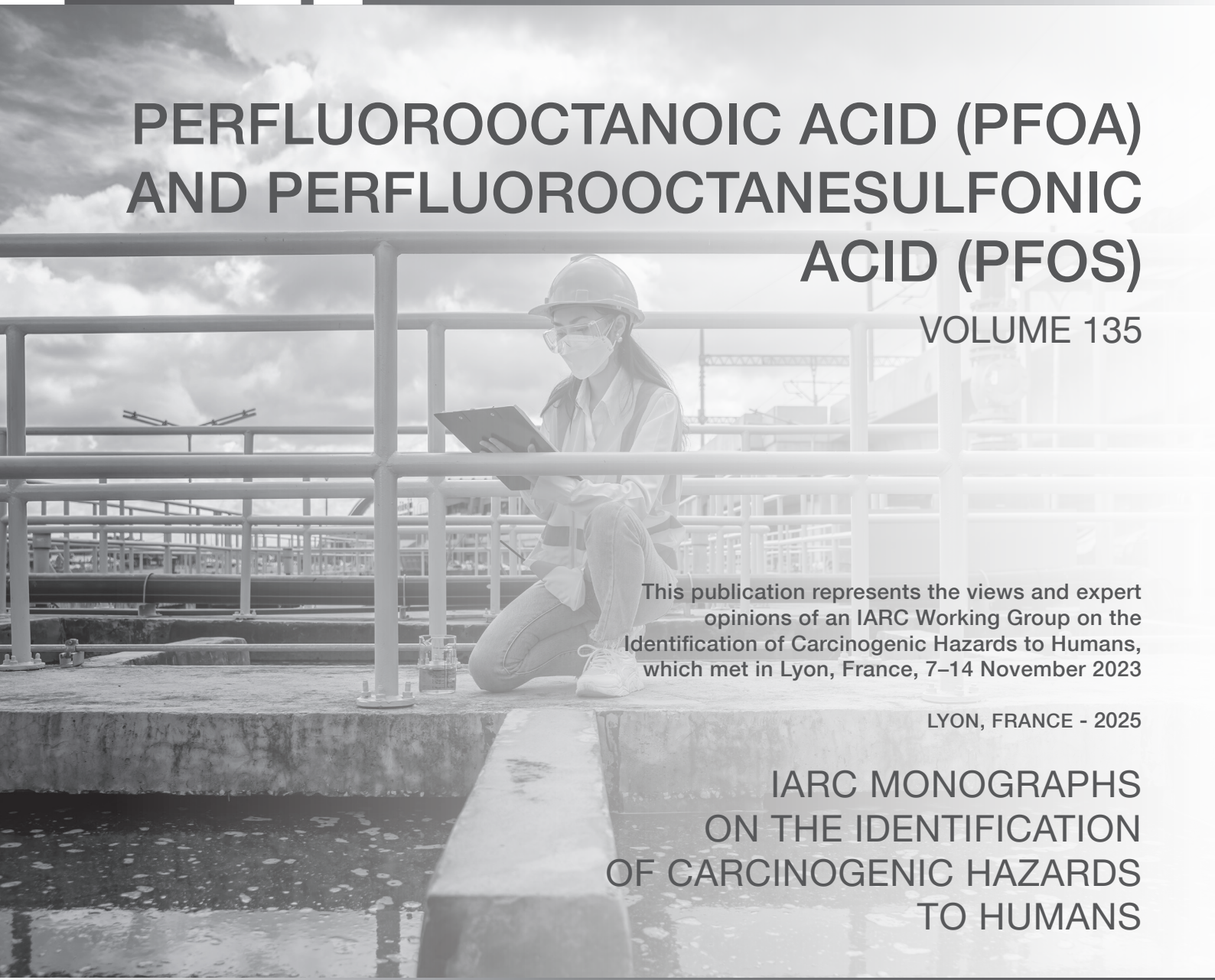
IARC MONOGRAPHS



PERFLUOROOCTANOIC ACID (PFOA) AND PERFLUOROOCTANESULFONIC ACID (PFOS)

VOLUME 135

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IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

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2. CANCER IN HUMANS

Since the previous evaluation of perfluorooctanoic acid (PFOA) by the *IARC Monographs* programme in 2014 (Volume 110; IARC, 2016), new epidemiological studies have investigated the occurrence of cancer in relation to exposure to PFOA and to perfluorooctanesulfonic acid (PFOS). A comprehensive search was conducted to identify the studies reporting cancer outcomes (defined as incidence or mortality) that were considered in the present evaluation, including studies of cohorts with occupational and high environmental exposure to PFOA or PFOS; prospective nested case–control or case–cohort studies in populations with background levels of exposure; case–control studies evaluating exposure to PFOA and/or perfluoroalkyl and polyfluoroalkyl substance(s) (PFAS), assessed after a cancer diagnosis; and an ecological study in a population with high contrast (determined through measured serum concentrations) between exposure to PFOA and relatively low exposures to other PFAS. The search identified several cohorts that were each reported in multiple publications and included the continuation of follow-up for cancer occurrence over time; in these instances, detailed reviews were conducted only for the most recent or most informative studies in a given cohort.

The Working Group excluded one ecological study of mortality conducted in the Veneto region of Italy, an area with a high level of PFOA contamination, because that study had notable limitations (Mastrantonio et al., 2018). The crude exposure assessment used (contaminated versus uncontaminated area) was based on drinking-water measurements without biological measurements in the population. Although serum concentrations were later assessed in a younger population (aged 15–39 years) in this region (Pitter et al., 2020), they were not available for the older population pertinent to the outcome investigated in the study (mortality). Human biomonitoring subsequent to the publication of Mastrantonio et al. (2018) detected substantial exposure in some areas previously classified as unexposed; this would have biased estimates towards the null value. In addition, many of the risk ratios reported for men and women combined fell outside of the range of the sex-specific risk ratios reported in the study, making it difficult to interpret the findings.

In total, 36 studies were reviewed in detail: 21 cohort studies (also comprising prospective nested case–control or case–cohort studies), some describing different cancer sites in several publications; 11 case–control studies; and 4 meta-analyses. In addition, the Working Group conducted an ecological analysis of orchiectomy rates as a surrogate for testicular cancer in residents of a contaminated area of northern Italy (see Section 2.3, and Annex 3, Supplementary analyses used in reviewing evidence on cancer in

humans, available from: https://publications.iarc.who.int/636). Section 2.1 summarizes the cohort studies, nested case–control and nested case–cohort studies, and two case–control studies on multiple cancer sites (reported in Vieira et al., 2013). Results for specific cancer sites are summarized in Sections 2.2 to 2.7, with findings from cohort and nested case–control or case–cohort studies described first, followed by findings obtained using other study designs. Studies of breast cancer were further sorted by design, with separate subsections for cohort-based studies and case–control studies or meta-analyses. The Working Group also conducted a meta-analysis of studies on kidney cancer, as well as a methodological simulation study to evaluate the representativeness of serum PFOA measurements from a single time point as a surrogate for longer-term measurements (over a period of 5–8 years); this is summarized in Annex 3 (Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636). Finally, a synthesis of the evidence relating to cancer in humans is presented in Section 2.8.

2.1 Cohort descriptions

See Table 2.1.

2.1.1 PFOA-production workers (Cottage Grove, Minnesota, USA)

Raleigh et al. (2014) updated data on cancer incidence and mortality in a previously investigated (Gilliland and Mandel, 1993; Lundin et al., 2009) cohort of workers exposed to PFOA at a facility manufacturing ammonium perfluorooctanoate (APFO, the ammonium salt of PFOA) (the Cottage Grove plant) in Minneapolis, Minnesota, USA. The cohort included 4668 workers (men, 79%) who were employed for ≥ 1 year between 1947 (when production of APFO was initiated) and 2002 (when production was terminated). A reference population was also followed, this being a cohort of 4359 workers (men, 88%) who were employed for ≥ 1 year before 1999 at a tape and abrasive production facility (the Saint Paul plant) where there was no production of APFO and that was located in the same suburban area and managed by the same company as the APFO-manufacturing facility.

Workers at the Cottage Grove plant were exposed by inhalation of PFOA vapour and ammonium salt particulates during regular production, through cleaning of equipment, changing filters, quality control checks, and maintenance, and through bystander exposure. For all cohort members, individual exposure by inhalation to APFO (in mg/m^3 of air), as a daily time-weighted average (TWA), was estimated from work history records (period, department, job title), industrial hygiene monitoring data (205 personal samples and 659 area samples collected in 1977–2000, from all processes and tasks in APFO-production areas in the chemical division of the Cottage Grove plant), information from former and current workers and from industrial hygiene professionals, and APFO-production levels. Daily TWAs for jobs in APFO production ranged from 1×10^{-4} to 4.0×10^{-1} g/m^3 [0.1 μg/m^3 to 400 μg/m^3]. Exposures for non-APFO production jobs in the chemical division and the non-chemical division ranged, according to expert judgement, from 1×10^{-8} to 3×10^{-5} mg/m^3 [1×10^{-5} and 3×10^{-2} μg/m^3] and from 1×10^{-8} to 1×10^{-6} mg/m^3 [1×10^{-5} and 1×10^{-3} μg/m^3], respectively. To account for ubiquitous background exposure, all workers (including the reference population) were assigned an exposure that was one order of magnitude lower than that for the workers in the Cottage Grove non-chemical division. The final cumulative exposure metric was quartiles of μg/m^3-years. Medical surveillance of 148 workers employed in the Cottage Grove chemical division in 2000 found a geometric mean serum concentration of PFOA of 815 ng/mL (2538, 979, and

Table 2.1 Description of cohort studies (including nested case–control studies) on exposure to PFOA or PFOS and cancer

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	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 an APFO-production plant for ≥ 365 days before 31 December 1997; most recent follow-up for some cancer sites (see those listed here), later follow-up by Raleigh et al. (2014) Exposure assessment method: based on job history; jobs classified as definite, probable, and no or minimal occupational APFO exposure	Large intestine, rectum, oesophagus, stomach Thyroid CNS Lymphatic and haematopoietic Lymphosarcoma-reticulosarcoma Hodgkin lymphoma Leukaemia	See Table S2.5[a] See Table 2.4 See Table S2.6[a] See Table S2.6[a] See Table S2.6[a] See Table S2.6[a] See Table S2.6[a]	*Exposure assessment critique*: Key strengths were the industrial hygiene review of jobs; weighting of jobs based on serum measurements; assignment of exposure weights based on blood monitoring (authors indicated that other weights were considered but felt that these weights allowed better differentiation between probable and definite exposures over time). Key limitations were the crude exposure assessment by job classification, and lack of job-specific data on PFOA serum levels (but serum PFOA levels for work areas were collected in 2000). *Other strengths*: Occupational cohort with relatively high exposures; analyses presented based on both job classification and cumulative exposure estimates. *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. Smoking data were collected but not included in the final models.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Raleigh et al. (2014) MN, USA Enrolment, 1947–2002/ follow-up, 1947–2008 (mortality), 1988–2008 (incidence) Cohort	9027 employees (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 ≥ 1 yr in 1947–2002 at an APFO facility (Cottage Grove; *n* = 4668); reference workers without any exposure to APFO employed at a tape and abrasives production facility located in the same suburban geographical area and managed by the same company (Saint Paul; *n* = 4359) Exposure assessment method: exposure matrix used production-process air measurements and expert judgement in applying production volume data and proximity to production areas to assign department and job exposures historically; exposure matrix and job history were used to calculate cumulative exposure (μg/m³-years)	Kidney Urinary bladder Prostate Breast Liver Pancreas All cancers combined	See Table 2.2 See Table 2.2 See Table 2.3 See Table 2.4 See Table S2.5[a] See Table S2.5[a] See Table S2.7[a]	*Exposure assessment critique*: Key strengths were that the only PFAS exposure in plant was to APFO (PFOA); cumulative co-exposure to TFE was estimated to be minimal Key limitations were that development of cumulative exposure metric was based on APFO air concentrations and not internal dose; reference population in APFO unexposed same plant was assumed to have exposures of the general population, but the method of determination was unclear (1×10^{-7} to 1×10^{-9} mg/m³). *Other strengths*: A reference population sharing similar socioeconomic characteristics as the exposed population and a long follow-up period. *Other limitations*: Lacking data on employees who left MN or WI. Lacking data on cancer-incidence before start of follow-up up to 40 yr after first exposure. No information on health behaviours (potential confounding). Small numbers of cancers of kidney, pancreas, liver, testis. No accounting for alcohol or smoking.
Alexander et al. (2003) Decatur (AL), USA Enrolment, 1961–1997/ follow-up, 1961–1998 (mortality) Cohort	2083 employees; Decatur (AL) PFOS cohort; production workers (men, 83%) who worked ≥ 365 days in a plant producing speciality films and fluorochemicals, a main one being 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: expert judgement; workers were categorized as ever in a "high" exposure job, ever in a "low" exposure job but not a "high" exposure job, only in jobs without POSF exposure, or ≥ 1 yr in a "high" exposure job	Breast Liver and bile ducts, large intestine, oesophagus, digestive organs and peritoneum Lymphatic and haematopoietic Melanoma Respiratory system Bronchus, trachea, lung All cancers combined	See Table 2.4 See Table S2.5[a] See Table S2.6[a] See Table S2.6[a] See Table S2.6[a] See Table S2.6[a] See Table S2.7[a]	*Exposure assessment critique*: A key strength was the range of workplace exposure durations and levels (a large exposure contrast). Key limitations were that exposure assessment did not use any measure of cumulative exposure, but simply categorized each worker in 1 of 3 ever/never/only job classifications, which could produce exposure misclassification; many likely co-exposures to potential carcinogens or other fluorochemicals, including PFOA (however, PFOA concentrations were probably low). *Other limitations*: Occupational cohort with few cancer deaths (overall, 39; high exposure group, 18), limited to mortality, lack of data on smoking and alcohol, mostly male (83%).

