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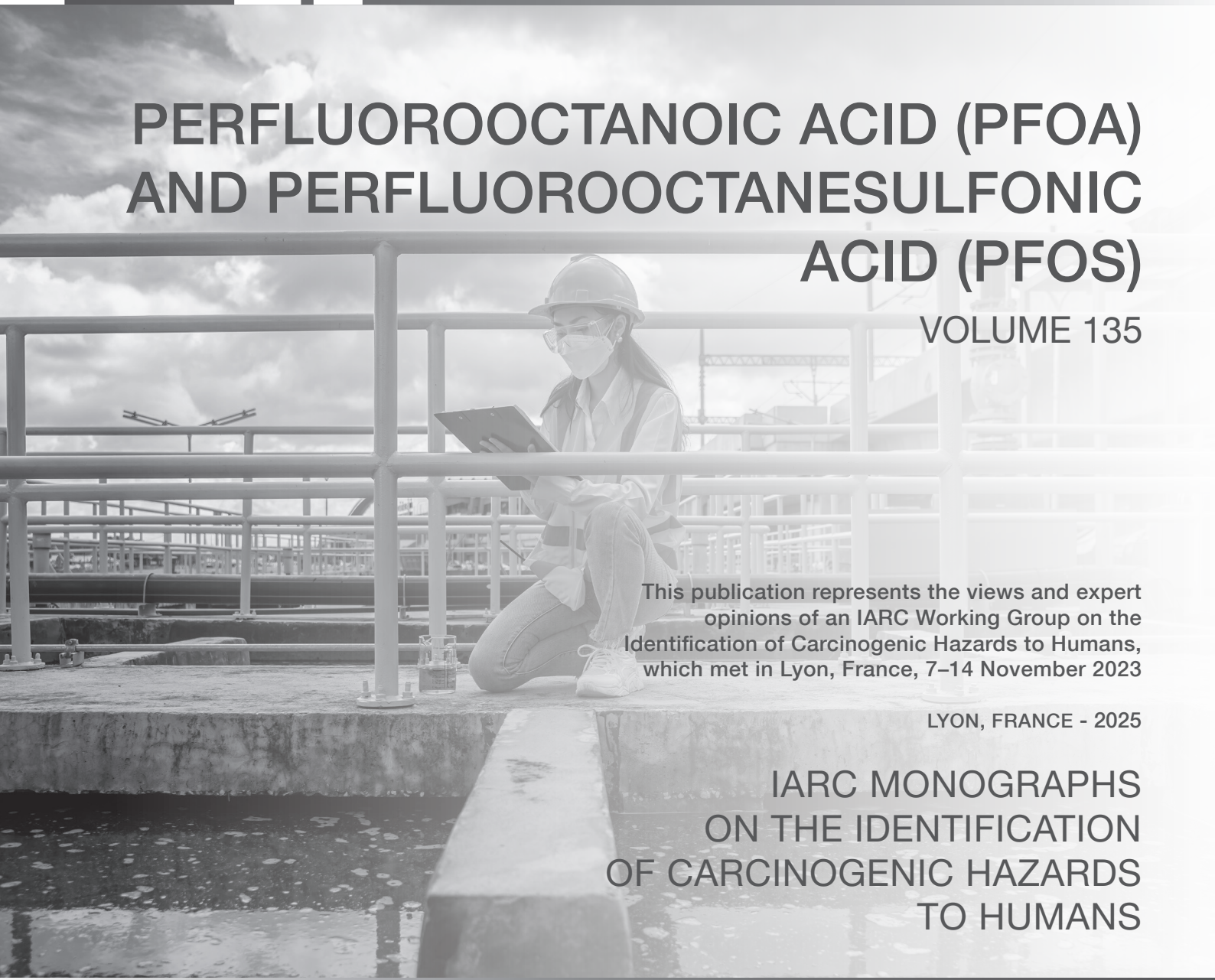

PERFLUOROOCTANOIC ACID (PFOA) AND PERFLUOROOCTANESULFONIC ACID (PFOS)

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International Agency for Research on Cancer

World Health Organization

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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	Large intestine, 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 occupational cohort with limited number of deaths; potential healthy-worker effect due to external comparison of rates from general population, limited information on covariates.
			Never	16	1.30 (0.75–2.12)		
			Ever probable/never definite	10	0.88 (0.42–1.62)		
			Ever definite	2	1.07 (0.13–3.86)		
		Rectum, mortality	Employed in APFO-exposed job (SMR, MN referent):			Age, sex, calendar period	
			Never	1	0.40 (0.01–2.22)		
			Ever probable/never definite	3	1.28 (0.26–3.76)		
			Ever definite	0	0 (0.00–9.24)		
		Oesophagus, mortality	Employed in APFO-exposed job (SMR, MN referent):			Age, sex, calendar period	
			Never	2	0.59 (0.07–2.13)		
			Ever probable/never definite	1	0.31 (0.01–1.70)		
			Ever definite	1	1.54 (0.04–8.57)		
		Stomach/gastric cancer, mortality	Employed in APFO-exposed job (SMR, MN referent):			Age, sex, calendar period	
			Never	3	0.74 (0.15–2.15)		

