFOA serum concentration (ng/mL) on the natural log scale, 10-yr lag):			Age, time-varying smoking, time-varying alcohol consumption, sex, education, birth year (5-yr calendar intervals)	
			Entire cohort	17	1.06 (0.79–1.41)		
			- Community residents	13	1.02 (0.68–1.52)		
			- Occupational workers	4	0.73 (0.32–1.67)		
		Leukaemia, incidence	Estimated cumulative PFOA serum concentration (ng/mL), no lag (HR):			Age, time-varying smoking, time-varying alcohol consumption, sex, education, birth year (5-yr calendar intervals)	
			Continuous (per unit on natural log scale)	66	1.01 (0.87–1.18)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
		Leukaemia, incidence	Estimated cumulative PFOA serum concentration (ng/mL), 10-yr lag (HR):			Age, time-varying smoking, time-varying alcohol consumption, sex, education, birth year (5-yr calendar intervals)	
			Continuous (per unit on natural log scale)	66	1.02 (0.88–1.18)		
		Lymphoma (type not specified), incidence	Estimated cumulative PFOA serum concentration (ng/mL), no lag (HR):			Age, time-varying smoking, time-varying alcohol consumption, sex, education, birth year (5-yr calendar intervals)	
			Continuous (per unit on natural log scale)	136	1.01 (0.91–1.12)		
		Lymphoma (type not specified), incidence	Estimated cumulative PFOA serum concentration (ng/mL), 10-yr lag (HR):			Age, time-varying smoking, time-varying alcohol consumption, sex, education, birth year (5-yr calendar intervals)	
			Continuous (per unit on natural log scale)	136	0.98 (0.88–1.10)		
		Melanoma, incidence	Estimated cumulative PFOA serum concentration (ng/mL), no lag (HR):			Age, time-varying smoking, time-varying alcohol consumption, sex, education,	
			Continuous (per unit on natural log scale)	241	1.00 (0.92–1.09)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
						birth year (5-yr calendar intervals)	
		Melanoma, incidence	Estimated cumulative PFOA serum concentration (ng/mL), 10-yr lag (HR):			Age, time-varying smoking, time-varying alcohol consumption, sex, education, birth year (5-yr calendar intervals)	
			Continuous (per unit on natural log scale)	241	1.04 (0.96–1.13)		
		Lung, incidence	Estimated cumulative PFOA serum concentration (ng/mL), no lag (HR):			Age, time-varying smoking, time-varying alcohol consumption, sex, education, birth year (5-yr calendar intervals)	
			Continuous (per unit on natural log scale)	108	0.88 (0.78–1.00)		
		Lung, incidence	Estimated cumulative PFOA serum concentration (ng/mL), 10-yr lag (HR):			Age, time-varying smoking, time-varying alcohol consumption, sex, education, birth year (5-yr calendar intervals)	
			Continuous (per unit on natural log scale)	108	0.92 (0.81–1.04)		
Consonni et al. (2013)	5879 male workers (4205 APFO-exposed); The pooled	Brain, mortality	SMR (national referent):			Age, calendar period, country	*Exposure assessment critique:* See Table 2.1
			Ever APFO-exposed	4	0.64 (0.17–1.63)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
USA, United Kingdom, Italy, Germany, the Netherlands Enrolment: 1950–200/follow-up: 1950–2008 Cohort	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 to 2002. The principal occupational exposures were TFE and APFO perfluorooctanoic acid (aiding production of TFE) Exposure assessment method: See Table 2.1	Lymphatic and haematopoietic, (ICD-9 200–208), mortality	SMR (national referent): Ever APFO-exposed	19	1.04 (0.62–1.62)	Age, calendar period, country	*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 less-common cancers; high correlations between exposure to TFE monomer and PFOA which precluded evaluation of effects of the individual compounds.