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Alexander and Olsen (2007) Decatur (AL), USA Enrolment, 1961–1997/ follow-up, 1970–2002 (mortality and incidence) Cohort	1588; Decatur (AL) PFOS cohort; production workers in the Alexander et al. (2003) cohort; living cohort members completed a questionnaire (response rate, 73.9%) to identify incident bladder cancer cases; bladder cancer decedents were identified using underlying cause of death from death certificates; analyses excluded 495 living cohort members who did not return the questionnaire Based on the exposure assessment described in Alexander et al. (2003), cumulative exposure was calculated weighing the exposure categories of nonexposed, low exposed and high exposed with a factor of 1, 3, and 10, respectively, for each year in that job.	Urinary bladder	See Table 2.2	*Exposure assessment critique*: Key strengths were the range of workplace exposure durations and levels; cumulative exposure was estimated using a weighted approach of exposure categories. Key limitations were that the crude weighted approach to calculate cumulative exposure could produce exposure misclassification; many likely co-exposures to potential carcinogens or other fluorochemicals (however, PFOA concentrations were probably low). *Other strengths*: use of incidence data with 74% participation rate in survey; attempt to validate self-reported cancer for survey respondents. *Other limitations*: occupational cohort with only 11 cases of bladder cancer, 2 in the highest category of exposure. Bladder cancer incidence identified by survey of cohort (6 cases) and death certificates (5 deaths) no cancer registry matching, only partial data on smoking, no ability to validate 5 cases of bladder cancer identified by death certificate, mostly male (83%).
Leonard et al. (2008) Parkersburg (WV), USA Enrolment, 1948–2002/follow-up, 1948–2002 (mortality) Cohort	6027 workers; Parkersburg (WV), polymer-production PFOA cohort; most recent follow-up for some cancer sites (see those listed here), later follow-up by Steenland and Woskie (2012); workers (men, 81%) at a polymer-manufacturing facility for ≥ 1 day in 1948–2002 Exposure assessment method: no quantitative exposure assessment; workers in a polymer-production facility were identified using the company's administrative records; ~30% worked in processes using APFO; all participants had detectable levels of serum PFOA	Large intestine, rectum, oesophagus, stomach Thyroid Melanoma	See Table S2.5[a] See Table 2.4 See Table S2.6[a]	*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 used a wide variety of chemicals including PFOA). Small numbers.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Steenland and Woskie (2012) Parkersburg (WV), USA Enrolment, 1948–2002/follow-up, 1952–2008 (mortality) Cohort	5791 workers; Parkersburg (WV), polymer-production PFOA cohort; workers (men, 81%) at a polymer-manufacturing facility who had potential exposure to fluoropolymers and sufficiently detailed work histories Exposure assessment method: JEM was based on a total of eight job category/job group combinations; jobs were classified on the basis of PFOA exposure potential and the JEM was improved through the use of blood samples to assign serum PFOA levels over time	Kidney Urinary bladder Testis Prostate Breast Liver and gallbladder Pancreas NHL Leukaemia Lung Mesothelioma All cancers combined	See Table 2.2 See Table 2.2 See Table 2.3 See Table 2.3 See Table 2.4 See Table S2.5[a] See Table S2.5[a] See Table S2.6[a] See Table S2.6[a] See Table S2.6[a] See Table S2.6[a] See Table S2.7[a]	*Exposure assessment critique*: Key strengths were that the JEM incorporated changes in exposure over time; because serum levels were used to construct the JEM, residential exposure to PFOA in drinking-water was included in estimates; any exposure misclassification is likely to be non-differential. A key limitation was the lack of description of other exposures. *Other strengths*: Ability to evaluate associations with PFOA in a population exposed to levels much higher than in the general population. *Other limitations*: Limited ability to evaluate mortality for some cancers due to small numbers of deaths, particularly for cancers among women (given the small number of female workers in the study) and cancers that are relatively rare and/or less likely to be fatal.
Steenland et al. (2015) Parkersburg (WV), USA Enrolment, 1948–2002/follow-up, 1951 to interview date in 2008–2011 (incidence) Cohort	3713 employees; a subset of the Parkersburg (WV) polymer-production PFOA cohort in Steenland and Woskie (2012); polymer-production workers (men, 80%) who responded (self or next-of-kin) to a questionnaire about health outcomes and for whom measured or estimated occupational and residential exposure estimates were available Exposure assessment method: cumulative PFOA serum concentrations estimated on the basis of JEMs and residential history; historical PFOA serum levels were modelled via a JEM based on > 2000 serum measurements (Woskie et al., 2012); non-occupational exposure from drinking-water (address-based) was also estimated;	Urinary bladder Prostate Colon and rectum Melanoma	See Table 2.2 See Table 2.3 See Table S2.5[a] See Table S2.6[a]	*Exposure assessment critique*: Key strengths were good characterization of exposure in both occupational and residential settings; minimal potential for non-differential exposure misclassification. A key limitation was that loss to follow-up of 40% of workers could lead to differential exposure misclassification if related to PFOA exposure. *Other strengths*: Ability to evaluate associations between PFOA and cancer incidence in a population exposed to levels much higher than in the general population. Use of medical records to confirm self-reported cancer diagnoses likely reduced non-differential outcome misclassification.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Steenland et al. (2015) Parkersburg (WV), USA Enrolment, 1948–2002/follow-up, 1951 to interview date in 2008–2011 (incidence) Cohort (cont.)	yearly serum estimates from the occupational exposure model were used for the years when people worked at the plant if these were higher than residential estimates, or if they were lower, the residential (community) estimates were used			*Other 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. Possible under-ascertainment of cases due to medical record confirmation.
Eriksen et al. (2009) Denmark Enrolment, 1 December 1993 to 31 May 1997/follow-up, 1 December 1993 to 1 July 2006 (incidence) Case–cohort	Case–cohort within the Diet, Cancer, and Health cohort, which included men and women aged 50–65 yr without cancer at enrolment. Cases: urinary bladder, 332; prostate, 713; liver, 67; pancreas, 128; incident cases identified through cancer registry linkage Comparison cohort: 772 (680 men, 92 women); subcohort of participants randomly selected without cancer at the end of follow-up Exposure assessment method: quantitative plasma measurements; analytical method was state-of-the-art; a single sample collected at enrolment (1993–1997) was analysed for PFOA and PFOS	Urinary bladder Prostate Liver Pancreas	See Table 2.2 See Table 2.3 See Table S2.5[a] See Table S2.5[a]	*Exposure assessment critique*: Key strengths were that plasma levels measured at baseline represent the combined exposure through all exposure pathways; measurement error low. Key limitations were that single samples collected at time of enrolment may not reflect exposure at crucial windows in cancer development; measured only PFOA and PFOS and no information on exposure to other PFAS. *Other strengths*: Large cohort with numerous incident cancers (n = 1240) followed 0–12 yr after baseline enrolment; control of confounders; internal comparison; low loss to follow-up. *Other limitations*: Low exposure contrast in a population with background exposure levels. Analyses only considered PFOA and PFOS separately.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Barry et al. (2013) Mid-Ohio Valley (OH and WV), USA Enrolment, August 2005 to August 2006/ follow-up, 1952 to 2011 (incidence) Cohort	32 254 (28 541 community members and 3713 workers); C8 Science Panel Study; included people enrolled in the C8 Health Project who lived, worked, or attended school for ≥ 1 yr between 1950 and 3 December 2004 in a district with contaminated water in the vicinity of a chemical plant using PFOA in manufacturing processes (Parkersburg, WV, polymer-production facility), as well as a subset of those from the original Parkersburg (WV) polymer-production PFOA occupational cohort who worked at the plant between 1948 and 2002 Exposure assessment method: residential and occupational exposure estimates were combined to estimate cumulative PFOA serum concentrations; historical PFOA serum levels were modelled via a JEM based on > 2000 serum measurements (Woskie et al., 2012); non-occupational exposure from drinking-water (address-based) was also estimated	Kidney Urinary bladder Testis Prostate Breast Liver, pancreas, colon and rectum, oesophagus, stomach Thyroid Brain Leukaemia, lymphoma Lung Melanoma	See Table 2.2 See Table 2.2 See Table 2.3 See Table 2.3 See Table 2.4 See Table S2.5[a] See Table 2.4 See Table S2.6[a] See Table S2.6[a] See Table S2.6[a] See Table S2.6[a]	*Exposure assessment critique*: Key strengths were that exposure assessment was done the same way for all participants; estimates accounted for both residential and occupational exposure to PFOA. A key limitation was that serum PFOA levels were available only in 2005–2006. *Other strengths*: Wide range of PFOA exposure levels; authors presented both no lag and 10-yr lag models; availability of detailed information on potential confounding factors; relatively high participation rates; and validation of cancer diagnoses through medical chart review and state registries. *Other limitations*: possibility of selection bias, particularly for cancers with a high rate of fatality; and relatively few validated cases for prospective analyses (after C8 Health Project enrolment). Potential limitation of a survivor cohort but unlikely to be biased unless those with higher exposure had lower post-diagnosis survival rates than those with lower exposure (Barry et al., 2015). *Other comments*: 62% of the polymer production plant cohort (Steenland and Woskie, 2012) is included in the study population (including workers who did and did not participate in the C8 Health Project).