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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
			Ever probable/never definite	4	1.06 (0.29–2.71)		
			Ever definite	0	0 (0.00–5.82)		
Raleigh et al. (2014) MN, USA Enrolment: 1947–2002/follow-up: 1947–2008 (mortality), 1988–2008 (incidence) 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 (Cottage Grove MN, *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	Liver, mortality	Exposed to APFO (SMR, MN referent):			Age, sex, calendar period	*Exposure assessment critique*: See Table 2.1 *Other strengths:* Unlikely tetrafluoroethylene (TFE) co-exposure; reference population shared similar socioeconomic characteristics as the exposed population; long follow-up period. *Other limitations:* Lacked data on workers that left MN or Wisconsin; lacked data on cancer incidence before follow-up, starting up to 40 yr after first exposure; lacking information on health behaviours (potential confounding); small numbers of liver and pancreatic cancer.
			Unexposed (Saint Paul Plant)	7	0.55 (0.22–1.14)		
			Exposed (Cottage Grove Plant)	8	0.81 (0.35–1.59)		
		Liver, 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)	4	1.40 (0.38–3.58)		
			2nd quartile (2.6×10^{-5} to $< 1.4 \times 10^{-4}$ μg/m^3-yr)	2	0.86 (0.10–3.09)		
			3rd quartile (1.4×10^{-4} to $< 7.3 \times 10^{-4}$ μg/m^3-yr)	2	0.75 (0.09–2.72)		
			4th quartile ($\geq 7.3 \times 10^{-4}$ μg/m^3-yr)	0	0.00 (0.00–1.79)		
		Liver, mortality	Estimated cumulative airborne APFO exposure quartile (HR):			Age, [sex], year of birth	
			Unexposed (Saint Paul Plant)	NR	1		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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 and 2nd quartiles (< 1.5×10^{-4} µg/m^3-yr)	NR	2.09 (0.69–6.31)		
			3rd and 4th quartiles (≥ 1.5×10^{-4} µg/m^3-yr)	NR	0.67 (0.14–3.27)		
		Pancreas, mortality	Exposed to APFO (SMR, MN referent):			Age, sex, calendar period	
			Unexposed (Saint Paul Plant)	30	1.09 (0.74–1.56)		
			Exposed (Cottage Grove Plant)	18	0.85 (0.50–1.34)		
		Pancreas, mortality	Estimated cumulative airborne APFO exposure quartile (SMR, MN referent):			Age, sex, calendar period	
			1st quartile (< 2.6×10^{-5} µg/m^3-yr)	2	0.32 (0.04–1.17)		
			2nd quartile (2.6×10^{-5} to < 1.4×10^{-4} µg/m^3-yr)	5	1.00 (0.32–2.33)		
			3rd quartile (1.4×10^{-4} to < 7.3×10^{-4} µg/m^3-yr)	5	0.87 (0.28–2.04)		
			4th quartile (≥ 7.3×10^{-4} µg/m^3-yr)	6	1.41 (0.52–3.06)		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
		Pancreas, mortality	Estimated cumulative airborne APFO exposure quartile (HR):			Age, [sex], year of birth	
			Unexposed (Saint Paul Plant)	NR	1		
			1st quartile (< 2.9×10^{-5} μg/m^3-yr)	NR	0.32 (0.08–1.35)		
			2nd quartile (2.9×10^{-5} to < 1.5×10^{-4} μg/m^3-yr)	NR	0.89 (0.34–2.31)		
			3rd quartile (1.5×10^{-4} to < 7.9×10^{-4} μg/m^3-yr)	NR	0.82 (0.32–2.12)		
			4th quartile (≥ 7.9×10^{-4} μg/m^3-yr)	NR	1.23 (0.50–3.00)		
		Pancreas, incidence	Estimated cumulative airborne APFO exposure quartile (HR):			Age, [sex], year of birth	
			Unexposed (Saint Paul Plant)	15	1		
			1st and 2nd quartiles (< 1.5×10^{-4} μg/m^3-yr)	1	0.13 (0.02–1.03)		
			3rd and 4th quartiles	9	1.36 (0.59–3.11)		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
			($\geq 1.5 \times 10^{-4}$ μg/m^3-yr)				
Alexander et al. (2003) Decatur, Alabama, USA Enrolment: 1961–1997/follow-up: 1961–1998 (mortality) Cohort	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). Most recent follow-up of all cancers except bladder, which is described in a later study by Alexander and Olsen (2007). Exposure assessment method: See Table 2.1	Liver and bile ducts, mortality	PFOS exposure group (SMR, Alabama referent):			Sex, age, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths:* Large exposure contrast. *Other limitations:* Few cancer deaths; limited to mortality; limited to non-exposed, low-exposed, high-exposed categories; lack of data on smoking; mostly men (83%).
			All jobs	2	1.61 (0.20–5.82)		
			Only non-exposed	0	0		
			Ever low, never high	1	3.94 (0.10–21.88)		
			Ever high	1	2.00 (0.05–11.1)		
		Large intestine, mortality	PFOS exposure group (SMR, Alabama referent):			Sex, age, calendar period	
			All jobs	1	0.30 (0.01–1.66)		
			Only non-exposed	0	0		
			Ever low, never high	1	1.43 (0.04–7.94)		
			Ever high	0	0		
		Oesophagus, mortality	PFOS exposure group (SMR, Alabama referent):			Age, sex, calendar period	
			All jobs	2	1.76 (0.21–6.35)		
			Only non-exposed	1	2.25 (0.06–12.51)		
			Ever low, never high	0	0		
			Ever high	1	2.16 (0.05–12.02)		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
		Digestive organs and peritoneum, mortality	PFOS exposure group (SMR, Alabama referent):			Age, sex, calendar period	
			All jobs	5	0.51 (0.17–1.19)		
			Only non-exposed	1	0.27 (0.01–1.49)		
			Ever low, never high	2	0.99 (0.12–3.57)		
			Ever high	2	0.51 (0.06–1.85)		
Leonard et al. (2008) Parkersburg, WV, USA Enrolment: 1948–2002/follow-up: 1948–2002 (mortality) Cohort	6027; Parkersburg (WV, USA), polymer-production PFOA cohort. Workers (81% male) at a US polymer-manufacturing facility for 1 day or more 1948–2002. Exposure assessment method: No quantitative exposure assessment. Workers in a polymer-production facility were identified using the company's administrative records. approximately 30% worked in processes using APFO. All participants had detectable levels of serum PFOA	Large intestine, mortality	Polymer-production facility 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 uses a wide variety of chemicals including PFOA); small numbers.