		NHL, (ICD-9 200, 202), mortality	SMR (national referent): Ever APFO-exposed	5	0.79 (0.26–1.84)	Age, calendar period, country	
		Multiple myeloma, (ICD-9 203), mortality	SMR (national referent): Ever APFO-exposed	2	0.66 (0.08–2.39)	Age, calendar period, country	
		Leukaemia, (ICD-9 204–208), mortality	Cumulative APFO exposure (SMR, national referent): Ever APFO-exposed	11	1.61 (0.80–2.88)	Age, calendar period, country	
			< 16 unit-yr	4	1.64 (0.45–4.20)		
			16–138 unit-yr	3	1.35 (0.28–3.94)		
			139+ unit-yr	4	1.85 (0.50–4.74)		
			Trend-test *P*-value, 0.58				
		Lung, mortality	Cumulative APFO exposure (SMR, national referent): Ever APFO-exposed	49	0.73 (0.54–0.97)	Age, calendar period, country	
			< 16 unit-yr	20	0.91 (0.56–1.41)		
			16–138 unit-yr	16	0.75 (0.43–1.22)		
			139+ unit-yr	13	0.54 (0.29–0.93)		
			Trend-test *P*-value, 0.34				
Girardi and Merler (2019) Vicenza province, Veneto Region, Italy	462 (PFAS workers); 1383 (railroad workers); Workers in perfluorocarbon production facility manufacturing PFOA, PFOS, other perfluorinated	Lymphatic and haematopoietic, (ICD-9 200–208.9), mortality	SMR (regional referent): All workers at same plant in Trissino	7	2.26 (1.08–4.73)	Age, calendar period	*Exposure assessment critique*: See Table 2.1
			Offices	0	0		

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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
Enrolment: 1960–2008/follow-up: 1970–2018 (mortality) Cohort	compounds and other chemicals in Trissino (Veneto, Italy). Comparison populations included regional general population and workers in a local railroad industry) not exposed to these chemicals. For both occupational cohorts, workers included were men employed ≥ 6 mo. Exposure assessment method: See Table 2.1		Never at PFAS department	5	3.24 (1.35–7.79)		*Other strengths:* A highly exposed occupational cohort with long and complete follow-up. *Other limitations:* Small cohort; inability to distinguish PFOA, PFOS and other exposures; only 20% deceased in the perfluorobutylsulfonyl fluoride cohort but 42% in the railroad worker cohort.
			Ever at PFAS department	2	3.07 (0.77–12.3)		
		Lymphatic and haematopoietic, (ICD-9 200–208.9), mortality	Cumulative PFOA concentration (SMR, regional referent):			Age, calendar period	
			1st tertile (≤ 4034 ng/mL-yr)	1	0.96 (0.14–6.82)		
			2nd tertile (4034–16 956 ng/mL-yr)	1	1.26 (0.18–8.96)		
			3rd tertile (> 16 956 ng/mL-yr)	5	3.94 (1.64–9.47)		
		Lymphatic and haematopoietic, (ICD-9 200–208.9), mortality	RR (relative to railroad workers):			Age, calendar period	
			Railroad workers	7	1		
			All workers at plant in Trissino	7	3.20 (1.09–8.94)		
			Offices	0	0		
			Never at PFAS department	5	4.33 (1.38–13.7)		
			Ever at PFAS department	2	4.38 (0.91–21.1)		
		Lymphatic and haematopoietic, (ICD-9 200–208.9), mortality	Cumulative PFOA concentration (RR, relative to railroad workers):			Age, calendar period	
			Railroad workers	7	1		
			1st tertile (≤ 4034 ng/mL-yr)	1	1.44 (0.18–11.8)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
			2nd tertile (4034–16 956 ng/mL-yr)	1	1.80 (0.22–14.6)		
			3rd tertile (> 16 956 ng/mL-yr)	5	5.06 (1.61–16.0)		
		NHL, (ICD-9 200, 202), mortality	SMR (regional referent):			Age, calendar period	
			All workers at plant in Trissino	3	2.66 (0.86–8.26)		
		NHL, (ICD-9 200, 202), mortality	RR (relative to railroad workers):			Age, calendar period	
			Railroad workers	2	1		
			All workers at plant in Trissino	3	4.77 (0.8–28.6)		
		Lung, mortality	SMR (regional referent):			Age, calendar period	
			All perfluorobutylsulfonyl fluoride plant workers	6	0.49 (0.22–1.09)		
		Lung, mortality	RR (relative to railroad workers):			Age, calendar period	
			Railroad workers	22	1		
			All workers at plant in Trissino	6	0.78 (0.31–1.92)		
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	Brain, 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; strong exposure contrast; unbiased inclusion; complete follow-up; long follow-
			Males: Never	56	0.93 (0.70–1.21)		
			Ever	24	1.29 (0.83–1.93)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
	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	Brain, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	up for part of the population; reference group from same municipality. *Other limitations:* Mixed exposure profile without possibility to single out effects due to specific compounds; limited information on potential confounders; multiple comparisons increased the risk of false positive associations.