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Consonni et al. (2013) USA, UK, Italy, Germany, Netherlands Enrolment, 1950–2002/follow-up, 1950–2008 Cohort	5879 male workers (APFO-exposed, 4205); The pooled international TFE cohort included male workers who were ever employed or employed for a minimum of 6 or 12 mo at one or more of six TFE production sites in North America and Europe between 1950 and 2002; the principal occupational exposures were TFE and APFO (facilitates production of TFE) Exposure assessment method: a JEM provided yearly semiquantitative estimates (in arbitrary units) of TFE and APFO exposure for relevant job titles at each production site, from the start of TFE production to 2002 (Sleeuwenhoek and Cherrie, 2012)	Kidney and other organs of the urinary tract	See Table 2.2	*Exposure assessment critique*: A key strength was the availability of job history for all participants. Key limitations were that only expert judgement was used to determine exposure levels; no measured exposures; high correlations between exposure to TFE monomer (IARC Group 2A) and PFOA, which precludes evaluation of effects of the individual compounds. *Other strengths*: The cohort included all TFE production sites worldwide during the entire period of production and had almost complete enrolment and follow-up. *Other limitations*: low statistical power to detect risk of rare cancers.
		Urinary bladder	See Table 2.2	
		Testis	See Table 2.3	
		Prostate	See Table 2.3	
		Liver and intrahepatic bile duct, pancreas, colon, rectum, oesophagus, stomach	See Table S2.5[a]	
		Brain	See Table S2.6[a]	
		Lymphatic and haematopoietic, NHL, multiple myeloma, leukaemia	See Table S2.6[a]	
		Lung	See Table S2.6[a]	
		All cancers combined	See Table S2.7[a]	
Ghisari et al. (2017) Denmark Enrolment, 1996–2002/follow-up, through 2010 Nested case–control	Nested within the Danish National Birth Cohort of ~100 000 pregnant women: nulliparous women at the time of blood draw during pregnancy were followed for breast cancer. Cases: 178 cases of breast cancer in nulliparous women at the time of blood draw during pregnancy Controls: 233; frequency-matched on age Exposure assessment method: quantitative serum measurement; analytical method was state-of-the-art; a single sample collected at enrolment (1996–2002) was analysed for PFAS at ascertainment for cases and controls	Breast (premenopausal)	See Table 2.4	*Exposure assessment critique*: Key strengths were that serum levels represent the combined exposure through all exposure pathways; measurement error low. Key limitations were that single samples at time of enrolment may not reflect exposure at crucial windows in cancer development; focused analysis on only 4 PFAS separately even though others had 98.8–100% samples detectable (PFHpS, PFNA) and others had 50–89% detectable (PFHpA, PFDA, PFDoA, PFUnA, PFTrA) (Bonefeld-Jørgensen et al., 2014). Did not sum PFAS in any way.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Ghisari et al. (2017) Denmark Enrolment, 1996–2002/follow-up, through 2010 Nested case–control (cont.)				*Other strengths*: Blood samples collected before breast cancer diagnosis; exposure during pregnancy may be an important exposure window for breast cancer; large sample of premenopausal cases; consideration of relevant SNPs. *Other limitations*: Focused on premenopausal breast cancer, did not consider postmenopausal breast cancer; no information on tumour characteristics; small exposure contrast. *Other comments*: Earlier follow-up by Bonefeld-Jørgensen et al. (2014). A few dozen breast cancer cases from that study were excluded here due to concern about status due to a coding error.
Hurley et al. (2018) CA, USA Enrolment, 1995–1996/follow-up, 1 January 2006 to 1 August 2014 (incidence) Nested case–control	Nested within the California Teachers Study; 133 479 female public-school teachers and other professionals were followed annually for cancer incidence Cases: 902 cases with a diagnosis of invasive breast cancer at age < 80 yr, no prior history of breast cancer, who provided a blood specimen, answered the questionnaire, and were continuous residents of CA; participation rate, 65% Controls: 858 women drawn from a probability sample of at-risk cohort members, frequency-matched on age, race/ethnicity, and residence; participation rate, 55% Exposure assessment method: quantitative serum measurements; analytical method was state-of-the-art; a single sample was collected after diagnosis of invasive breast cancer (average, 35 mo) and analysed for PFAS	Breast	See Table 2.4	*Exposure assessment critique*: Key strengths were that serum levels represent the combined exposure through all exposure pathways; measurement error low. Key limitations were that blood samples were collected on average 35 mo (range, 9 mo to 8.5 yr) after diagnosis, which may not reflect exposure at crucial windows in cancer development; if breast cancer alters ADME of PFAS, there could be possible differential exposure misclassification; did not account for mixtures of PFAS and did not use all PFAS measurement data available. *Other strengths*: Case ascertainment with statewide cancer registry linkage and pathology confirmation; considered several established breast cancer risk factors as confounders/modifiers; evaluated associations by combined ER and PR status and menopausal status; large number of cancer-registry identified cases and controls.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Girardi and Merler (2019) Vicenza province, Veneto Region, Italy Enrolment, 1960–2008/follow-up, 1970–2018 (mortality) Cohort	462 PFAS workers; 1383 railroad workers (comparison cohort); workers in a perfluorocarbon-production facility in Trissino manufacturing PFOA, PFOS, other perfluorinated compounds, and other chemicals; comparison populations included the regional general population and workers in a local railroad industry who were not exposed to chemicals; for both occupational cohorts, the workers included were men employed for ≥ 6 mo Exposure assessment method: cumulative serum levels were estimated for each worker's history, 1970–2008; serum data collected in 2000–2013 were used to model historical exposures in three job categories by incorporating fixed effects for variables related to subject of measurement as well as historical data on PFOA production.	Liver and intrahepatic bile ducts (ICD-9, 155) Colon Oesophagus, stomach Lymphatic and haematopoietic, NHL Lung All cancers combined	See Table S2.5[a] See Table S2.5[a] See Table S2.5[a] See Table S2.6[a] See Table S2.6[a] See Table S2.7[a]	*Exposure assessment critique*: Key strengths were that historical exposures were modelled using serum measurements and estimation of cumulative exposures to PFOA (ng/mL-years); the study evaluated whether workers' home drinking-water was in contaminated area (Red Zone), but unclear how this information was used; APFO exposures were accounted for in PFOA measurements as it dissociates to PFOA in the body. Key limitations were that few samples were available to model serum levels in job categories 2 and 3; other PFAS exposures in plant were not accounted for (including PFOS and perfluorobutylsulfonyl fluoride); other potential carcinogenic co-exposures within factory were not accounted for, nor were alcohol or smoking use assessed. *Other strengths*: High exposure contrast; internal comparisons with non-exposed workers. *Other limitations*: Included only men; small occupational cohort with few deaths (n = 107); few cancer deaths for liver and lympho-haematopoietic (7 each) (the 2 causes with positive trends with exposure); no data on some causes of death of interest (e.g. bladder, prostate).

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Mancini et al. (2020a) France Enrolment, 1990/ follow-up, through 2013 (incidence) Nested case–control	Nested within the E3N cohort of 98 995 women born in 1925–1950 and covered by the French National Education System insurance; participants were invited to complete follow-up questionnaires (including dietary) every 2–3 yr and donate blood between 1994 and 1999 Cases: 194 incident cases of post-menopausal breast cancer diagnosed among women with serum (≥ 3 aliquots) collected before diagnosis, a completed dietary questionnaire in 1993, and randomly selected from 240 eligible cases of breast cancer Controls: 194; density-sampled at time of case occurrence and matched on age within 2 yr, menopausal status at blood collection, BMI at blood collection, and year of blood collection Exposure assessment method: quantitative serum measurements; analytical method was state-of-the-art; a single sample collected before diagnosis of breast cancer was analysed for total PFOA and PFOS, not for isomers of PFOA or PFOS	Breast (post-menopausal)	See Table 2.4	*Exposure assessment critique*: Key strengths were that serum levels represent the combined exposure through all exposure pathways; measurement error low. Key limitations were that single samples before diagnosis may not reflect exposure at crucial windows in cancer development. *Other strengths*: Blood samples collected before diagnosis with a long follow-up period; extensive adjustment for plausible confounders; inclusion of hormone receptor subtype information; low loss to follow-up. *Other limitations*: Limited statistical power, particularly when exploring differences by subtype; low exposure contrast in general population sample; did not include premenopausal breast cancer cases. *Other comments*: Frenoy et al. (2022) conducted additional exposure–response analyses.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Shearer et al. (2021) USA Recruitment: 1993–2001, Follow-up (from blood drawn): median 8.8 yr (incidence) Nested case–control	Nested within the PLCO cohort, which comprises ~150 000 adults aged 55–74 yr from study centres in 10 cities; about half (assigned to the screening arm) provided a blood sample at baseline and were followed for incident cancer Cases: 324; source of cancer diagnosis not reported. Controls: 324; density-sampled on calendar time and individually matched on age categories, sex, race and ethnicity, study centre, and year of blood draw Exposure assessment method: quantitative serum measurements; analytical method was state-of the-art; blood samples collected at enrolment into PLCO study; samples from cases and controls were analysed at the same time for PFAS in serum	Kidney (RCC)	See Table 2.2	*Exposure assessment critique*: Key strengths were that serum levels represent the combined exposure through all exposure pathways; measurement error low. A key limitation was that single measurement of serum levels may not have reflected cumulative or long-term exposure, although only minor misclassification of long-term exposure over a period of 5–8 yr was seen, based on a simulation study (see Annex 3 in the present monograph). *Other strengths*: Large number of kidney cancer cases (n = 324); an average of 8 yr of follow-up following baseline serum measurement of a variety of PFAS; good data on confounders; internal comparisons with control over kidney function; adjustment for exposure to other PFAS. *Other limitations*: Low exposure contrast in a population with background levels. *Other comments*: PFAS concentrations were missing for two (excluded) cases.
Chang et al. (2023) USA Enrolment, 1993–2001/ follow-up, through November 2013 (incidence) Nested case–control	Nested within the PLCO cohort (see Shearer et al., 2021) Cases: 621; all incident cases of invasive breast cancer diagnosed among postmenopausal women who were not using MHT at baseline (unless their cancers were hormone receptor-negative) Controls: 621; controls were selected using incidence-density sampling; all were postmenopausal, still alive and cancer-free at the time of case diagnosis; matching on age at baseline, date of blood draw, and baseline MHT use	Breast (post-menopausal)	See Table 2.4	*Exposure assessment critique*: Key strengths were that serum levels represent the combined exposure through all exposure pathways; exposure was assessed before outcome; any misclassification is likely to be non-differential. Key limitations were that single measurement of serum levels may not capture relevant window of exposure for cancer development, especially among the cases diagnosed close to sample collection (but the authors conducted analyses stratified by time since blood draw, which addresses this concern); also, only minor misclassification of long-term exposure over a period of 5–8 yr, based on a simulation study (Annex 3); exposure assessment relied upon relative quantification of PFOA and PFOS (but relative measures have correlated well with targeted absolute concentration measurements).

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Chang et al. (2023) USA Enrolment, 1993–2001/ follow-up, through November 2013 (incidence) Nested case–control (cont.)	Exposure assessment method: PFOA and PFOS serum levels were measured using a non-targeted method (unclear whether both branched and linear isomers were included); in the same participants, untargeted serum levels were correlated with levels measured using a standard, targeted method (Spearman correlation coefficient was 0.76 and 0.77 for total PFOS and total PFOA, respectively)			*Other strengths*: Large number of breast cancer cases (n = 621); an average of 8 yr of follow-up after serum measurements on a variety of PFAS at baseline; good data on confounders, internal comparisons; adjustment for exposure to other PFAS; stratified analyses by hormone status of cancer. *Other limitations*: Low exposure contrast in a population with background levels; limited power to consider hormone receptor negative tumours, no premenopausal cases. *Other comments*: PFAS concentrations were missing for two (excluded) cases.
Rhee et al. (2023a) USA Recruitment, 1993–2001, follow-up (from blood draw), median, 9 yr (incidence) Nested case–control	Nested within the PLCO cohort (see Shearer et al., 2021) Cases: 750 cases of aggressive prostate cancer (defined as stage III or IV, Gleason score ≥ 8, or Gleason score 7 and death from prostate cancer), diagnosed > 300 days after blood collection Controls: 750; alive and cancer-free at time of case diagnosis, and individually matched to cases on age at baseline, race/ethnicity, study centre, calendar and study year of blood collection, and prior freeze–thaw cycle Exposure assessment method: quantitative serum measurements; analytical method was state-of-the-art; a single sample was collected at time of enrolment into PLCO; time between blood draw and diagnosis was 9 yr (median IQR, 5.13 yr)	Prostate (aggressive/ advanced)	See Table 2.3	*Exposure assessment critique*: Key strengths were that serum levels represent the combined exposure through all exposure pathways; measurement error low; PFAS were measured in blood samples collected before diagnosis; analysis of blood samples collected 0,1, and 5 yr after enrolment showed a high degree of reproducibility with ICCs of > 0.7 for PFOA and PFOS. *Other strengths*: large case control study with 750 cases and matched controls; data on a broad range of confounders; smoking was controlled for in the analysis; other exposures are unlikely to be correlated with PFAS in this general population sample; mutual adjustment for other PFAS under study. *Other limitations*: general population with low exposure contrast; large number of comparisons.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Cohn et al. (2020) Oakland (CA), USA Enrolment, at birth between 1959–1967/ follow-up, birth to March 2013 (incidence) Nested case–control	Nested within the CHDS pregnancy cohort, which includes 19 044 live births from pregnant members of the Kaiser Foundation Health Plan who received obstetric care between 1959 and 1967 and who provided blood specimens during pregnancy and at birth; > 99% of eligible women enrolled, and 74% of cases had a blood sample and complete information on potential confounders and effect modifiers Cases: 102 incident cases of invasive or non-invasive breast cancer diagnosed by age 52 yr, with a maternal perinatal blood sample and complete information on potential confounders and effect modifiers Controls: 310; 3 per case, density-sampled on case age and matched on birth year and trimester of maternal blood draw Exposure assessment method: quantitative serum measurements; analytical method was state-of-the-art; maternal blood samples were collected before offspring birth; blood samples from cases and controls were retrieved ~50 yr later for PFAS analysis	Breast	See Table 2.4	*Exposure assessment critique*: Key strengths were that serum levels represent the combined exposure through all exposure pathways; measurement error low; perinatal exposure may be relevant for later breast cancer; misclassification of exposure is unlikely because cases were matched to controls for year of enrolment in the study (thus, changes in concentration over time were addressed). Key limitations were that PFAS exposure was not measured directly in study participants; only one maternal blood sample (during pregnancy or after labour) was used, while PFAS levels may vary during pregnancy; no information on exposures during the individual's lifetime. *Other strengths*: long follow-up; cases were likely to have been accurately determined via the California cancer registry. *Other limitations*: Only cases diagnosed before age 52 yr were included; risk of incomplete or biased case ascertainment; small sample size and limited statistical power; no information concerning tumour hormone-receptor status; adjustment only on potential maternal confounders and no variable collected at the daughter's individual level; lack of information on migration out of state.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Li et al. (2022a) Ronneby, southern Sweden Enrolment,1985–201/ follow-up, 1985–2016 (incidence) Cohort	60 507; the Ronneby Register cohort includes all individuals who ever lived in the Ronneby municipality in 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 in 1985–2013 (individuals considered to have "ever-high" exposure, 15 811); subsets with long-term exposure (≥ 11 yr) in the latest part of the follow-up period (2005–2013) were considered to be more highly exposed Exposure assessment method: residential location (water source) used to categorize participants into groups of potential exposure based on time period or duration of residency, or a residence in a neighbouring reference municipality; serum levels collected in 2014–2015 for residents and the neighbouring municipality were used to validate categories	Kidney	See Table 2.2	*Exposure assessment critique*: Key strengths were that categories reflect serum levels, which include exposure through all pathways; attempted to incorporate length of exposure period in analysis. Key limitations were the potential for misclassification of exposures, since there was no information on individual water consumption patterns or use of bottled water or filtration at home; no cumulative years of exposure used, except two categories of short and long high exposure; no accounting for potential co-exposures; lack of historical information on area-level PFAS drinking-water contamination, particularly during earlier years of the study period. *Other strengths*: Large study population; strong exposure contrast; unbiased inclusion; complete follow-up; long follow-up for part of the population; reference group from same municipality. *Other limitations*: Mixed exposure profile without possibility to single out effects due to specific compounds; little information on potential confounders. *Other comments*: PFAS exposure mainly PFOS, PFHxS, together comprising > 90% of total PFAS in water, and PFOA (water and blood samples).
		Urinary bladder	See Table 2.2	
		Testis	See Table 2.3	
		Prostate	See Table 2.3	
		Breast	See Table 2.4	
		Liver, bile duct or gall bladder, pancreas, colon, rectum, oesophagus, stomach	See Table S2.5[a]	
		Thyroid	See Table 2.4	
		Brain	See Table S2.6[a]	
		NHL, multiple myeloma, chronic lymphocytic leukaemia, chronic myelogenous leukaemia	See Table S2.6[a]	
		Melanoma	See Table S2.6[a]	
		Trachea and lung	See Table S2.6[a]	
		All cancers combined	See Table S2.7[a]	