			Referent US population	17	[0.668 (0.389–1.070)]		
			Referent WV population	17	[0.681 (0.397–1.091)]		
			Referent other workers (same company and region)	17	[0.783 (0.456–1.254)]		
		Rectum, mortality	Polymer-production facility cohort (SMR):			Sex, age, calendar period	
			Referent US population	5	[0.917 (0.298–2.139)]		
			Referent WV population	5	[0.836 (0.271–1.951)]		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
			Referent other workers (same company and region)	5	[1.321 (0.429–3.082)]		
		Oesophagus, mortality	Polymer-production facility cohort (SMR):			Sex, age, calendar period	
			Referent US population	4	[0.410 (0.112–1.051)]		
			Referent WV population	4	[0.469 (0.128–1.201)]		
			Referent other workers (same company and region)	4	[0.831 (0.226–2.127)]		
		Stomach/gastric cancer, mortality	Polymer-production facility cohort (SMR):			Sex, age, calendar period	
			Referent US population	3	[0.300 (0.062–0.876)]		
			Referent WV population	3	[0.360 (0.074–1.053)]		
			Referent other workers (same company and region)	3	[0.521 (0.107–1.522)]		
Steenland and Woskie (2012) Parkersburg, WV, USA Enrolment: 1948–	5791; Parkersburg (WV, USA), polymer-production PFOA cohort. Workers (81% male) at a US polymer-manufacturing facility who had potential exposure to	Liver and gallbladder (ICD-9 155–156), mortality	PFOA-exposed workers (SMR):			Age, sex, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths:* Evaluated associations with PFOA in a
			Other workers referent (same company and region)	10	1.07 (0.51–1.96)		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
2002/follow-up: 1952–2008 (mortality) Cohort	fluoropolymers with sufficiently detailed work histories. Earlier follow-up by Leonard et al. (2008). Steenland et al. (2015) presents incidence follow-up for a subset of this cohort. Exposure assessment method: See Table 2.1		US referent	10	0.77 (0.35–1.47)		population exposed to levels much higher than in the general population. *Other limitations:* small numbers of liver and pancreatic cancer
		Liver and gallbladder (ICD-9 155–156), 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)	4	2.39 (0.65–6.13)		
			2nd quartile (904 to < 1520 ppm-yrs)	0	0.00 (0.00–1.81)		
			3rd quartile (1520 to < 2700 ppm-yrs)	5	2.01 (0.65–4.68)		
			4th quartile (≥ 2700 ppm-yrs)	1	0.32 (0.01–1.76)		
		Pancreas, mortality	PFOA-exposed workers (SMR):			Age, sex, calendar period	
			Other workers referent (same company and region)	18	1.04 (0.62–1.64)		
			US referent	18	0.85 (0.51–1.35)		
		Pancreas, 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)	4	1.18 (0.32–3.03)		
			2nd quartile (904 to < 1520 ppm-yrs)	4	1.02 (0.28–2.61)		
			3rd quartile (1520 to < 2700 ppm-yrs)	5	1.09 (0.35–2.54)		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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 (≥ 2700 ppm-yrs)	5	0.92 (0.30–2.16)		
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 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 cases of incident colorectal cancer. Exposure assessment method: See Table 2.1	Colon and rectum, incidence	Cumulative PFOA exposure, no lag (RR): 1st quartile (< 3.03 µg/mL-yrs) 2nd quartile (3.03 to < 6.16 µg/mL-yrs) 3rd quartile (6.16 to < 11.42 µg/mL-yrs) 4th quartile (≥ 11.42 µg/mL-yrs) Trend-test *P*-value, 0.68	 NR NR NR	 1 0.58 (0.18–1.87) 1.43 (0.49–4.19) 1.20 (0.39–3.62)	Age, sex, race, education, BMI, time-varying smoking, time-varying alcohol consumption, year of birth	*Exposure assessment critique*: See Table 2.1 *Other strengths:* Evaluated associations with PFOA in a population exposed to levels much higher than in the general population; adjusted for established cancer risk factors (e.g. BMI, smoking, alcohol consumption). *Other limitations:* Possibility of selection bias given that the investigation included the subset of workers; few colorectal cancer cases.
Eriksen et al. (2009) Denmark Enrolment: 1 December 1993 to 31 May 1997/follow-up: 1 December 1993 to 1 July 2006 Case–cohort	Case–cohort within the Diet, Cancer and Health cohort (See Table 2.1). Cases: 67 liver, 128 pancreas incident cases Comparison cohort: 772 (680 men, 92 women); Subcohort of participants randomly selected without cancer at the end of follow-up. Exposure assessment method: See Table 2.1.	Liver, incidence	Baseline plasma PFOA concentration (IRR): 1st quartile 2nd quartile 3rd quartile 4th quartile Continuous (per 1 ng/mL increase)	 17 17 17 16 67	 1 1.00 (0.44–2.23) 0.49 (0.22–1.09) 0.60 (0.26–1.37) 0.95 (0.86–1.06)	Age, sex, smoking status, years of school attendance, alcohol intake, occupation associated with liver cancer risk (waiter or cook)	*Exposure assessment critique*: See Table 2.1 *Other strengths:* Large cohort with numerous incident cancers (n = 1240) followed 0–12 yr after baseline enrolment; good control of confounders; use of internal comparison group. *Other limitations:* Low exposure contrast in a population with background exposure levels.
		Liver, incidence	Baseline plasma PFOS concentration (IRR):				