			Females: Never	52	0.73 (0.55–0.96)		
			Ever	18	0.82 (0.49–1.30)		
		Brain, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	109	1		
			Ever	42	1.24 (0.86–1.77)		
		Brain, incidence	Time period of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	109	1		
			Early (1985–2004)	26	1.20 (0.78–1.84)		
			Late (2005–2013)	16	1.31 (0.76–2.26)		
		Brain, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	109	1		
			Short (1–10 yr)	21	1.06 (0.66–1.69)		
			Long (≥ 11 yr)	21	1.50 (0.92–2.44)		
		NHL, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Males: Never	87	1.00 (0.80–1.23)		
			Ever	26	0.97 (0.63–1.41)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
		NHL, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Females: Never	62	0.99 (0.76–1.27)		
			Ever	15	0.78 (0.44–1.29)		
		NHL, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	149	1		
			Ever	41	0.94 (0.67–1.34)		
		NHL, incidence	Time period of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	149	1		
			Early (1980–2004)	25	0.83 (0.54–1.27)		
			Late (2005–2013)	16	1.22 (0.71–2.10)		
		NHL, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	149	1		
			Short (1–10 yr)	20	0.78 (0.49–1.25)		
			Long (≥ 11 yr)	21	1.19 (0.74–1.91)		
		Multiple myeloma, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Males: Never	39	1.02 (0.72–1.39)		
			Ever	11	0.94 (0.47–1.69)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
		Multiple myeloma, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Females: Never	30	0.93 (0.63–1.33)		
			Ever	9	0.91 (0.42–1.73)		
		Multiple myeloma, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	69	1		
			Ever	20	0.95 (0.58–1.57)		
		Multiple myeloma, incidence	Time period of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	69	1		
			Early (1980–2004)	10	0.74 (0.38–1.45)		
			Late (2005–2013)	10	1.36 (0.67–2.76)		
		Multiple myeloma, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	69	1		
			Short (1–10 yr)	13	1.25 (0.69–2.27)		
			Long (≥ 11 yr)	7	0.66 (0.30–1.45)		
		NHL (CLL), incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Males: Never	35	1.33 (0.92–1.85)		
			Ever	9	1.24 (0.57–2.35)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
		NHL (CLL), incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Females: Never	17	1.10 (0.64–1.77)		
			Ever	4	0.88 (0.24–2.25)		
		NHL (CLL), incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	52	1		
			Ever	13	0.84 (0.46–1.54)		
		NHL (CLL), incidence	Time period of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	52	1		
			Early (1980–2004)	8	0.73 (0.34–1.54)		
			Late (2005–2013)	5	1.13 (0.43–2.99)		
		NHL (CLL), incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	52	1		
			Short (1–10 yr)	9	1.12 (0.55–2.28)		
			Long (≥ 11 yr)	4	0.53 (0.19–1.49)		
		Leukaemia (CML), incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Males: Never	7	1.72 (0.69–3.54)		
			Ever	3	2.56 (0.53–7.47)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
		Leukaemia (CML), incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Females: Never	4	0.95 (0.26–2.43)		
			Ever	2	1.71 (0.21–6.19)		
		Melanoma, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Males: Never	115	1.27 (1.05–1.53)		
			Ever	34	1.20 (0.83–1.67)		
		Melanoma, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Females: Never	103	0.96 (0.79–1.17)		
			Ever	43	1.21 (0.88–1.63)		
		Melanoma, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	218	1		
			Ever	77	1.09 (0.84–1.41)		
		Melanoma, incidence	Time period of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	218	1		
			Early (1980–2004)	36	0.82 (0.58–1.17)		
			Late (2005–2013)	41	1.54 (1.09–2.19)		
		Melanoma, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
			Never	218	1		
			Short (1–10 yr)	40	1.04 (0.74–1.46)		
			Long (≥ 11 yr)	37	1.14 (0.80–1.64)		
		Trachea, lung, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Males: Never	177	1.11 (0.96–1.29)		
			Ever	64	1.42 (1.09–1.81)		
		Trachea, lung, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Females: Never	100	0.94 (0.76–1.14)		
			Ever	29	0.88 (0.59–1.27)		
		Trachea, lung, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	277	1		
			Ever	93	1.14 (0.9–1.45)		
		Trachea, lung, incidence	Time period of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	277	1		
			Early (1980–2004)	55	1.05 (0.79–1.41)		
			Late (2005–2013)	38	1.32 (0.92–1.88)		
		Trachea, lung, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	277	1		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