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Feng et al. (2022) Shiyan, China Enrolment, September 2008 to June 2010 and April to October 2013/ follow-up, 2008–2018 (incidence) Case–cohort	Case–cohort within the Dongfeng-Tongji cohort, which included 18 387 female retirees of automotive companies, without cancer at enrolment, with sufficient blood samples Cases: 226; the total number of diagnoses of incident breast cancer included 13 diagnoses in the comparison cohort Comparison cohort: 990 (including 13 cases); women randomly selected according to age strata The 13 cases included in the comparison cohort of 990 women served as controls until they received a cancer diagnosis Exposure assessment method: quantitative serum measurements; analytical method was state-of-the-art; a single serum sample collected before diagnosis of breast cancer was analysed for six PFAS (including PFOA and PFOS), but not for isomers of PFOA or PFOS	Breast	See Table 2.4	*Exposure assessment critique*: Key strengths were that serum levels represent the combined exposure through all exposure pathways; measurement error low; availability of prediagnostic serum samples (mean, 9.6 yr before diagnosis); measurement of several PFAS compounds. A key limitation was that single samples before diagnosis may not reflect exposure at crucial windows in cancer development. *Other strengths*: cases identified by reviewing medical records or death certificates; information on potential confounding variables collected through face-to-face interview and physical examination; high baseline participation. *Other limitations*: study population limited to retired workers; no information concerning tumour hormone-receptor status; no information on the likely completeness of diagnoses; cases identified by death certificate only (number not identified) would have an unknown diagnosis date; low exposure contrast. *Other comments*: ~10% lost to follow-up; does not mention how age-stratification was used to select comparison cohort; 90% of cases were postmenopausal; examined individual PFAS (6) and summed categories of PFCAs and PFSAs as well as sum of all PFAS.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Wen et al. (2022) USA Enrolment, 1999–2014/ follow-up, 1999–2015 (mortality) Cohort	11 747 from the NHANES cohort, a nationally representative cross-sectional survey of adults (aged ≥ 18 yr) followed for mortality through 2015 Exposure assessment method: quantitative serum measurements; analytical method was state-of-the-art; a single serum sample collected before death was analysed for 12 PFAS, but not for isomers of PFOA or PFOS	All cancers combined	See Table S2.7[a]	*Exposure assessment critique*: Key strengths were that serum levels represent the combined exposure through all exposure pathways; considered mixtures of PFAS; measurement error low. Key limitations were that single samples before death may not reflect exposure at crucial windows in cancer development; unclear timing of blood sample relative to diagnosis/treatment. *Other strengths*: NDI linkage, nationally representative of the USA; relatively good control for potential confounders; adjustment for other PFAS. *Other limitations*: Short follow-up time (median, 81 mo); heterogenous outcome, representative of incidence only in the case of high fatality of cancers; use of volunteer-based population that may be healthier than the general population. *Other comments*: Analysed PFOA and PFOS separately as well as total PFAS, total PFAS excluding PFOA and total PFAS excluding PFOS to address mixture issues.
Goodrich et al. (2022) CA and HI, USA Enrolment, 1993–1996/ follow-up, from mid-1990s for > 20 yr Nested case–control	Nested within the MEC cohort, which is a community sample of 215 251 men and women aged 45–75 yr enrolled during 1993–1996 in HI and CA (primarily Los Angeles county) when responding to a 26-page postal questionnaire on mainly diet, demographic, and health issues Cases: 50 incident cases of non-viral HCC Controls: 50 individuals from the MEC, matched on age, sex, race/ethnicity, and study area	Liver (HCC)	See Table S2.5[a]	*Exposure assessment critique*: Key strengths were use of prediagnostic plasma PFAS measurements; plasma levels represent the combined exposure through all exposure pathways; measurement error low. A key limitation was that single samples before diagnosis (at recruitment) may not reflect exposure at relevant windows in HCC development.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Goodrich et al. (2022) CA and HI, USA Enrolment, 1993–1996/ follow-up, from mid-1990s for > 20 yr Nested case–control (cont.)	Exposure assessment method: quantitative plasma measurements; analytical method state-of-the-art; a single plasma sample was collected at recruitment, before HCC diagnosis, and analysed for 6 PFAS including PFOA and PFOS, but not for isomers of PFOA or PFOS			*Other strengths*: Exposure and outcome were ascertained independently and with high accuracy, with a median 7.2 yr between blood sample and diagnosis; BMI and diabetes status considered as potential confounders. *Other limitations*: Insufficient information on attrition, completeness of follow-up, statistical analysis; low exposure contrast (general population sample); did not account for mixture of PFAS in analysis of exposures.
Rhee et al. (2023b) CA and HI, USA Enrolment, 1993–1996; Follow-up through 2018 Nested case–control	Nested within the MEC cohort; see Goodrich et al. (2022) Cases: 428; all RCC cases identified as of 2018 in the MEC study with available pre-diagnostic serum sample; incident cases identified through linkage with the SEER HI registry and the CA state cancer registry Controls: 428 controls who were MEC participants alive at the time of the matched case diagnosis and matched 1:1 to cases on sex, race/ethnicity, study centre, age and date at serum collection, time of serum collection, and fasting status Exposure assessment method: quantitative plasma measurements; analytical method was state-of-the-art and included isomers of PFOA and PFOS; single plasma sample collected before or after (21%) RCC diagnosis; all were analysed for 11 PFAS, including PFOA and PFOS; separate analysis of linear and branched isomers of PFOS and PFOA was performed but only the summed results were reported.	Kidney (RCC)	See Table 2.2	*Exposure assessment critique*: Key strengths were the availability of pre-diagnostic sample for most participants, plasma levels represent the combined exposure through all exposure pathways; measurement error low. Key limitations were that single samples may not reflect exposure at crucial windows in RCC disease development; if RCC development alters ADME of PFAS, there could be possible differential exposure misclassification for samples collected after diagnosis (21%). *Other strengths*: Large sample size; consideration of multiple PFAS adjustment; stratification by race/ethnicity. *Other limitations*: Some stratified analyses by race/ethnicity had low statistical power. *Other comments*: pre-diagnostic sample collected between 1994–2006; in 1994, samples were collected only among participants selected to be included in case–control studies, then between 2001–2006, samples were taken from all survivors in the MEC cohort.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Purdue et al. (2023) USA Enrolment, 1988–2017/ follow-up, through 2018 Nested case–control	Nested within a cohort of active-duty US Air Force servicemen with ≥ 1 serum sample stored in the Department of Defence Serum Repository between 1988 and 2017; further eligibility criteria were no prior history of cancer 1990–2018 and age ≤ 39 yr Cases: 530 overall (187 with two samples); TGCTs diagnosed in the Department of Defence Cancer Registry Controls: 530 overall (187 with two samples); one control per case density-sampled with replacement among eligible US Air Force servicemen on active duty and cancer-free as of the case diagnosis date and matched on date of birth, race/ethnicity (seven groups), year entering military service, year of baseline serum sample collection, and year of second sample collection (if applicable) Exposure assessment method: quantitative serum measurements; analytical method was state-of-the-art; stored serum samples were analysed for PFAS; in analyses of men with two samples, categories based on above or below the median at each time were evaluated	Testis	See Table 2.3	*Exposure assessment critique*: Key strengths were that serum levels represent the combined exposure through all exposure pathways; low potential for exposure misclassification; measurements of several PFAS compounds including PFOS and PFOA isomers; 2 repeated prediagnostic samples several years apart in a subset of the population; other military related PFAS exposures were considered (drinking-water). Key limitations were that for most participants only one serum measurement was available; no information on other exposures; no cumulative exposure metric and in particular inability to examine specific exposure windows in early life. *Other strengths*: Nested design; well characterized source population; large number of cases; serum samples obtained 0–19 yr before diagnosis; reasonable exposure contrast, analyses adjusted for other PFAS compounds, information on a range of covariates. *Other limitations*: Loss to follow-up (men leaving the military) and completeness of case ascertainment not quantified; large percentage (29%) excluded due to missing serum specimens; residual confounding by prenatal PFAS concentrations is an unresolved issue of potential importance; data on strong determinants of TGCT are lacking.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Madrigal et al. (2024) Finland Enrolment, 1986–2010/ follow-up, through 2016 Nested case–control	Nested in the Finnish Maternity Cohort, a national registry of women who donated serum during the first trimester of pregnancy (> 90% of pregnancies in Finland between 1983 and 2016) Cases: 400 cases were randomly selected from those diagnosed among women who donated serum for their first pregnancy and had a live, full-term birth delivered between 1987 and 2010, and who had no prior diagnosis of cancer at enrolment Controls: 400 controls individually matched on year of delivery (4–5 yr increments) and age at first birth (3 yr increments) Exposure assessment method: quantitative serum measurements; analytical method was state-of-the-art; a single serum sample was collected ≥ 3 yr before diagnosis	Thyroid (papillary)	See Table 2.4	*Exposure assessment critique*: Key strengths were that prediagnostic serum sample levels were measured, which represent the combined exposure through all exposure pathways; all samples analysed in the same manner; measurement error low; selected Group 1 carcinogens were measured in the blood samples. A key limitation was that single sample collected during pregnancy may not reflect exposure at crucial windows in cancer development, although only minor misclassification of long-term exposure over a period of 5–8 yr, based on a simulation study (Annex 3). *Other strengths*: Analyses controlled for 19 PFAS as well as several PCBs, organochlorine pesticides, and PBDEs; the age of the cohort during follow-up included peak years of thyroid cancer incidence. *Other limitations*: Low-level exposure with small exposure contrast; controls were not matched on the exact year of delivery, but on increments of 4–5 yr, which might affect comparison of PFAS levels because of temporal trends in levels of PFAS; data on pre-pregnancy body mass index, a thyroid cancer risk factor, was largely missing; no information was available on medical or environmental exposure radiation.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
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, one within the ATBC study, the other within PLCO study (for PLCO see Shearer et al., 2021) ATBC is a randomized trial in White male smokers (aged 50–69 yr at recruitment) to evaluate the chemopreventive effects of alpha-tocopherol and beta-carotene on lung cancer (n = 29 246) Cases: 251 from ATBC and 360 from 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 NDI Controls: 251 from ATBC, 360 from PLCO; in both cohorts, controls were individually matched on age and date of blood draws, and sex; there was additional matching on race in PLCO only Exposure assessment method: PFOA and PFOS levels were measured in serum using a non-targeted method; a single serum sample was collected before diagnosis	Pancreas (ductal adenocarcinoma)	See Table S2.5[a]	*Exposure assessment critique*: Key strengths were that prediagnostic serum levels represent the combined exposure through all exposure pathways; measurement error low; long follow-up time (median time between blood draw and diagnosis was 9–12 yr). Key limitations were that non-targeted analyses prevented comparison of sample concentrations across studies; single samples may not reflect exposure at crucial windows in cancer, although only minor misclassification of long-term exposure over a period of 5–8 yr, based on a simulation study (Annex 3); exposure assessment relied upon relative quantification of PFOA and PFOS, but relative measures have correlated well with targeted absolute concentration measurements. *Other strengths*: Information on potential confounders collected by trained staff through questionnaires and for height and weight in the ATBC Study; excellent case ascertainment. *Other limitations*: Low-level exposure with small exposure contrast; included only White men who smoke. *Other comments*: ATBC study participants were aged 50–69 yr at baseline and PLCO participants were aged 55–74 yr at baseline; the two nested case–controls were analysed separately.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
van Gerwen et al. (2023) Mount Sinai (NY), USA Enrolment, 2008–2021 Nested case–control	Nested within Bio*Me*, a medical record-linked biobank within the Institute for Personalized Medicine at the Icahn School of Medicine at Mount Sinai, including residents of New York City and the larger metropolitan area Cases: 88 adult patients diagnosed with thyroid cancer according to ICD codes 193 (9th revision) and C73 (10th revision) Controls: 88 healthy (non-cancer) participants, pair-matched on sex, age (± 5 yr), race/ethnicity, BMI, smoking status (ever/never), and calendar year of sample collection Exposure assessment method: PFOA and PFOS levels were measured in plasma using an untargeted analytical method; a single plasma sample was collected, only 35% of these were collected > 1 yr before diagnosis; all samples were analysed for 8 PFAS including PFOA and PFOS; analysed linear and branched isomers of PFOS, but not PFOA separately	Thyroid	See Table 2.4	*Exposure assessment critique*: Key strengths were that plasma levels represent the combined exposure through all exposure pathways; plasma samples were collected ≥ 1 yr before diagnosis for a subset, albeit small, of the cases. Key limitations were the use of untargeted analysis with semiquantitative measurements, so concentrations not known or comparable with other studies (however, participant exposures can be ranked); single samples may not reflect exposure at crucial windows in cancer development, especially since 65% samples were collected < 1 yr before diagnosis; if thyroid cancer development alters ADME of PFAS there could be possible differential exposure misclassification for those samples collected after diagnosis. *Other strengths*: Source population represents a diverse racial/ethnic and socioeconomic population; availability of histologic data for the cases; analyses adjusted for age, sex, race, and body mass index, and sample storage time, and, for some analyses, adjustment of analyses of specific PFAS compounds for other PFAS compounds. *Other limitations*: Small sample size, particularly for cases with plasma collected > 1 yr before diagnosis; short follow-up time; the possibility of detection bias, given cases were identified in a hospital and ambulatory practice setting (however, this was minimized by selection of controls from the same network, and patients and practitioners were unaware of PFAS measurements).