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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
			1st quartile	17	1	Age, sex, smoking status, years of school attendance, alcohol intake, occupation associated with liver cancer risk (waiter or cook)	
			2nd quartile	17	0.62 (0.29–1.33)		
			3rd quartile	17	0.72 (0.33–1.56)		
			4th quartile	16	0.59 (0.27–1.27)		
			Continuous (per 10 ng/mL increase)	67	0.97 (0.79–1.19)		
		Pancreas, incidence	Baseline plasma PFOA concentration (IRR):			Age, sex, smoking status, smoking intensity, smoking duration, dietary fat intake, fruit and vegetable intake	
			1st quartile	32	1		
			2nd quartile	32	0.88 (0.49–1.57)		
			3rd quartile	32	1.33 (0.74–2.38)		
			4th quartile	32	1.55 (0.85–2.80)		
			Continuous (per 1 ng/mL increase)	128	1.03 (0.98–1.10)		
		Pancreas, incidence	Baseline plasma PFOS concentration (IRR):			Age, sex, smoking status, smoking intensity, smoking duration,	
			1st quartile	32	1		
			2nd quartile	32	1.02 (0.57–1.84)		
			3rd quartile	32	1.24 (0.67–2.31)		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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	32	0.91 (0.51–1.65)	dietary fat intake, fruit and vegetable intake	
			Continuous (per increase of 10 ng/mL)	128	0.99 (0.86–1.14)		
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 cohort who worked at the plant between 1948 and 2002. Exposure assessment method: See Table 2.1	Liver, 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)	*Exposure assessment critique*: See Table 2.1 *Other strengths:* Large cohort; fairly high participation rate among eligible residents. *Other limitations:* Potential limitation of a survivor cohort but unlikely to be biased unless those with higher exposure had lower post-diagnosis survival rates and those with lower exposure (Barry et al., 2015).
			Continuous (per unit on natural log scale)	9	0.73 (0.43–1.23)		
		Liver, 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)	9	0.74 (0.43–1.26)		
		Pancreas, incidence	Estimated cumulative PFOA serum concentration (ng/mL), no lag (HR):			Age, time-varying smoking, time-varying alcohol	
			Continuous (per unit on natural log scale)	24	1.00 (0.78–1.29)		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
						consumption, sex, education, birth year (5-yr calendar intervals)	
		Pancreas, 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)	24	0.96 (0.75–1.22)		
		Colon and rectum, 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)	264	0.99 (0.92–1.07)		
		Colon and rectum, incidence	Estimated cumulative PFOA serum concentration (ng/mL), 10-yr lag (HR):			Age, time-varying smoking, time-varying alcohol	
			Continuous (per unit on natural log scale)	264	0.99 (0.92–1.07)		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
						consumption, sex, education, birth year (5-yr calendar intervals)	
		Oesophagus, 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)	15	0.96 (0.70–1.32)		
		Oesophagus, 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)	15	0.97 (0.72–1.31)		
		Stomach/gastric cancer, incidence	Estimated cumulative PFOA serum concentration (ng/mL), no lag (HR):			Age, time-varying smoking, time-varying alcohol	
			Continuous (per unit on natural log scale)	12	0.72 (0.45–1.14)		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
						consumption, sex, education, birth year (5-yr calendar intervals)	
		Stomach/gastric cancer, 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)	12	0.77 (0.49–1.22)		
Consonni et al. (2013) USA, United Kingdom, Italy, Germany, 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 APFO (aiding production of PTFE) Exposure assessment method: See Table 2.1	Liver and intrahepatic bile ducts (ICD-9 155), 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 for rarer cancers; high correlations between exposure to TFE monomer and PFOA precludes evaluation of effects of the individual compounds.
			Ever APFO-exposed	7	1.43 (0.57–2.94)		
			< 16 unit-yr	1	0.70 (0.02–3.87)		
			16–138 unit-yr	2	1.25 (0.15–4.52)		
			139+ unit-yr	4	2.14 (0.58–5.49)		
			Trend-test *P*-value, 0.24				
		Pancreas, mortality	Cumulative APFO exposure (SMR, national referent):				