			Short (1–10 yr)	52	1.23 (0.92–1.66)		
			Long (≥ 11 yr)	41	1.04 (0.74–1.46)		
Winquist et al. (2023) 20 US states Enrolment 1998–2001/follow-up through 30 June 2015 Case–cohort	Case cohort within the CPS-II Lifelink Cohort (See Table 2.1). Cases: 3762 overall (635 haematopoietic). Incidence cases from the CPS-II Lifelink Cohort (surviving CPS-II Nutrition cohort participants) with first cancer diagnosis of leukaemia or lymphoma cancers, detected through self-report or NDI linkage and verified through medical records review or cancer registry. All participants with incident cancers. Controls: 999; A sex-stratified simple random sample of 499 women and 500 men (approximately 3% of the eligible cohort). Stratification sampling was to ensure an adequate number of subcohort participants in sex-specific analyses (for breast and prostate cancers). Exposure assessment method: See Table 2.1	Lymphatic and haematopoietic, haematological (incidence)	Serum PFOA concentration (HR):			Sex, year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	*Exposure assessment critique*: See Table 2.1 *Strengths:* See Table 2.1 *Limitations*: See Table 2.1
			1st quartile (< 3.800 ng/mL)	148	1		
			2nd quartile (3.800 to < 5.000 ng/mL)	162	1.01 (0.74–1.38)		
			3rd quartile (5.000 to < 6.700 ng/mL)	158	0.99 (0.72–1.36)		
			4th quartile (≥ 6.700 ng/mL)	158	0.84 (0.62–1.15)		
			Continuous (per unit on log base 2 scale)	626	0.92 (0.80–1.06)		
		Lymphatic and haematopoietic, haematological (incidence)	Serum PFOA concentration (HR):			Year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			Females: Continuous (per unit on log base 2 scale)	281	0.88 (0.73–1.06)		
		Lymphatic and haematopoietic, haematological (incidence)	Serum PFOA concentration (HR):			Year of serum sample collection, age at serum collection, race, education, smoking status,	
			Males: Continuous (per unit on log base 2 scale)	345	0.94 (0.75–1.17)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
						alcohol consumption	
		Lymphatic and haematopoietic, haematological (incidence)	Serum PFOS concentration (HR):			Sex, year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			1st quartile (< 12.000 ng/mL)	130	1		
			2nd quartile (12.000 to < 17.000 ng/mL)	159	0.82 (0.59–1.13)		
			3rd quartile (17.000 to < 24.000 ng/mL)	170	0.95 (0.69–1.31)		
			4th quartile (≥ 24.000 ng/mL)	167	0.79 (0.57–1.09)		
			Continuous (per unit on log base 2 scale)	626	0.92 (0.81–1.04)		
		Lymphatic and haematopoietic, haematological (incidence)	Serum PFOS concentration (HR):			Year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			Females: Continuous (per unit on log base 2 scale)	281	0.79 (0.66–0.95)		
		Lymphatic and haematopoietic, haematological (incidence)	Serum PFOS concentration (HR):			Year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			Males: Continuous (per unit on log base 2 scale)	345	1.00 (0.84–1.20)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
Vieira et al. (2013) Ohio and WV, USA 1996–2005 (incidence) Case–control	Cases: Study 1 506 brain, 674 leukaemia, 285 multiple myeloma, 1124 NHL, 1428 melanoma, 4926 lung; Study 2: 150 brain, 191 leukaemia, 83 multiple myeloma, 347 NHL, 429 melanoma, 1526 lung; Index cancer cases were retrieved from cancer registries covering a community sample with relatively high exposure to PFOA due to contamination of drinking-water from the Parkersburg (WV, USA), PTFE-manufacturing plant in WV, USA. Controls: Study 1: 23 205 (for thyroid), 23 042 (for brain), 22 874 (for leukaemia), 23 263 (for multiple myeloma), 22 424 (for NHL), 22 120 (for melanoma), 18 622 (for lung); Study 2: 7245 (for thyroid), 7189 (for brain), 7148 (for leukaemia), 7256 (for multiple myeloma), 6992 (for NHL), 6910 (for melanoma), 5813 (for lung); For each cancer site evaluated, controls were cases of cancer for all other sites, with the exclusion of four cancers of a	Brain, incidence	Analysis 1. Residence in a PFOA-contaminated water district (OH and WV) (OR):			Age, sex, diagnosis year, insurance provider, smoking status	*Exposure assessment critique*: See Table 2.1 *Other strengths:* A relatively large study population with a strong exposure contrast, independent and likely accurate outcome information. *Other limitations:* Exposure misclassification resulting in attenuated risk estimates is likely; limited number of high-level exposed cases results in uncertain risk estimates.