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
van Gerwen et al. (2023) Mount Sinai (NY), USA Enrolment, 2008–2021 Nested case–control (cont.)				*Other comments*: Analyses were conducted for all thyroid cancer cases, cases whose plasma collection was < 1 yr before diagnosis (cross-sectional group) and cases whose plasma collection was ≥ 1 yr before diagnosis (longitudinal group).
Winquist et al. (2023) 20 US states Enrolment 1998–2001; follow-up through 30 June 2015 Case–cohort	Case–cohort design within the CPS-II Lifelink Cohort (n =39 371); participants in the CPS-II Nutrition cohort (recruitment, 1992–1993) who were alive and agreed to a blood sample collection between 1998 and 2001 Cases: 3762 incident cases with a first cancer diagnosis of kidney, bladder, breast (females only), prostate (males only), or pancreatic cancer, leukaemia, or lymphoma, detected through self-report or NDI linkage and verified through medical records review or cancer registry Controls: 999; a sex-stratified simple random sample of 499 women and 500 men (~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: quantitative plasma measurements; analytical method was state-of-the-art, except no branched isomers of PFOA and PFOS were analysed; a single plasma sample was collected before diagnosis	Kidney (all combined) Kidney (RCC) Urinary bladder Prostate Breast (post-menopausal) Pancreas Haematological malignancies	See Table 2.2 See Table 2.2 See Table 2.2 See Table 2.3 See Table 2.4 See Table S2.5[a] See Table S2.6[a]	*Exposure assessment critique*: Key strengths were that prediagnostic plasma levels represent the combined exposure through all exposure pathways; measurement error low. A key limitation was that single samples may not reflect exposure at crucial windows in cancer development, although only minor misclassification of long-term exposure is expected over a period of 5–8 yr, based on a simulation study (Annex 3). *Other strengths*: Large number of cases. *Other limitations*: Survivor cohort with blood collected from persons mostly over aged 65, thus the study would not include persons who may have had PFOA- or PFOS-related cancer developed earlier in life, resulting in downward bias.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Vieira et al. (2013) OH and WV, USA 1996–2005 (incidence) Case–control	Cases: 25 107 index cancer cases were retrieved from cancer registries covering a community sample with relatively high exposure to PFOA because of contamination of drinking-water from the Parkersburg (WV) polymer-production plant; 18 different cancers were analysed Controls: number varied; 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, testis, pancreas, and liver) that have been associated with PFOA in studies in experimental animals or humans Two case–control studies are described, one including both WV and OH cases (first), the other only OH cases (second)	Kidney (urinary pelvis/ UUT) Urinary bladder Testis Prostate Breast Liver Pancreas Colon and rectum Thyroid Brain Leukaemia, multiple myeloma, NHL, melanoma Lung	See Table 2.2 See Table 2.2 See Table 2.3 See Table 2.3 See Table 2.4 See Table S2.5[a] See Table S2.5[a] See Table S2.5[a] See Table 2.4 See Table S2.6[a] See Table S2.6[a] See Table S2.6[a]	*Exposure assessment critique*: Key strengths were the availability of data on measured serum levels for a large number of residents of contaminated water districts, permitting analyses by approximate levels of exposure in each water district; exposure reconstruction for OH provided detailed exposure assessment; any misclassification is likely to be non-differential; the second case–control study based in OH estimated serum level for individuals based on a model shown to be able to predict well observed levels for 30 000 residents of the six contaminated water districts at one point in time (2005/2006, Spearman correlation 0.71). Key limitations were the assignment of an ecological exposure (by water district) in the first case–control study; the use of estimated individual serum levels in the 2nd case–control study based in OH, and the somewhat arbitrary assumption in that second study that the estimated serum levels 10 yr before case diagnosis were the most relevant, as well as the assumption that cases and controls had remained in the same residence for 10 yr; no other exposures (except smoking) were considered.

Table 2.1 (continued)

Reference, location, enrolment/follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology)	Exposure category or level	Comments
Vieira et al. (2013) OH and WV, USA 1996–2005 (incidence) Case–control (cont.)	Exposure assessment method: address at diagnosis was used to assign PFOA exposure; individuals from OH (about one third of the sample) were geocoded whereas individuals from WV were assigned exposure on the basis of geographical unit; water-district PFOA levels were available for all individuals; for individuals from OH, PFOA serum values could be estimated on the basis of exposure models (Shin et al., 2011a, b) A five-level exposure variable was created			*Other strengths*: The large number of incident cancers from cancer registries; the reasonably large number of exposed cases in the contaminated water districts for many specific cancers (although for analyses of rarer cancers by categories of exposure small numbers were sometimes an issue); the large exposure contrasts between water districts as well as within individuals in the second case–control study. *Limitations*: Fairly few potential confounders used in the analyses; the use of controls with cancer was a less marked limitation.

ADME, absorption, distribution, metabolism, and excretion; AL, Alabama; approx., approximately; APFO, ammonium perfluorooctanoate; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention; BMI, body mass index; CA, California; CHDS, Offspring in the Child Health and Development Studies; CI, confidence interval; CNS, central nervous system; CPS-II, Cancer Prevention Study II; E3N, Etude épidémiologique auprès de femmes de la Mutuelle générale de l'Education nationale; HCC, hepatocellular carcinoma; HI, Hawaii; ICD, International Classification of Diseases; IQR, interquartile range; JEM, job-exposure matrix; MEC, Multiethnic Cohort; MHT, menopausal hormone therapy; MN, Minnesota; mo, month(s); NDI, National Death Index; NHANES, National Health and Nutrition Examination Survey; NHL, non-Hodgkin lymphoma; NY, New York; OH, Ohio; PCB, polychlorinated biphenyl; PBDE, polybrominated diphenyl ethers; PFCA, perfluoroalkyl carboxylic acid; PFDA, perfluorodecanoic acid; PFDoA, perfluorododecanoic acid; PFHpA, perfluoroheptanoic acid; PFHpS, perfluoroheptanesulfonic acid; PFHxS, perfluorohexanesulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PFSA, perfluorosulfonic acid; PFTrA, perfluorotridecanoic acid; PFUnA, perfluoroundecanoic acid; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; POSF, perfluorooctanesulfonyl fluoride; RCC, renal cell carcinoma; SEER, Surveillance, Epidemiology, and End Results; SMR, standardized mortality ratio; SNP, single-nucleotide polymorphism; TFE, tetrafluoroethylene; TGCT, testicular germ cell tumour; UK, United Kingdom; USA, United States of America; WI, Wisconsin; WV, West Virginia.

[a] Tables S2.5, S2.6, and S2.7 are available in Annex 4, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.who.int/636.

282 ng/mL in workers with all work, some work, and no work, respectively, in PFOA production) versus 4.5 ng/mL in blood donors in the same area (Raleigh et al., 2014). The toxicokinetics of PFOA were not considered when modelling the cumulative exposure metric, which was based solely on air concentration and duration of exposure.

Vital status was ascertained by the National Death Index (NDI) until the end of 2008 for 99.3% of the population, and cases of incident cancer were identified by linkage to the Minnesota Cancer Surveillance System and the Wisconsin Cancer Reporting System; reporting of cancer had been mandatory since 1988. The case capture of the cohort was estimated to be about 85%, and higher for highly exposed workers (individual out-of-region migration data were not available).

Standardized mortality ratios (SMRs) for cancers of the prostate, pancreas, urinary bladder, female breast, kidney, and liver were estimated from 1960 through 2008 using the entire Minnesota population as the referent.

The follow-up period for cancer incidence was from 1 January 1988 until the end of 2008. In total, 665 incident cancers of the prostate, kidney, pancreas, bladder, liver, breast, testis, and thyroid were identified. [Estimates for testicular, thyroid, and liver cancer were not provided.] Relations between cancer-specific risk and time-dependent cumulative APFO exposure were estimated by Cox regression, with adjustment for sex, year of birth, and age.

[The Working Group noted several strengths associated with this primarily male cohort, including individual assessment of cumulative air exposure, with some evidence that this exposure metric was correlated with serum concentration; limited and minimal co-exposure to tetrafluoroethylene (TFE); a relatively large number of some incident cancers in the exposed cohort (prostate, bladder, breast); a reference population with socioeconomic characteristics that were similar to those of the exposed population; and a long follow-up period. Limitations were the lack of information on dermal exposure; the fact that this was a survivor cohort (in which follow-up for cancer incidence began many years after the start of follow-up) with the potential for downward healthy-worker survivor bias; the lack of data on workers who left Minnesota or Wisconsin (although the out-migration of the workers with higher exposure was similar to that of the reference workers); and the small numbers of some cancers (kidney, pancreas, liver, testes, and thyroid). Risk estimates were most probably biased towards the null, because measurement error is likely to be non-differential. Finally, a discrepancy was noted between the description of the adjustment for Cox regression models in the text (age, year of birth, and sex) and that in the tables (age and year of birth only).]

2.1.2 PFOS-production workers (Decatur, Alabama, USA)

Alexander et al. (2003) studied a cohort of 3512 production workers who had been exposed to perfluorooctanesulfonyl fluoride (POSF), which is degraded or metabolized to PFOS, at a plant in Decatur, Alabama, USA, that produced speciality films and fluorochemicals in two different facilities. All the cohort members had worked at the plant between 1961 and 1997. The study was limited to those who had worked for ≥ 1 year at the plant (n = 2083; men, 83%). Follow-up for mortality was conducted between 1961 and 1998. Exposure was estimated using serum concentration of PFOS, based on a sample of 232 employees randomly selected for serum sampling in 1998, with 80% participation (chemical plant, n = 126; film plant, n = 60). The authors noted that there was also exposure to PFOA in this subsample, at slightly lower levels; serum PFOA concentrations correlated well with serum PFOS concentrations. PFOA manufacturing at this plant started in 1998; this was the same year that serum samples were

collected, but there may have been incidental exposure previously. Chemical plant workers had high serum concentrations of PFOS (geometric mean, 0.9 ppm [900 μg/L]), whereas film plant workers had lower concentrations (geometric mean, 0.1 ppm [100 μg/L]). On the basis of these measurements, a job-exposure matrix (JEM) was developed for all workers, jobs being classified into three exposure groups. The groups were defined as having: (i) no or minimal workplace exposure to PFOS (e.g. jobs in film plant); (ii) low potential workplace exposure to PFOS (e.g. engineers, quality control technicians, environmental health and safety workers, administrative assistants, managers); or (iii) high potential workplace exposure to PFOS (e.g. cell operators, chemical operators, maintenance workers, mill operators, waste operators, crew supervisors). Cumulative exposure (duration multiplied by intensity of exposure) was estimated after accounting for changing jobs over time, based on assigned weights of 1, 3, and 10, respectively, for jobs in the three exposure groups. The SMRs were calculated by comparing the mortality of all workers with that of residents of Alabama; in further analyses, each worker subgroup was compared with the Alabama population. Of the 2083 workers included, 47% (982) had worked at some time in jobs in which exposure to PFOS was considered high, 14% (289) worked in low-exposure areas, but never held a job in the high-exposure areas, and 812 (39%) were considered to have no or minimal workplace exposure to fluorochemicals. In the cohort, 145 deaths were identified (including 39 deaths from cancer); there were 65 deaths in the high-exposure group, 27 in the low-exposure group, and 53 in the non-exposed group. Deaths were ascertained using the NDI and the US Social Security Death Index. There were 3 deaths from bladder cancer, which was the cause of death that showed the highest excess, compared with the reference population.