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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 APFO-exposed	10	1.05 (0.51–1.94)	Age, calendar period, country	
			< 16 unit-yr	0	0		
			16–138 unit-yr	4	1.30 (0.35–3.33)		
			139+ unit-yr	6	1.84 (0.67–4.00)		
			Trend-test *P*-value, 0.34				
		Colon, mortality	SMR (national referent):			Age, calendar period, country	
			Ever APFO-exposed	7	0.48 (0.19–0.99)		
		Rectum, mortality	SMR (national referent):			Age, calendar period, country	
			Ever APFO-exposed	6	1.03 (0.38–2.25)		
		Oesophagus, mortality	Cumulative APFO exposure (SMR, national referent):			Age, calendar period, country	
			Ever APFO-exposed	11	1.44 (0.72–2.57)		
			< 16 unit-yr	4	1.62 (0.44–4.14)		
			16–138 unit-yr	4	1.54 (0.42–3.93)		
			139+ unit-yr	3	1.16 (0.24–3.39)		
			Trend-test *P*-value, 0.60				
			SMR (national referent):				

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
		Stomach/gastric cancer, mortality	Ever APFO-exposed	5	0.52 (0.17–1.21)	Age, calendar period, country	
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 the Trissino (Veneto, Italy) perfluorocarbon production facility manufacturing mostly exposed to PFOA, with some PFOS, other perfluorinated compounds and other chemicals. 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	Liver and intrahepatic bile ducts (ICD-9 155), mortality	SMR (regional referent):			Age, calendar period	*Exposure assessment critique*: See Table 2.1 *Other strengths:* High exposure contrast; internal comparisons with non-exposed workers. *Other limitations:* Small cohort with few deaths (n = 107); limited to men; no data on confounders; small number of cancer deaths for liver (7) (the two causes with positive trends with exposure); no data on some causes of death of interest (e.g. bladder, prostate).
			All workers at Trissino plant	7	2.32 (1.11–4.87)		
			Offices	0	0		
			Never at PFAS department	4	2.71 (1.02–7.22)		
			Ever at PFAS department	3	4.71 (1.52–14.6)		
		Liver and intrahepatic bile ducts (ICD-9 155), mortality	Cumulative PFOA concentration (SMR, regional referent):			Age, calendar period	
			1st tertile (≤ 4034 ng/mL-yr)	1	1.02 (0.12–7.21)		
			2nd tertile (4034–16 956 ng/mL-yr)	2	2.76 (0.69–11.0)		
			3rd tertile (> 16 956 ng/mL-yr)	4	3.07 (1.15–8.18)		
		Liver and intrahepatic bile ducts (ICD-9 155), mortality	RR (relative to other workers):			Age, calendar period	
			Railroad workers	3	1		
			All workers at Trissino plant	7	6.69 (1.71–26.2)		
			Offices	0	0		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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 at PFAS department	4	8.00 (1.79–35.8)		
			Ever at PFAS department	3	15.3 (3.09–76.0)		
		Liver and intrahepatic bile ducts (ICD-9 155), mortality	Cumulative PFOA concentration (RR, relative to railroad workers):			Age, calendar period	
			Railroad workers	3	1		
			1st tertile (≤ 4034 ng/mL-yr)	1	3.07 (0.31–30.0)		
			2nd tertile (4034–16 956 ng/mL-yr)	2	8.39 (1.40–50.3)		
			3rd tertile (> 16 956 ng/mL-yr)	4	9.28 (2.07–41.5)		
		Colon, mortality	SMR (regional referent):			Age, calendar period	
			All workers at Trissino plant	5	1.72 (0.72–4.14)		
		Colon, mortality	RR (relative to railroad workers):			Age, calendar period	
			Railroad workers	4	1		
			All workers at Trissino plant	5	2.84 (0.74–10.9)		
		Oesophagus, mortality	SMR (regional referent):			Age, calendar period	
			All workers at Trissino plant	3	2.31 (0.68–6.50)		
		Oesophagus, mortality	RR (relative to railroad workers):			Age, calendar period	
			Railroad workers	2	1		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
			All workers at Trissino plant	3	3.62 (0.59–22.3)		
		Stomach/gastric cancer, mortality	SMR (regional referent):			Age, calendar period	
			All workers at Trissino plant	3	1.30 (0.42–4.02)		
		Stomach/gastric cancer, mortality	RR (relative to railroad workers):			Age, calendar period	
			Railroad workers	4	1		
			All workers at Trissino plant	3	2.43 (0.54–10.9)		
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	Liver, 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:* A large general population sample with complete ascertainment and follow-up due to the high-quality Swedish population registers; a strong documented exposure contrast. *Other limitations:* The mixed exposure profile without possibility to single out effects due to specific compounds; small number of cases and lack of information on important confounders such as smoking, alcohol drinking, and BMI.
			Males: Never	24	1.12 (0.72–1.66)		
			Ever	9	1.52 (0.70–2.89)		
		Liver, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Females: Never	9	0.98 (0.45–1.86)		
			Ever	4	1.52 (0.41–3.88)		
		Bile duct/gallbladder, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
			Males: Never	11	0.56 (0.28–1.00)		
			Ever	6	1.10 (0.40–2.40)		
		Bile duct/gallbladder, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Females: Never	32	1.21 (0.83–1.70)		
			Ever	7	0.99 (0.40–2.05)		
		Bile duct/gallbladder, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	43	1		
			Ever	13	1.15 (0.62–2.15)		
		Bile duct/gallbladder, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	43	1		
			Short (1–10 yr)	7	0.98 (0.44–2.20)		
			Long (≥ 11 y)	6	1.46 (0.59–3.61)		
		Pancreas, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
			Males: Never	38	0.84 (0.60–1.16)		
			Ever	6	0.46 (0.17–1.01)		
		Pancreas, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Females: Never	39	0.93 (0.66–1.27)		
			Ever	10	0.81 (0.39–1.50)		
		Pancreas, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	77	1		
			Ever	16	0.71 (0.41–1.22)		
		Pancreas, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	77	1		
			Short (1–10 yr)	11	0.89 (0.47–1.67)		
			Long (≥ 11 y)	5	0.49 (0.19–1.22)		
		Colon, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
			Males: Never	172	1.01 (0.87–1.18)		
			Ever	50	0.99 (0.73–1.30)		
		Colon, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Females: Never	156	0.88 (0.75–1.03)		
			Ever	45	0.84 (0.62–1.13)		
		Colon, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	326	1		
			Ever	93	0.98 (0.78–1.23)		
		Colon, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	326	1		
			Short (1–10 yr)	51	1.02 (0.76–1.37)		
			Long (≥ 11 yr)	42	0.93 (0.67–1.30)		
		Rectum, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
			Males: Never	109	0.96 (0.79–1.16)		
			Ever	41	1.25 (0.89–1.69)		
		Rectum, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Females: Never	80	1.00 (0.79–1.24)		
			Ever	32	1.33 (0.91–1.88)		
		Rectum, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	190	1		
			Ever	73	1.25 (0.95–1.64)		
		Rectum, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	190	1		
			Short (1–10 yr)	33	1.16 (0.80–1.69)		
			Long (≥ 11 yr)	40	1.34 (0.94–1.90)		
		Oesophagus, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
			Males: Never	33	1.02 (0.70–1.44)		
			Ever	7	0.71 (0.29–1.47)		