			Unexposed	446	1		
			Any exposed water district	60	1.0 (0.8–1.3)		
			Little Hocking	1	0.2 (0.0–1.5)		
			Lubeck	7	0.8 (0.4–1.8)		
			Tuppers Plains	9	1.1 (0.5–2.1)		
			Belpre	11	1.2 (0.6–2.2)		
			Pomeroy	3	1.7 (0.5–5.4)		
			Mason	29	1.1 (0.7–1.6)		
		Brain, incidence	Analysis 2. Individual-level annual PFOA serum exposure, assuming 10-yr residency and latency (OH only) (OR):			Age, race, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	118	1		
			Low (3.7–12.8 µg/L)	12	1.5 (0.8–2.7)		
			Medium (12.9–30.7 µg/L)	16	1.8 (1.1–3.2)		
			High (30.8–109 µg/L)	4	0.6 (0.2–1.6)		
			Very high (110–655 µg/L)	0	-		
		Brain, incidence	Analysis 2. Cumulative PFOA serum exposure, assuming 10-yr residency and latency (OH only) (OR):			Age, race, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	NR	1		
			Low (3.8–88 µg/L-yr)	NR	1.5 (0.8–2.7)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
	priori interest (kidney, testicular, pancreas, and liver) which have been associated with PFOA in animal or human studies.		Medium (89–197 µg/L-yr)	NR	1.7 (1.0–2.9)		
			High (198–599 µg/L-yr)	NR	0.7 (0.3–1.8)		
	Exposure assessment method: See Table 2.1		Very high (600–4679 µg/L-yr)	0	-		
		Brain, incidence	Analysis 2. Individual-level annual PFOA serum exposure, assuming 10-yr residency and no latency (OH only) (OR):			Age, race, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	NR	1		
			Low (3.7–12.8 µg/L)	NR	1.3 (0.6–2.7)		
			Medium (12.9–30.7 µg/L)	NR	1.7 (0.9–3.1)		
			High (30.8–109 µg/L)	NR	1.1 (0.6–2.1)		
			Very high (110–655 µg/L)	0	-		
		Brain, incidence	Analysis 2. Individual-level annual PFOA serum exposure, assuming 10-yr residency and latency with alternative control group (no exclusions) (OH only) (OR):			Age, race, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	NR	1		
			Low (3.7–12.8 µg/L)	NR	1.5 (0.8–2.7)		
			Medium (12.9–30.7 µg/L)	NR	1.8 (1.1–3.2)		
			High (30.8–109 µg/L)	NR	0.6 (0.2–1.6)		
			Very high (110–655 µg/L)	0	-		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
		Leukaemia, incidence	Analysis 1. Residence in a PFOA-contaminated water district (OH and WV) (OR):			Age, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	602	1		
			Any exposed water district	72	0.9 (0.7–1.1)		
		Leukaemia, incidence	Analysis 2. Individual-level annual PFOA serum exposure, assuming 10-yr residency and latency (OH only) (OR):			Age, race, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	155	1		
			Low (3.7–12.8 μg/L)	14	1.2 (0.7–2.1)		
			Medium (12.9–30.7 μg/L)	12	1.0 (0.6–1.9)		
			High (30.8–109 μg/L)	8	0.9 (0.4–1.8)		
			Very high (110–655 μg/L)	2	0.6 (0.1–2.3)		
		Multiple myeloma, incidence	Analysis 1. Residence in a PFOA-contaminated water district (OH and WV) (OR):			Age, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	249	1		
			Any exposed water district	36	1.1 (0.8–1.6)		
		Multiple myeloma, incidence	Analysis 2. Individual-level annual PFOA serum exposure, assuming 10-yr residency and latency (OH only) (OR):			Age, race, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	65	1		
			Low (3.7–12.8 μg/L)	7	1.4 (0.7–3.2)		
			Medium (12.9–30.7 μg/L)	6	1.1 (0.5–2.6)		
			High (30.8–109 μg/L)	4	1.0 (0.3–2.7)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
			Very high (110–655 μg/L)	1	0.6 (0.1–4.7)		
		NHL, incidence	Analysis 1. Residence in a PFOA-contaminated water district (OH and WV) (OR):			Age, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	972	1		
			Any exposed water district	152	1.2 (1.0–1.5)		
		NHL, incidence	Analysis 2. Individual-level annual PFOA serum exposure, assuming 10-yr residency and latency (OH only) (OR):			Age, race, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	271	1		
			Low (3.7–12.8 μg/L)	20	1.0 (0.6–1.6)		
			Medium (12.9–30.7 μg/L)	28	1.5 (1.0–2.2)		
			High (30.8–109 μg/L)	17	1.1 (0.7–1.9)		
			Very high (110–655 μg/L)	11	1.8 (1.0–3.4)		
		Melanoma, incidence	Analysis 1. Residence in a PFOA-contaminated water district (OH and WV) (OR):			Age, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	1260	1		
			Any exposed water district	168	0.9 (0.8–1.1)		