Alexander and Olsen (2007) further followed the PFOS cohort studied by Alexander et al. (2003), focusing on bladder cancer. A postal questionnaire sent to all living current and former employees of the facility in 2002 (n = 1895) to identify cases of incident bladder cancer was returned by 1400 cohort members (response rate, 74%). The underlying cause of death (ascertained through the NDI) from death certificates for 188 deceased workers was used to identify bladder cancer decedents. The analysis drew on data from questionnaire respondents and from decedents (1588 cohort members); 11 cases of bladder cancer were included (6 identified in the questionnaire and 5 identified using death certificates). Cumulative exposure was analysed for the same three groups as before (none, low, high). Serum concentrations of PFOS were estimated from a subsample, as described in Alexander et al. (2003). Job categories assigned to no, low, and high exposure had geometric mean serum PFOS concentrations of 0.11–0.29 μg/mL, 0.39–0.89 μg/mL, and 1.30–1.97 μg/mL, respectively (slightly different from the values reported in Alexander et al., 2003). The incidence of bladder cancer was analysed using national rates from 1970 to 2002, adjusted for age, sex, and calendar year. Internal analyses used Poisson regression, adjusting for age and sex.

[The Working Group noted that this cohort, the same in both studies, had large exposure contrast, and that some serum measurements were available, although they were not used in the exposure assessment. Cancer incidence data were published by Alexander and Olsen (2007), who also used internal comparisons. Limitations included the small number of observed cancers. Alexander et al. (2003) limited their study to mortality, reporting a large excess for bladder cancer on the basis of only 3 cases, and analyses only against national rates. Alexander and Olsen (2007) studied only 11 cases of incident bladder cancer (with no bladder cancer excess). Another limitation was co-exposure to PFOA, which was measured at somewhat similar levels to those of PFOS in a sample of employees in 1998

(Alexander and Olsen, 2007), and correlated with PFOS serum concentrations – although PFOA was not produced until 1998 and earlier levels were probably lower. Both studies were limited by sparse data on smoking, but there were fewer concerns about confounding by smoking in the study by Alexander and Olsen (2007) because the authors conducted an internal analysis (which is less subject to confounding) as well as external comparisons. Another limitation was the failure to adjust for other PFAS in the plant, and in general for other workplace exposures in a chemical plant. The Working Group also noted that perfluorooctanesulfonyl fluoride (POSF), the predecessor of PFOS used in this plant, is itself a reactive compound and may be toxic.]

2.1.3 *Polymer-production workers in Parkersburg (West Virginia, USA)*

The polymer-production plant in Parkersburg, West Virginia, USA, was a facility producing several types of polymer from a wide variety of monomers and other chemicals; it began operating in 1948. Workers in the plant, especially those involved in various activities related to the production of certain polymers or copolymers, were exposed to PFOA. Steenland and Woskie (2012) conducted an updated investigation of mortality in a previously studied cohort of plant workers (Leonard et al., 2008). Briefly, this cohort included 6027 workers who were employed at the plant for ≥ 1 day between 1948 and 2002. The analyses by Steenland and Woskie (2012) focused on 5791 workers (women, 19%) with sufficiently detailed work histories for PFOA exposure estimation and non-missing values for date of birth. Workers were followed for mortality from 1952 through 2008; deaths were identified using the NDI (for 1979 or later), or from death certificate data (from the US Social Security Administration and state death certificates) for earlier years. For the PFOA exposure assessment, the investigators used serum PFOA concentrations determined from 2125 blood samples collected from 1308 workers between 1979 and 2004 to produce regression models estimating serum PFOA levels for eight different combinations of job category and job group over time. Comparisons of modelled PFOA levels with the serum concentrations measured for this study population demonstrated high agreement (Spearman rank correlation coefficient, $\rho = 0.8$) (Woskie et al., 2012). The SMRs for mortality from cancer overall and for specific cancers – liver, pancreas, lung, breast, prostate, testis, kidney, and bladder, and mesothelioma, non-Hodgkin lymphoma (NHL), and leukaemia – were calculated for workers in the cohort (overall and by quartiles of cumulative estimated PFOA exposure) compared with workers at other plants in the Appalachian region and managed by the same company, as well as with reference rates for the general US population. A total of 1084 deaths were recorded during follow-up (with a mean length of follow-up of 30 years). In a subsequent investigation for a subset of 3713 workers, who were all included in both the occupational cohort and the C8 Science Panel study (described in Section 2.1.5) by Steenland et al. (2015), the incidence of selected cancers for which there were 20 or more cases during follow-up (melanoma and cancers of the bladder, colorectum, and prostate) was evaluated for workers aged from 20 years or from the year 1951 (whichever was later) until the period (2008–2011) when interviews were conducted with workers or their next of kin (the latter making up 6% of the interviews included in the analysis). Analyses focused on self-reported cancers or cancers reported by the next of kin that were validated by a review of medical records (355 valid cases). Cox proportional hazards regression analyses were used to estimate the risks of developing specific cancers in relation to quartiles of estimated cumulative PFOA exposure with age, as the underlying

timescale, with adjustment for sex, race, education, body mass index (BMI), and time-varying smoking and alcohol consumption.

[The Working Group noted several strengths of this study, including the detailed historical exposure assessment and the ability to evaluate associations between PFOA and cancer in a population exposed to levels much higher than those in the general population. The estimated average annual serum PFOA concentration in the cohort overall (mean, 350 ng/mL) was nearly two orders of magnitude higher than the measured serum PFOA concentration (geometric mean, 3.9 ng/mL) reported in the US National Health and Nutrition Examination Survey (NHANES) in 2003–2004 (Calafat et al., 2007). The modelled PFOA exposure levels were highly correlated with serum PFOA concentrations in the more than 2000 measurements available for this study population (Spearman correlation, 0.8), indicating a valid model. Exposure to PFOS or other PFAS was not characterized in the cohort but was considered likely to be low, given the nature of the polymer-production work at the plant at the time of the study. Although some processes in the production of fluoropolymers involve TFE (classified by IARC as *probably carcinogenic to humans*, Group 2A; IARC, 2016), the Working Group noted that, owing to its high volatility and explosive potential, processes involving TFE were conducted in a separate area of the plant with limited access and that exposure control measures (e.g. closed systems) were used to prevent emissions of this gas. Therefore, workers' exposure to TFE in the plant was probably minimal during normal operations.

The use of a reference group of workers from other plants in the same region was also a strength of the mortality analysis, in terms of addressing the potential downward bias of the risk estimates because of the healthy-worker effect. However, exposures to other potential carcinogens were not assessed for the reference workers; if such exposures were higher or more prevalent in the reference group, or both, then the resulting risk estimates for some cancers could have been biased towards the null. The Working Group noted that mortality from mesothelioma was elevated in the cohort (on the basis of 6 deaths among the PFOA-exposed workers), suggesting possible exposure to asbestos in this population. However, the potential for confounding by asbestos exposure in analyses for other cancer sites of particular interest with respect to PFOA was considered likely to be low. Other limitations of the mortality analysis included the inability to evaluate some cancers because of the small numbers of deaths, in particular for cancers among women (given the small number of female workers included in the cohort) and for cancers that are less likely to be fatal (e.g. testicular cancer).]

[The Working Group did not consider the overlap between the subset of workers included in both the investigation of cancer incidence by Steenland et al. (2015) and the C8 Science Panel investigation (Barry et al., 2013) to be a major limitation, given that workers comprised a small proportion of the population in the latter study. In addition to the strengths of the PFOA exposure assessment already noted, a strength of the study by Steenland et al. (2015) was the ability to control for established cancer risk factors (e.g. BMI, smoking, and alcohol consumption) that might have confounded the associations between PFOA and specific cancers. The use of medical records to confirm self-reported cancer diagnoses probably reduced non-differential outcome misclassification, thereby potentially improving the ability to detect any true associations with PFOA. However, this approach might also have resulted in the underascertainment of cancer cases. Taken together with the relatively small sample size, this might have further limited the statistical power for analyses of specific cancers, and there were too few cases to evaluate cancers of the kidney and testis. Finally, the Working Group noted that the subset of workers in this analysis were less likely to have died than those

who were not included, and also differed with respect to several demographic characteristics (e.g. those who were included were younger and more likely to be female), raising the possibility of selection bias if the exposure–response patterns differed between the workers who were included and those who were excluded. The potential effect of such selection bias (if present) on the direction and magnitude of the reported risk estimates was unclear.]

2.1.4 Diet, Cancer, and Health Cohort

Eriksen et al. (2009) studied data collected for 57 053 participants enrolled in a prospective Danish cohort between 1993 and 1997 – the Diet, Cancer, and Health Cohort. Approximately 160 000 potential participants were recruited from the general population, with data accessible from a national database, in two counties in Denmark (Aarhus and Copenhagen) (Tjønneland et al., 2007); of these, 57 053 agreed to participate. Participants were Danish citizens aged 50–65 years with no previous cancer diagnosis at enrolment. Plasma concentrations of PFOA and PFOS were measured at baseline using liquid chromatography and tandem mass spectrometry (LC-MS/MS). Virtually all samples had concentrations above the limits of detection, and 50 random samples were measured twice, with good agreement between measurements. Cancer incidence data for the cohort were available from the Danish Cancer Register. Investigators identified 1240 cases of cancer of the prostate, bladder, pancreas, or liver (in 1111 men and 129 women), diagnosed in 1993–2006, with a follow-up period of 0–12 years (median, 7 years) after baseline. Cancers of the prostate, bladder, pancreas, and liver (713, 332, 128, and 67 cases, respectively) were analysed in relation to baseline plasma concentrations of PFOA and PFOS. A subcohort of 680 men and 92 women who were randomly selected and had not had a diagnosis of cancer at the end of the follow-up period were used as controls for the cancer cases, according to a case–cohort design. Median plasma levels (5th and 95th percentiles) of PFOA and PFOS in those not later diagnosed with cancer were 6.6 (3.0–13.0) ng/mL and 34.3 (16.2–61.8) ng/mL, respectively. Information on potential confounders (BMI, smoking, occupation, education, alcohol intake, diet) was collected using a questionnaire and differed according to cancer type. Analyses were conducted by quartile of PFOA or PFOS concentration. Linearity was first evaluated using spline models; where there was no significant deviation from linearity, a linear trend was assessed using a continuous variable for plasma PFOA or PFOS concentration.

[The strengths of this study included the use of a large cohort with numerous incident cancers identified using a reliable cancer registry (n = 1240), the measurement of plasma PFOA and PFOS concentrations at baseline, good control for confounders (e.g. age, sex, BMI, detailed smoking data, diet), internal comparisons, and little loss to follow-up. Limitations were a relatively low exposure contrast in a population with background exposure levels, the characterization of exposure on the basis of a single measurement at enrolment, and a somewhat limited period of follow-up.]

2.1.5 C8 Science Panel study

The C8 Science Panel conducted a cohort study of community residents and workers exposed to PFOA (C8 is a synonym of PFOA) from a fluoropolymer-production plant in the Mid-Ohio Valley on the border of West Virginia and Ohio, USA (Barry et al., 2013). Between the 1950s and the early 2000s, PFOA was released from the plant in air emissions and as liquid and solid waste, contaminating local public water supplies and private wells. A settlement from a class action lawsuit initially funded a large community health study known as the C8 Health Project, which was conducted in 2005–2006

(Frisbee et al., 2009). The C8 Science Panel investigated a cohort of adults aged ≥ 20 years enrolled in the C8 Health Project (Winquist et al., 2013), as well as individuals who were employed in the plant and included in an occupational cohort, as described in Section 2.1.3; analyses were restricted to individuals who had completed at least one subsequent survey between 2008 and 2011 and who had retrospective environmental or occupational PFOA exposure estimates. These surveys solicited detailed information on demographic and health characteristics; an extensive residential history was included. Of the 32 254 individuals included in the analytical cohort, 28 541 were community cohort participants and 3713 had worked at the plant. For community participants, annual estimates of serum PFOA concentrations were calculated using an environmental fate and transport model for each year of life between 1952 and 2011, as described in Shin et al. (2011a, b). For the workers, estimates of occupational PFOA exposure were calculated as described in Section 2.1.3 and combined with environmental exposure estimates. Barry et al. (2013) conducted an investigation of cancer incidence among cohort participants, who were followed up from age 20 years onwards for an average of 33 years. For this analysis, cancers reported by participants in the surveys conducted in 2008–2011 were confirmed by consulting state cancer registries in Ohio and West Virginia or a review of medical records; a total of 2507 validated cancer diagnoses were identified and included in the statistical analyses. Proportional hazard regression models were used to estimate the risk of developing specific cancers at each year of age in relation to estimated serum PFOA concentrations (modelled per 1-unit increase on the natural log scale) both up to the time of diagnosis or censoring (unlagged analysis) and for estimated exposures 10 years in the past (lagged analyses). Exposure–response associations based on quartiles of estimated PFOA concentrations were also reported for kidney, testicular, and thyroid cancers. All models were run with age as the timescale and were adjusted for sex, education, 5-year birth year period, and time-varying smoking and alcohol consumption. Data from this study and a nested case–control study of Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO study) (Shearer et al., 2021) were combined for a pooled analysis of renal cell carcinoma (RCC) (Steenland et al., 2022).