		Oesophagus, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Females: Never	11	1.03 (0.51–1.83)		
			Ever	2	0.64 (0.08–2.31)		
		Stomach/gastric cancer, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Males: Never	82	1.00 (0.80–1.24)		
			Ever	24	1.10 (0.70–1.64)		
		Stomach/gastric cancer, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Females: Never	37	0.85 (0.60–1.17)		
			Ever	13	1.03 (0.55–1.76)		
		Stomach/gastric cancer, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	119	1		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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	37	1.14 (0.79–1.66)		
		Stomach/gastric cancer, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	119	1		
			Short (1–10 yr)	16	0.86 (0.51–1.46)		
			Long (≥ 11 yr)	21	1.56 (0.95–2.55)		
Goodrich et al. (2022) California and Hawaii Enrolment: 1993–1996/follow-up: from mid-1990s for > 20 yr Nested case–control	Nested case–control study within the Multiethnic Cohort (MEC) cohort (see Table 2.1) Cases: 50; MEC study participants with incident non-viral hepatocellular carcinoma (HCC). Controls: 50; individuals from the MEC, matched by age, sex, race/ethnicity, and study area. Exposure assessment method: See Table 2.1	Liver/hepatocellular carcinoma, incidence	Pre-diagnostic plasma PFOA concentration (OR):			Age, sex, race/ethnicity, study area	*Exposure assessment critique:* See Table 2.1 *Other strengths:* Exposure and outcome are ascertained independently and with high accuracy; comprehensive data on potential confounders *Other limitations:* No information on exposure-response.
			≤ 8.6 ng/mL (85th percentile)	NR	1		
			> 8.6 ng/mL	NR	1.20 (0.52–2.80)		
			Continuous (per increase of one SD)	50	0.86 (0.64–1.20)		
		Liver/hepatocellular carcinoma, incidence	Pre-diagnostic plasma PFOA concentration (OR):			Age, sex, race/ethnicity, study area, BMI	
			≤ 8.6 ng/mL (85th percentile)	NR	1		
			> 8.6 ng/mL	NR	0.86 (0.34–2.20)		
		Liver/hepatocellular carcinoma, incidence	Pre-diagnostic plasma PFOS concentration (OR):			Age, sex, race/ethnicity, study area	
			≤ 54.9 ng/mL (85th percentile)	NR	1		
			> 54.9 ng/mL	NR	4.50 (1.20–16.00)		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
			Continuous (per increase of one SD)	50	1.20 (0.91–1.60)		
		Liver/hepatocellular carcinoma, incidence	Pre-diagnostic plasma PFOS concentration (OR):			Age, sex, race/ethnicity, study area, BMI	
			≤ 54.9 ng/mL (85th percentile)	NR	1		
			> 54.9 ng/mL	NR	2.90 (0.78–10.00)		
Zhang et al. (2023) ATBC cohort: Finland, PLCO: USA ATBC: Enrolment: 1985–1988/follow-up through 2011; PLCO: Enrolment: 1993–2001;/follow-up through 2010 Nested case–control	Two nested case–control studies nested within (1) the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) and (2) Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) (See Table 2.1) Cases: 251 from ATBC, and 360 from the PLCO; Cases from the ATBC study were male smokers who participated in a prevention trial who developed pancreatic ductal adenocarcinoma identified in the Finnish Cancer Registry. Cases from the PLCO study were men and women ascertained by annual mail-in surveys, cancer registries and/or the National Death Index. Controls: 251 from ATBC, 360 from PLCO; In both cohorts, controls were individually matched on age and date of blood draws, and	Pancreas, ductal adenocarcinoma, incidence	PFOA relative metabolite levels (OR):			Age at blood draw, date of blood draw, years smoked, cigarettes per day, diabetes, BMI	*Exposure assessment critique*: See Table 2.1 *Other strengths:* See Table 2.1 *Limitations:* See Table 2.1
			ATBC cohort: 1st quintile	30	1		
			2nd quintile	55	1.94 (1.05–3.59)		
			3rd quintile	41	1.45 (0.77–2.72)		
			4th quintile	63	2.27 (1.19–4.33)		
			5th quintile	62	2.37 (1.24–4.51)		
			Continuous (per SD increase (0.19) on the log base 10 scale)	251	1.27 (1.04–1.56)		
			Trend-test *P*-value, 0.01				
		Pancreas, ductal adenocarcinoma, incidence	PFOS relative metabolite levels (OR):			Age at blood draw, date of blood draw,	
			ATBC cohort: 1st quintile	22	1		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
	sex. Matching on race in PLCO only. Exposure assessment method: See Table 2.1.		2nd quintile	31	1.57 (0.69–3.57)	years smoked, cigarettes per day, diabetes, BMI	
			3rd quintile	18	0.77 (0.32–1.86)		
			4th quintile	23	0.89 (0.38–2.11)		
			5th quintile	36	1.82 (0.82–4.03)		
			Continuous (per SD increase (0.23) on the log base 10 scale)	130	1.13 (0.88–1.45)		
			Trend-test *P*-value, 0.34				
		Pancreas, ductal adenocarcinoma, incidence	PFOA relative metabolite levels (OR):				
			PLCO cohort: 1st quintile	62	1	Age at blood draw, date of blood draw, smoking status (never, former quit ≥ 15 yr, former quit < 15 yr, current, missing), diabetes, BMI, sex, race	
			2nd quintile	78	1.26 (0.78–2.04)		
			3rd quintile	81	1.43 (0.88–2.31)		
			4th quintile	78	1.30 (0.79–2.13)		
			5th quintile	61	0.95 (0.57–1.59)		
			Continuous (per SD increase (0.24) on the log base 10 scale)	360	0.97 (0.82–1.15)		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
			Trend-test *P*-value, 0.87				
		Pancreas, ductal adenocarcinoma, incidence	PFOA relative metabolite levels (OR):			Age at blood draw, date of blood draw, smoking status (former quit ≥ 15 yr, former quit < 15 yr, current, missing), diabetes, BMI, race	
			PLCO cohort (Male current or ever smokers): 1st quintile	20	1		
			2nd quintile	19	0.44 (0.13–1.49)		
			3rd quintile	16	0.83 (0.23–2.97)		
			4th quintile	19	0.78 (0.25–2.47)		
			5th quintile	9	0.49 (0.14–1.70)		
			Continuous (per SD increase (0.24) on the log base 10 scale)	83	0.86 (0.58–1.29)		
			Trend-test *P*-value, 0.44				
		Pancreas, ductal adenocarcinoma, incidence	PFOS relative metabolite levels (OR):			Age at blood draw, date of blood draw, smoking status (never, former quit ≥ 15 yr, former quit	
			PLCO cohort: 1st quintile	80	1		
			2nd quintile	65	0.86 (0.51–1.44)		
			3rd quintile	72	1.03 (0.63–1.70)		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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 quintile	75	1.05 (0.65–1.70)	< 15 yr, current, missing), diabetes, BMI, sex, race	
			5th quintile	68	0.88 (0.53–1.48)		
			Continuous (per SD increase (0.23) on the log base 10 scale)	360	0.97 (0.83–1.14)		
			Trend-test *P*-value, 0.88				
		Pancreas, ductal adenocarcinoma, incidence	PFOS relative metabolite levels (OR):				
			PLCO cohort (Male current or ever smokers): 1st quintile	25	1	Age at blood draw, date of blood draw, smoking status (former quit ≥ 15 yr, former quit < 15 yr, current, missing), diabetes, BMI, race	
			2nd quintile	14	0.57 (0.18–1.83)		
			3rd quintile	14	0.45 (0.16–1.28)		
			4th quintile	16	0.52 (0.17–1.62)		
			5th quintile	14	0.73 (0.21–2.52)		
			Continuous (per SD increase (0.23) on the log base 10 scale)	83	0.90 (0.62–1.30)		
			Trend-test *P*-value, 0.40				
		Pancreas, incidence	Serum PFOA concentration (HR):				*Exposure assessment critique*:

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
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: 172 pancreas; Incidence cases from the CPS-II Lifelink Cohort (surviving CPS-II Nutrition cohort participants) with first cancer diagnosis of pancreatic cancer detected through self-report or NDI linkage and verified through medical records review or cancer registry. All participants with incident cancers. Comparison cohort: 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		1st quartile (< 3.850 ng/mL)	43	1	Sex, year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	See Table 2.1 *Strengths:* See Table 2.1 *Limitations:* See Table 2.1
			2nd quartile (3.850 to < 5.100 ng/mL)	42	1.03 (0.63–1.68)		
			3rd quartile (5.100 to < 6.300 ng/mL)	41	1.25 (0.75–2.06)		
			4th quartile (≥ 6.300 ng/mL)	45	0.75 (0.46–1.23)		
			Continuous (per unit on log base 2 scale)	171	0.94 (0.74–1.21)		
		Pancreas, 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)	81	1.14 (0.78–1.67)		
		Pancreas, incidence	Serum PFOA concentration (HR):			Year of serum sample collection, age at serum collection, race, education, smoking	
			Males: Continuous (per unit on log base 2 scale)	90	0.71 (0.52–0.96)		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
						status, alcohol consumption	
		Pancreas, 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)	39	1		
			2nd quartile (12.000 to < 18.000 ng/mL)	44	0.64 (0.39–1.06)		
			3rd quartile (18.000 to < 25.000 ng/mL)	42	0.75 (0.45–1.24)		
			4th quartile (≥ 25.000 ng/mL)	46	0.75 (0.45–1.25)		
			Continuous (per unit on log base 2 scale)	171	0.87 (0.70–1.10)		
		Pancreas, 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)	81	0.89 (0.63–1.25)		
		Pancreas, incidence	Serum PFOS concentration (HR):			Year of serum sample collection, age at serum collection, race,	
			Males: Continuous (per unit on log base 2 scale)	90	0.87 (0.63–1.21)		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
						education, smoking status, alcohol consumption	
Vieira et al. (2013) Ohio and WV, USA 1996–2005 (incidence) Case–control	Cases: Study 1: 179 liver, 495 pancreas, 3543 colon and rectum; Study 2: 61 liver, 162 pancreas, 1149 colon and rectum; 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), Teflon-manufacturing plant in WV, USA. Controls: Study 1: 23 548 (for liver, pancreas), 20 005 (for colon and rectum); Study 2: 7339 (for liver, pancreas), 6190 (for colon and rectum); For each cancer site evaluated, controls were cases of cancer for all other sites, with the exclusion of four cancers of a priori interest (kidney, testicular, pancreas, and liver) which have been associated with PFOA in animal or human studies. Exposure assessment method: See Table 2.1	Liver, 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:* Well ascertained cases based on case registries.
			Unexposed	156	1		
			Any exposed water district	23	1.1 (0.7–1.6)		
		Liver, incidence	Analysis 2. Individual-level annual PFOA serum exposure, assuming 10-yr residency and latency (OH only) (OR):			Age, race, sex, diagnosis year,	