		Melanoma, incidence	Analysis 2. Individual-level annual PFOA serum exposure, assuming 10-yr residency and latency (OH only) (OR):			Age, race, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	334	1		
			Low (3.7–12.8 μg/L)	27	1.2 (0.8–1.8)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
			Medium (12.9–30.7 μg/L)	38	1.3 (0.9–1.8)		
			High (30.8–109 μg/L)	21	1.0 (0.6–1.5)		
			Very high (110–655 μg/L)	9	0.9 (0.5–1.9)		
		Lung, incidence	Analysis 1. Residence in a PFOA-contaminated water district (OH and WV) (OR):			Age, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	4294	1		
			Any exposed water district	632	1.2 (1.1–1.3)		
		Lung, incidence	Analysis 2. Individual-level annual PFOA serum exposure, assuming 10-yr residency and latency (OH only) (OR):			Age, race, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	1233	1		
			Low (3.7–12.8 μg/L)	91	1.0 (0.7–1.2)		
			Medium (12.9–30.7 μg/L)	95	1.0 (0.8–1.3)		
			High (30.8–109 μg/L)	78	1.2 (0.9–1.6)		
			Very high (110–655 μg/L)	29	1.0 (0.7–1.6)		
Chen et al. (2024) California, USA 1983–2013 Case–control	Cases: 501 (497 after removal of outliers); Children under 5 yr, born in California from 1983–2011 and diagnosed between 1983–2013, selected from the California Cancer Registry with code 050 of ICCC-3 (International	Retinoblastoma, incidence	Serum PFOA (OR):			Birth year, maternal age, maternal race and ethnicity, maternal birthplace, maternal education attainment,	*Exposure assessment critique*: Key strengths were that blood levels represent the combined exposure through all exposure pathways; blood spot samples collected before diagnosis; all samples analysed in the same manner.
			Continuous (IQR increase)	497	1.03 (0.97–1.09)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
	Classification of Childhood Cancer, Third edition) Controls: 899 (893 after removal of outliers); Controls were randomly selected from California birth rolls and frequency-matched by year of birth (20:1 matching ratio) Exposure assessment method: Semiquantitative non-targeted method. Single blood spot sample collected. Blood collected in new-borns, Average age of diagnosis for unilateral retinoblastoma was 22.1 mo, while the average age of diagnosis for bilateral retinoblastoma was 9.3 mo.	Retinoblastoma, incidence	Serum PFOA (OR): US-born mothers: Continuous (IQR increase)	272	1.06 (0.98–1.16)	census tract SES Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	Key limitations were that the quantification method used was non-targeted and thus semiquantitative, therefore exact concentrations are not available (however, ranking of levels was likely accurate); blood spot methods may have higher uncertainty compared to methods for serum, plasma and whole blood due potential differences in haematocrit levels between individuals, but this was considered a minor uncertainty compared to that related to the non-targeted approach; if retinoblastoma alters ADME of PFAS there could be possible differential exposure misclassification (however, given that samples were collected before diagnosis this is unlikely); single samples may not reflect exposure at crucial windows in cancer development (in particular length of breastfeeding, which might have a large influence on postnatal exposure, was not included in the statistical analyses). *Other strengths:* Population-based design and the use of pre-diagnostic sample collected for
		Retinoblastoma, incidence	Serum PFOA (OR): Mexico-born mothers: Continuous (IQR increase)	130	0.97 (0.86–1.09)	Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	
		Retinoblastoma, incidence	Serum PFOS (OR): Continuous (IQR increase)	497	1.02 (0.95–1.09)	Birth year, maternal age, maternal race and ethnicity, maternal birthplace, maternal education attainment, census tract SES	
			Serum PFOS (OR):				

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
		Retinoblastoma, incidence	US-born mothers: Continuous (IQR increase)	272	1.09 (0.97–1.23)	Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	medical reason unrelated to the case-status minimized selection bias. *Other limitations:* limited sample size for the stratified analysis by mother birthplace