[The Working Group considered this cohort study to be highly informative, in light of several important features and strengths. With 32 254 participants, it is, to the knowledge of the Working Group, the largest cohort to evaluate cancer risk in community members and workers with high exposure to PFOA. Based on measurements of serum PFOA concentration from the C8 Health Project in 2005–2006, exposure levels were found in the investigation of Barry et al. (2013) to be considerably higher in the overall cohort, compared with the general US population (medians of 26.1 ng/mL and 4.0 µg/L [ng/mL], respectively) (Winquist et al., 2013). Among C8 Health Project participants (Frisbee et al., 2009), serum concentrations of perfluorohexanesulfonic acid (PFHxS) and perfluorononanoic acid (PFNA) were more modestly elevated, relative to the general US population (geometric means were 39% and 73% higher, respectively, compared with 2003–3004 US NHANES data), and serum PFOS concentrations were similar to those observed in the general population. A particular strength of the C8 Science Panel study was the detailed characterization of estimated serum PFOA concentrations from 1952 or the participant's year of birth (whichever was later) through 2011; modelled serum PFOA concentrations corresponded well (Spearman correlation, 0.71) with measured serum concentrations for the cohort in 2005–2006 (Winquist et al., 2013). This assessment of PFOA enabled analyses of exposure–response associations with cancer incidence in both unlagged and lagged analyses. The adjustment for established cancer risk

factors (e.g. smoking, alcohol consumption) that might have confounded the associations between PFOA and specific cancers was also a strength of the analyses in this cohort. A strength of the outcome ascertainment was the validation of self-reported cancer cases by linking with Ohio and West Virginia cancer registries and medical chart reviews; this approach could have reduced the potential for attenuation of risk estimates, owing to non-differential disease misclassification. Finally, there were high rates of participation in the target populations of community members in the C8 Health Project and workers in the occupational cohort (81.5% and 72.9%, respectively) (Winquist et al., 2013), reducing the likelihood of selection bias affecting the direction or magnitude of the observed associations. The Working Group also noted several limitations of this study. Direct measurements of serum PFOA concentrations were available only in 2005–2006; this might not have reflected PFOA exposure during etiologically relevant time periods when data on measured concentrations were not available. However, as noted previously, modelled estimates and measurements of serum PFOA concentrations were highly correlated, and any exposure misclassification would be non-differential and more likely to bias risk estimates towards the null. Also, given the design of the study as a survivor cohort, community members and workers who died before the cohort enumeration would not have been included, resulting in the potential underascertainment of cancers with a high rate of fatality in this population. However, given that PFOA exposure was considered to be unlikely to be related to survival time, the effect of this aspect of the study design on the resulting risk estimates was considered likely to be minimal (Barry et al., 2015). Despite the large sample size, the study had relatively limited statistical power to detect associations with some less common cancers, and for prospective analyses of cancer risk (i.e. for cases diagnosed after enrolment in the C8 Health Project). Finally, the Working Group noted that the cancer cases included in this study probably overlapped with those included in the study by Vieira et al. (2013), although the case ascertainment approaches differed for the two studies. The study of Barry et al. (2013) included self-reported cases of cancer that were confirmed either by linking with West Virginia or Ohio cancer registries or by medical record abstraction, including those diagnosed in other states or before the availability of data from state registries. In contrast, the study of Vieira et al. (2013) considered cancer cases from 13 counties in West Virginia and Ohio (including both contaminated water districts and other adjacent areas without water contamination) that were identified from West Virginia and Ohio cancer registries for the years 1996–2005. However, the degree of overlap of the cases included by Barry et al. (2013) and Vieira et al. (2013) was unknown.]

2.1.6 Pooled cohort of international tetrafluoroethylene workers

This pooled cohort of international TFE workers included workers employed at one or more of six TFE synthesis and polymerization sites in North America and Europe (Gendorf, Germany; Dordrecht, the Netherlands; Spinetta Marengo, Italy; Thornton-Cleveleys, UK; Bayonne, New Jersey, USA; Parkersburg, West Virginia, USA) that, at the time of the study, comprised the entire population of workers in TFE manufacture in Europe and the USA (Consonni et al., 2013). TFE is a flammable and explosive gas and is mainly used in closed systems as a monomer in the production of fluorinated polymers, including polytetrafluoroethylene (PTFE), which is widely used in consumer products such as waterproof and breathable membranes for clothes and as coatings on carpets. APFO, the ammonium salt of PFOA, is used as a polymerization aid in PTFE production.

Excluding 778 female workers and 122 male workers with missing data, the cohort included

5879 male workers who, for ≥ 1 day (in three plants), 6 months (in one plant), or 1 year (the other plants), were employed at a TFE-manufacturing facility in 1950–2002. Enrolment of eligible workers was based on company rosters. [Completeness of enrolment of eligible workers was not reported.]

The synthesis and polymerization of TFE entail potential exposure to the TFE monomer and to PFOA, which is released from its ammonium salt (APFO) during production. Individual semiquantitative levels of work-related exposure to TFE and PFOA were estimated using expert judgement to create a plant- and job-specific exposure matrix with yearly estimates (in arbitrary units) of exposure, declining by 10% for each decade from the start of TFE production until 2002 (Sleeuwenhoek and Cherrie, 2012). Only a few measurements of TFE air concentrations at the various plants were available to assist the exposure assessment (Sleeuwenhoek and Cherrie, 2012). The number of workers who had ever been exposed to TFE was 4773 (81.2%), while 1081 (18.4%) workers had never been exposed. Among workers who had ever been exposed to TFE, 4205 were also exposed to APFO. All workers exposed to APFO were also potentially exposed to TFE, mainly through accidental leaks, from opening of autoclaves, and from decomposition of PTFE. There was a high correlation between TFE and PFOA exposure intensities (Sleeuwenhoek and Cherrie, 2012), based on arbitrary units (Spearman correlation, 0.72). At two of the plants (Gendorf, Thornton-Cleveleys), previous exposure to vinyl chloride monomer might have occurred. No information was available on occupational exposure to agents known to promote the development of leukaemia. The largest TFE-production site (Parkersburg, West Virginia, USA) accounted for the largest number of unexposed workers.

Ascertainment of vital status (complete for 98.8% of the study population) and, where appropriate, cause of death was determined by epidemiology units at the company level (UK, USA), by university epidemiology departments (Germany, the Netherlands), or by local health units (Italy), through record-linking procedures or individual follow-up. [Record-linking procedures are expected to give a higher degree of completeness.] The mortality follow-up period was 1950–2008. Causes of death were recorded from death certificates according to the International Classification of Diseases (ICD) ICD-9 or ICD-10 classification. The mean values were 55 years for attained age, 9.2 years for duration of exposure to TFE, and 23 years for time since first exposure to TFE. For selected cancers, SMRs compared with national data were provided for ever APFO-exposed ($n = 4205$) and by cumulative APFO exposure, divided into four levels, among ever TFE-exposed and among three categories (low, medium, high) of cumulative TFE exposure ($n = 4773$). There were 534 deaths among men who had ever been exposed to APFO, of which 159 deaths were caused by cancer.

[The cohort included all TFE-production and polymerization sites worldwide at the time of the study and benefited from near-complete follow-up. Limitations were mainly related to the semiquantitative exposure assessment, with only a few TFE and no PFOA measurements available, no validation of estimated exposures by measurement, a low statistical power to detect less common cancers, and a high correlation between potential exposure to TFE monomer (classified as *probably carcinogenic to humans*, Group 2A; IARC, 2016) and PFOA. However, exposure to TFE among workers at the Parkersburg facility was considered very unlikely for the vast majority of workers, because processes involving TFE were conducted in a separate area of the plant with limited access, and strict hygiene-control practices (e.g. closed systems) were used to prevent emissions of this highly flammable and explosive compound. Moreover, possible exposure to other occupational and non-occupational carcinogens was not accounted for.]

2.1.7 Danish National Birth Cohort

The Danish National Birth Cohort was recruited for a nationwide cohort study that included data on about 100 000 pregnancies that occurred from 1996 through 2002 (Olsen et al., 2001). Approximately 50% of Danish women who were pregnant during this period were invited to participate when consulting their general practitioner during their first pregnancy visit, usually at weeks 6–12 of gestation; of those invited, about 60% agreed to participate in the cohort. Study participants completed questionnaires on lifestyle factors and environmental exposures, including diet, body size, alcohol intake, and smoking history, during a computer-administered interview at two time points during pregnancy as well as at two time points after pregnancy (6 and 18 months after delivery). Blood samples were collected once during the first trimester and once during the second trimester of pregnancy; cord blood was also collected at delivery.

A nested case–control study was designed to evaluate serum PFAS from blood samples collected during the first trimester of pregnancy in relation to risk of premenopausal breast cancer in mothers recruited to the Danish National Birth Cohort. Linkage to a nationwide cancer registry was used to identify 250 women who had received diagnoses of premenopausal breast cancer, with follow-up until 2010. These 250 women with breast cancer were matched to 233 randomly selected controls, with frequency-matching by age and limitation to those who were nulliparous (Bonefeld-Jørgensen et al., 2014). [The Working Group interpreted this nulliparity restriction to refer to women who, at the time of their blood sample during pregnancy, had not had a previous live birth.] In a follow-up analysis focused on gene–environment interaction, 72 of the original cases included as part of the study of Bonefeld-Jørgensen et al. (2014) were excluded because they had been withdrawn from the Danish National Patient Register for unknown reasons, resulting in a case group of 178, with a control group of 233 (Ghisari et al., 2017). [The Working Group noted that the removal of the 72 cases probably had no implication on the matching, since the age distribution among cases and controls appeared to be balanced after this removal (Ghisari et al., 2017).] Bonefeld-Jørgensen et al. (2014) conducted sensitivity analyses excluding these 72 cases and observed some differences in their findings. [The Working Group prioritized the results presented by Ghisari et al. (2017), given the withdrawal of some of the women from the study; the article by Bonefeld-Jørgensen et al. (2014) was, therefore, not tabulated as part of this monograph.]

The first-trimester blood samples (taken some time in weeks 6–14 of gestation) were stored and used for PFAS analysis. For cases, the average age at blood sampling was 30.6 years (range, 21–42 years), and the average at diagnosis was 41.1 years (range, 32–53 years). Serum concentrations of PFAS, including PFOA and PFOS, were assessed using LC-MS/MS. The association between PFAS and breast cancer risk was evaluated using unconditional logistic regression models, with PFAS concentrations transformed using a natural log transformation characterized as a continuous variable, and with adjustment for potential confounders (age at blood sampling, BMI before pregnancy, gravidity, oral contraceptive use, age at menarche, smoking during pregnancy, alcohol intake during pregnancy, maternal education, physical activity).

[The Working Group noted some strengths of this analysis, including a fairly large sample size of premenopausal cases of breast cancer and the measurement of PFAS serum concentration years before breast cancer diagnosis. The study included only a single PFAS concentration as a measure of exposure, assessed during the first trimester of pregnancy; in itself, this is not expected to introduce confounding because it was collected early in pregnancy (Sagiv et al., 2018). Further, the Working Group noted that

while only having a single measure of PFAS may be considered a limitation, there is some evidence, from analyses of repeat sampling of PFOA, that a single sample may represent long-term averages over a 5–8 year period, with potential misclassification resulting in only minor bias towards the null (Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636). However, a concern remained that single measurements of PFOA or PFOS, despite their long half-life, might not represent average exposure over the longer periods that may be relevant to cancer etiology. Although many key plausible confounders were adjusted for in the study, it would have been better, given temporal trends in PFAS, to match or adjust for the year of blood sampling and consider adjustment for other PFAS. Pregnancy might be an important window of susceptibility for breast cancer, but this design might also limit the comparability of these results with those obtained using measurements for serum samples collected from non-pregnant women. There was a lack of data on cancer subtypes (e.g. histology, hormone-receptor status), and results were presented for all cancer subtypes combined, which could mask cancer subtype-specific associations and bias the overall risk estimate towards the null. Other limitations include relatively small exposure contrasts in a population with background exposures, and the potential non-applicability of the findings to postmenopausal breast cancer. The reasoning behind the exclusion of the 72 women, who might, in fact, not have had breast cancer is a limitation and resulted in a smaller sample size, but the Working Group noted that although the results of analyses slightly differed with and without them, the conclusions remained similar.]