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
			Unexposed	50	1	insurance provider, smoking status	
			Low (3.7–12.8 µg/L)	4	1.1 (0.4–3.1)		
			Medium (12.9–30.7 µg/L)	4	0.9 (0.3–2.5)		
			High (30.8–109 µg/L)	3	1.0 (0.3–3.1)		
			Very high (110–655 µg/L)	0	-		
		Pancreas, incidence	Analysis 1. Residence in a PFOA-contaminated water district (OH and WV) (OR):			Age, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	437	1		
			Any exposed water district	58	1.0 (0.8–1.3)		
		Pancreas, 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	129	1		
			Low (3.7–12.8 µg/L)	12	1.3 (0.7–2.3)		
			Medium (12.9–30.7 µg/L)	10	0.9 (0.5–1.7)		
			High (30.8–109 µg/L)	9	1.1 (0.6–2.3)		
			Very high (110–655 µg/L)	2	0.6 (0.1–2.5)		

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
		Colon and rectum, incidence	Analysis 1. Residence in a PFOA-contaminated water district (OH and WV) (OR):			Age, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	3160	1		
			Any exposed water district	383	0.9 (0.8–1.0)		
		Colon and rectum, 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	937	1		
			Low (3.7–12.8 µg/L)	72	1.0 (0.8–1.3)		
			Medium (12.9–30.7 µg/L)	64	0.9 (0.7–1.2)		
			High (30.8–109 µg/L)	63	1.3 (1.0–1.7)		
			Very high (110–655 µg/L)	13	0.6 (0.3–1.0)		
Cao et al. (2022) China Enrolment: 2019–2021 Case–control	Cases: 203; incident cases with liver cancer obtained from a hospital in Hangchou, China, from 2019–2021. Cases had no other diseases.	Liver, incidence	Serum PFOA concentration (ng/g) (OR)			Age, sex, BMI, education, income	*Exposure assessment critique*: Key strengths were that serum levels represent the combined exposure through all exposure pathways; measurement error low.
			Continuous (per unit on log scale)	203	1.036 (1.002–1.070)		
			Trend-test *P*-value, 0.07				
	Controls: 203; Healthy controls also taken from the same Chinese hospital 2019–2021.	Liver, incidence	Serum PFOS concentration (ng/g) (OR)			Age, sex, BMI, education, income	Key limitations were that timing of sample collection relative to time point of diagnosis was not reported; if liver cancer alters ADME of PFAS there could be
	Exposure assessment method: Quantitative serum measurements;		Continuous (per unit on log scale)	203	2.609 (1.179–4.029)		
			Trend-test *P*-value, 0.001				

Table S2.5 Epidemiological studies on exposure to PFOA or PFOS and cancers of the digestive tract

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
	analytical method was state of art. Single blood sample collected. Blood collected before treatment.						possible differential exposure misclassification; single samples at time of case hospitalization may not reflect exposure at crucial windows in cancer development. *Other limitations:* No information on diseases of controls taken from same hospital as cases

ADME, absorption, distribution, metabolism, and excretion; AL, Alabama; APFO, ammonium perfluorooctanoate; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BMI, body mass index; CI, confidence interval; CPS-II, Cancer Prevention Study II; HCC, hepatocellular carcinoma; HR, hazard ratio; ICD, International Classification of Diseases; IRR, incidence rate ratio; MEC, Multiethnic Cohort; MN, Minnesota; mo, month(s); NDI, National Death Index; NR, not reported; OH, Ohio; OR, odds ratio; ppm, parts per million; PFAS, perfluoroalkyl and polyfluoroalkyl substance(s); PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; POSF, perfluorooctanesulfonyl; PTFE, polytetrafluoroethylene; RR, rate ratio; SD, standard deviation; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TFE, tetrafluoroethylene; US, United States; USA, United States of America; WV, West Virginia; yr, year(s).

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