		Retinoblastoma, incidence	Serum PFOS (OR): Mexico-born mothers: Continuous (IQR increase)	130	1.04 (0.93–1.17)	Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	
		Unilateral retinoblastoma, incidence	Serum PFOA (OR): Continuous (IQR increase)	279	1.04 (0.96–1.13)	Birth year, maternal age, maternal race and ethnicity, maternal birthplace, maternal education attainment, census tract SES	
		Unilateral retinoblastoma, incidence	Serum PFOA (OR): US-born mothers: Continuous (IQR increase)	156	1.09 (0.98–1.23)	Birth year, maternal age, maternal race and ethnicity,	

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
						maternal education attainment, census tract SES	
		Unilateral retinoblastoma, incidence	Serum PFOA (OR): Mexico-born mothers: Continuous (IQR increase)	66	0.93 (0.81–1.08)	Birth year, maternal age, maternal race and ethnicity, education attainment, census tract SES	
		Unilateral retinoblastoma, incidence	Serum PFOS (OR): Continuous (IQR increase)	279	1.03 (0.95–1.14)	Birth year, maternal age, maternal race and ethnicity, maternal birthplace, maternal education attainment, census tract SES	
		Unilateral retinoblastoma, incidence	Serum PFOS (OR): US-born mothers: Continuous (IQR increase)	156	1.15 (0.99–1.35)	Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
		Unilateral retinoblastoma, incidence	Serum PFOS (OR): Mexico-born mothers: Continuous (IQR increase)	66	1.04 (0.90–1.22)	Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	
		Bilateral retinoblastoma, incidence	Serum PFOA (OR): Continuous (IQR increase)	218	1.02 (0.94–1.11)	Birth year, maternal age, maternal race and ethnicity, maternal birthplace, maternal education attainment, census tract SES	
		Bilateral retinoblastoma, incidence	Serum PFOA (OR): US-born mothers: Continuous (IQR increase)	116	1.04 (0.94–1.17)	Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	
		Bilateral retinoblastoma, incidence	Serum PFOA (OR): Mexico-born mothers: Continuous (IQR increase)	64	1.02 (0.87–1.22)	Birth year, maternal age, maternal race and ethnicity,	

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
						maternal education attainment, census tract SES	
		Bilateral retinoblastoma, incidence	Serum PFOS (OR): Continuous (IQR increase)	218	0.99 (0.91–1.09)	Birth year, maternal age, maternal race and ethnicity, maternal birthplace, maternal education attainment, census tract SES	
		Bilateral retinoblastoma, incidence	Serum PFOS (OR): US-born mothers: Continuous (IQR increase)	116	1.02 (0.88–1.20)	Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	
		Bilateral retinoblastoma, incidence	Serum PFOS (OR): Mexico-born mothers: Continuous (IQR increase)	64	1.04 (0.89–1.23)	Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
		Retinoblastoma, incidence	Serum PFOA (OR):			Birth year, maternal age, maternal race and ethnicity, maternal birthplace, maternal education attainment, census tract SES	
			Below-mean (log_2-transformed)	NR	1		
			Above-mean (log_2-transformed)	377	1.16 (0.90–1.50)		
		Retinoblastoma, incidence	Serum PFOA (OR):			Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	
			US-born mothers: Below-mean (log_2-transformed)	NR	1		
			Above-mean (log_2-transformed)	210	1.41 (1.00–2.02)		
		Retinoblastoma, incidence	Serum PFOA (OR):			Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	
			Mexico-born mothers: Below-mean (log_2-transformed)	NR	1		
			Above-mean (log_2-transformed)	92	0.76 (0.47–1.26)		
		Retinoblastoma, incidence	Serum PFOS (OR):			Birth year, maternal age, maternal race	
			Below-mean (log_2-transformed)	NR	1		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
			Above-mean (log_2-transformed)	372	1.29 (1.00–1.67)	and ethnicity, maternal birthplace, maternal education attainment, census tract SES	
		Retinoblastoma, incidence	Serum PFOS (OR):			Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	
			US-born mothers: Below-mean (log_2-transformed)	NR	1		
			Above-mean (log_2-transformed)	224	1.30 (0.89–1.93)		
		Retinoblastoma, incidence	Serum PFOS (OR):			Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	
			Mexico-born mothers: Below-mean (log_2-transformed)	NR	1		
			Above-mean (log_2-transformed)	85	1.67 (1.06–2.66)		
		Unilateral retinoblastoma, incidence	Serum PFOA (OR):			Birth year, maternal age, maternal race and ethnicity, maternal birthplace, maternal education	
			Below-mean (log_2-transformed)	NR	1		
			Above-mean (log_2-transformed)	208	1.10 (0.81–1.51)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
						attainment, census tract SES	
		Unilateral retinoblastoma, incidence	Serum PFOA (OR):			Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	
			US-born mothers: Below-mean (log_2-transformed)	NR	1		
			Above-mean (log_2-transformed)	120	1.43 (0.94–2.22)		
		Unilateral retinoblastoma, incidence	Serum PFOA (OR):			Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	
			Mexico-born mothers: Below-mean (log_2-transformed)	NR	1		
			Above-mean (log_2-transformed)	42	0.57 (0.31–1.05)		
		Unilateral retinoblastoma, incidence	Serum PFOS (OR):			Birth year, maternal age, maternal race and ethnicity, maternal birthplace, maternal education attainment, census tract SES	
			Below-mean (log_2-transformed)	NR	1		
			Above-mean (log_2-transformed)	214	1.42 (1.03–1.97)		
			Serum PFOS (OR):				

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
		Unilateral retinoblastoma, incidence	US-born mothers: Below-mean (log_2-transformed)	NR	1	Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	
			Above-mean (log_2-transformed)	134	1.71 (1.04–2.90)		
		Unilateral retinoblastoma, incidence	Serum PFOS (OR):			Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	
			Mexico-born mothers: Below-mean (log_2-transformed)	NR	1		
			Above-mean (log_2-transformed)	41	1.42 (0.80–2.58)		
		Bilateral retinoblastoma, incidence	Serum PFOA (OR):			Birth year, maternal age, maternal race and ethnicity, maternal birthplace, maternal education attainment, census tract SES	
			Below-mean (log_2-transformed)	NR	1		
			Above-mean (log_2-transformed)	169	1.29 (0.91–1.85)		
		Bilateral retinoblastoma, incidence	Serum PFOA (OR):			Birth year, maternal age, maternal race and ethnicity,	
			US-born mothers: Below-mean (log_2-transformed)	NR	1		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
			Above-mean (log_2-transformed)	90	1.45 (0.90–2.40)	maternal education attainment, census tract SES	
		Bilateral retinoblastoma, incidence	Serum PFOA (OR):			Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	
			Mexico-born mothers: Below-mean (log_2-transformed)	NR	1		
			Above-mean (log_2-transformed)	50	1.18 (0.61–2.42)		
		Bilateral retinoblastoma, incidence	Serum PFOS (OR):			Birth year, maternal age, maternal race and ethnicity, maternal birthplace, maternal education attainment, census tract SES	
			Below-mean (log_2-transformed)	NR	1		
			Above-mean (log_2-transformed)	158	1.14 (0.82–1.62)		
		Bilateral retinoblastoma, incidence	Serum PFOS (OR):			Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	
			US-born mothers: Below-mean (log_2-transformed)	NR	1		
			Above-mean (log_2-transformed)	90	0.95 (0.58–1.60)		

Table S2.6 Epidemiological studies on exposure to PFOA or PFOS and cancers of the brain, haematolymphoid system, and other cancers

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
		Bilateral retinoblastoma, incidence	Serum PFOS (OR):			Birth year, maternal age, maternal race and ethnicity, maternal education attainment, census tract SES	
			Mexico-born mothers: Below-mean (log_2-transformed)	NR	1		
			Above-mean (log_2-transformed)	44	2.06 (1.12–3.92)		

ADME, absorption, distribution, metabolism, and excretion; AL, Alabama; APFO, ammonium perfluorooctanoate; BMI, body mass index; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; CPS-II, Cancer Prevention Study II; HL, Hodgkin lymphoma; HR, hazard ratio; ICCC-3, International Classification of Childhood Cancer, 3rd edition); ICD, International Classification of Diseases; IQR, interquartile range; MN, Minnesota; mo, month(s); NDI, National Death Index; NHL, non-Hodgkin lymphoma; 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; UK, United Kingdom; US, United States; USA, United States of America; WV, West Virginia; yr, year(s).

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