2.1.8 California Teachers Study

The California Teachers Study (CTS) is an ongoing prospective cohort study that includes women who were current and former public-school professionals in California, USA, who were enrolled in the California State Teachers Retirement System in 1995 (Bernstein et al., 2002). A self-administered baseline questionnaire was posted to 329 684 women, with approximately 40% responding (Bernstein et al., 2002). In 1995–1996, 133 479 women were enrolled in the cohort by completing the questionnaire. The baseline questionnaire covered menstrual and reproductive history, use of exogenous hormones, diet, smoking, alcohol use, height, weight, family history of cancer, and individual's medical history. The mean baseline age for the study participants was 54.1 years (standard deviation, 14.8 years); the ethnicity of the cohort was primarily non-Hispanic White (86.7%) (Bernstein et al., 2002).

Study participants were followed up annually to update details on cancer diagnoses, deaths, and residential moves. Participants were also sent more detailed follow-up questionnaires, focusing on exposures of interest. The study also uses linkages to state and national mortality files and reports from next of kin for dates and causes of death (Hurley et al., 2018).

A nested breast cancer case–control study (913 cases, 1270 controls) was conducted within the CTS and included blood sample collection and an interview-administered questionnaire (Hurley et al., 2018). Women were eligible if they had received a diagnosis of invasive breast cancer between 1 January 2006 and 1 August 2014, were aged < 80 years at the time of diagnosis, had no previous history of breast cancer at the time of entry into the CTS, and had resided in California continuously from the time of cohort entry to the time of diagnosis. Breast tumours were identified by linkage to the California Cancer Registry and were confirmed by pathology (99%). Thus,

as long as participants remained in California, they were actively followed up for cancer diagnosis. Controls were randomly sampled with frequency-matching by 5-year age group, race or ethnicity, and the California Cancer Registry regional entry of residence. Participation rates were 55% for controls and 65% for cases.

Phlebotomist-collected blood samples were stored and assayed for serum PFAS using LC-MS/MS. For the cases, blood samples were collected, on average, 35 months after a diagnosis of breast cancer (range, 9 months to 8.5 years). Samples collected before October 2011 were excluded, owing to concerns regarding time trends in PFAS levels and time trends in sample collection by case status, primarily affecting controls. [The Working Group noted that it was unlikely that this exclusion would introduce any bias, since it resulted largely in the exclusion of controls, rather than cases.] After exclusions, the final sample size was 902 cases and 858 controls. The associations between each PFAS detected in the serum samples and the risk of breast cancer were estimated using unconditional logistic regression (given the breaking of initial matching), adjusting for confounders (age at baseline, race or ethnicity, region of residence, blood draw date, the square of blood draw date, season of blood draw, total pack-years smoking, BMI, family history of breast cancer, age at first full-term pregnancy, menopausal status at blood draw, and pork consumption). Concentrations of PFAS were considered both as continuous variables ($\log_{10}$-transformed) and as categorical variables (based on tertiles of PFAS concentrations in the controls). Estimates were stratified by menopausal status at blood draw, estrogen receptor and progesterone receptor (ER/PR) status of the tumour, and other factors.

[The Working Group noted that the strengths of this study included a large number of cases identified through the cancer registry and population-based controls. Other strengths included adjustment for a large number of potential confounders and the stratified analysis by a number of important factors regarding breast cancer, including hormone-receptor status of the tumour. The primary limitation was the use of a single blood sample collected between 9 months and 8.5 years after diagnosis and presumably after at least initial treatment, both of which might affect blood PFAS concentration, and that this did not reflect the probable etiologically relevant period. This limitation rendered the study of minimal informativeness.]

2.1.9 Perfluorocarbon-production workers

Girardi and Merler (2019) studied the association between PFAS (including PFOA and PFOS) and mortality in a cohort of 462 male employees who had worked ≥ 6 months before 2009 in a factory in Italy. There were 14 658 person-years and 107 deaths, with an average follow-up time of 31.7 years. The factory had produced PFOA, POSF, and other chemicals (including one other PFAS, perfluorobutylsulfonyl fluoride) since 1968. Follow-up covered the period 1970 to 2018. Information on the underlying causes of death was obtained from the regional epidemiological department and, if not available, from the local health unit register for deaths after 1990, or from the complete death certificate, as recorded by the birth and death register of the municipality where the death had occurred before 1990. Results were given for a wide variety of outcomes, including all cancers combined and six specific cancer types: oesophagus, stomach, colon, liver, lung, all lymphoma or haematopoietic cancers, and NHL.

Measurements of PFOA serum concentration in workers, available for a subsample of the cohort (n = 120), were used to develop a regression model for job-specific levels across time. These models were then used to estimate a cumulative serum PFOA concentration for each cohort member. Employees were classified: (i) by three PFAS (either PFOA or PFOS) exposure categories (office workers, never in PFAS-exposed

department, ever in PFAS-exposed department); and (ii) by tertiles of estimated cumulative PFOA serum concentrations. SMRs were calculated for the exposed cohort compared with the regional population (adjusted for age, sex, calendar time). Poisson regression risk ratios were also calculated, taking workers of a nearby metalworking factory, who were working with the Italian train system, as referents. [The Working Group noted that there was some exposure to asbestos in the metalworking factory, which might have biased deaths from lung disease towards the null.] Additional analyses were conducted to calculate SMRs and risk ratios across categories of probability of PFAS exposure and tertiles of cumulative serum PFOA concentration using the regional population and the metalworking cohort as the referent, respectively.

Serum PFOA concentrations among 120 workers in the period 2000–2013 (696 measurements) showed a geometric mean of 4048 ng/mL (range, 19–91 900 ng/mL). For these same 120 workers (615 measurements), serum PFOS results showed a much lower geometric mean of 148.8 ng/mL (range, 10–3386 ng/mL). The intra-sample correlation between the PFOA and PFOS concentrations was high (Spearman correlation, $\rho = 0.59$; $P < 0.001$).

[The Working Group noted the exceptionally higher levels of PFOA exposure than in other occupational cohorts, with a resulting high exposure contrast, as a strength. The use of a JEM and some serum measurements to build a model of cumulative PFOA exposure that had evidence of a good fit to observed data, and comparisons with non-exposed workers, which might reduce confounding, were also strengths. While there was exposure to PFOS, serum PFOS concentrations were much lower than those of PFOA, and PFOS was not considered to be a potential confounder. Limitations were: a small occupational cohort with few deaths (107 deaths, 42 from cancer), no data on confounders (although the use of a worker comparison population might reduce confounding), a small number of deaths (7 each) from liver cancer and lymphohaematopoietic cancer (the two causes with positive trends with exposure), no data on some causes of death of major interest (e.g. cancers of the bladder, prostate, or testis). This study was of moderate informativeness, owing to the documented high exposure, but was limited by the small number of cancer outcomes.]

2.1.10 E3N cohort

E3N (Etude épidémiologique auprès de femmes de la Mutuelle générale de l'Education nationale) is a prospective population-based cohort study of 98 995 women in France that was initiated to identify risk factors for cancer and other chronic diseases in women (Clavel-Chapelon et al., 2015). In 1990, a questionnaire was sent to almost 500 000 women aged 40–65 years who were part of a national health insurance programme for workers, primarily teachers from the French national education system, inviting them to enrol in the study. Approximately 20% responded to the questionnaire, with 98 995 participants enrolling in the cohort.

At baseline, participants completed a self-administered questionnaire and consented to the study team accessing their health insurance records. Participants completed follow-up questionnaires every 2–3 years after baseline, with an average response rate of approximately 80%, and with limited loss to follow-up (< 3%). These questionnaires included information on a range of demographic and lifestyle factors and suspected risk factors for cancer. Between 1994 and 1999, approximately 25 000 participants (participation rate, 40%) donated blood samples. Sample aliquots were stored in liquid nitrogen in a biobank.

A nested prospective case–control study was conducted to evaluate serum PFOA and PFOS concentrations in relation to breast cancer risk

(Mancini et al., 2020a). Cases of breast cancer were identified by self-report, from the health insurance files, or through death certificates. Deaths could be reported by next of kin or ascertained from the health insurance files; cause of death was identified using the NDI. Pathology reports were available for most of the cases (93%), but self-reported cases without a pathology report were included in the analysis. In the cohort, 281 cases of breast cancer were identified that were diagnosed before 2013 and for which at least three aliquots of serum were available. Cases for which the dietary questionnaire had not been completed or diagnosed before the blood sampling or before completing the dietary questionnaire were excluded. The length of time between drawing of the blood sample and cancer diagnosis was not reported. From the eligible 240 cases of incident cancer remaining after exclusions, 194 cases of incident postmenopausal breast cancer were randomly selected for the study; this reduction was due to budgetary constraints. A control (also n = 194) was sampled from the cohort for each case, using a density-sampling approach based on not having a breast cancer at the time that the corresponding case was diagnosed, with matching by age (± 2 years), menopausal status and BMI at blood collection, and year of blood collection. Mean age at diagnosis was 68.8 years (range, 58.3–84.9 years). Information on tumour hormone-receptor expression was available for ER for 158 cases (77%), and for PR for 155 cases (80%). In total, 132 tumours were positive for ER (ER+) and 98 were positive for PR (PR+).

Concentrations of PFOA and PFOS were measured using LC-MS/MS. Both PFOA and PFOS, categorized in quartiles, were evaluated in relation to breast cancer risk using conditional logistic regression. [The Working Group noted that while collection of a single blood sample might be considered a limitation, there is some evidence, from repeat sampling of PFOA, that single samples may represent long-term averages over a 5–8 year period, with potential misclassification resulting in only minor bias to the null (Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636). However, there remains the concern that single measurements of PFOA or PFOS, despite the long half-life of these chemicals, might not represent average exposure over longer periods that might be relevant to cancer etiology.] Mancini et al. (2020a) explored several statistical models for confounder adjustment and considered a large number of confounders, selected a priori (total serum lipids, BMI, smoking status, physical activity, education level, history of benign breast disease, family history of breast cancer, parity or age at first full-term pregnancy, breastfeeding duration, age at menarche, age at menopause, use of oral contraceptives, current use of menopausal hormone therapy, adherence to a "Western" or "Mediterranean" diet). Stratified analyses evaluated how these associations varied by ER and PR status of the tumour.

[The Working Group noted that strengths included the prospective design and collection of blood specimens, the availability of blood data before diagnosis, extensive confounder control, limited loss to follow-up, and the availability of detailed diagnostic information (e.g. ER and PR status for nearly all cases of breast cancer). Limitations included relatively small exposure contrasts in a general population sample with background serum PFOA and PFOS concentrations and a lack of cases in premenopausal women. The response rate for the blood donation was low, which might affect the generalizability of the findings. The analyses by hormone-receptor subtype, while important, were limited by the small sample sizes, and there was a lack of information on the time between blood sampling and diagnosis.]

2.1.11 PLCO Cancer Screening Trial cohort

The PLCO was a large randomized controlled trial (about 150 000 adults; 76 685 men and 78 216 women), aged 55–74 years from 10 large cities in the USA), conducted in 1993–2001, and designed and sponsored by the National Cancer Institute. The goal was to determine the effects of screening on cancer-related mortality and secondary end-points in men and women aged 55–74 years, recruited between 1993 and 2001 (Prorok et al., 2000; Rhee et al., 2023a). The target populations for recruitment differed between the 10 clinical sites in the trial; recruitment methods included mass mailings using purchased mailing lists or lists of patients in local areas. Eligible women had not previously received diagnoses of cancer and had not undergone the screening tests in the 3 years preceding enrolment for testing in the trial. In the PLCO Trial, blood samples were to be collected from participants in the screening arm and stored for future etiological research (Hayes et al., 2000): blood samples were collected from 95% of screening-arm participants at baseline. Serum PFAS concentrations in the controls of the PLCO study were similar to those in the US NHANES study collected at about the same time, suggesting that the studied population was representative of the US population (Shearer et al., 2021).

Four separate nested case–control studies were conducted for the PLCO Trial cohort, investigating the association between PFOA or PFOS and cancers of the kidney, prostate, breast, and pancreas.

Shearer et al. (2021) conducted a nested case–control study within the PLCO cohort; this study involved 324 cases (216 men, 108 women) with RCC (the main subtype of kidney cancer) and 324 matched controls who were alive and free of RCC after the diagnosis dates of their corresponding matched case. Controls were matched individually on age at enrolment, sex, race and ethnicity, study centre, and year of blood draw. Exposure assessment was based on PFOA, PFOS, and other PFAS measured in serum collected 2–18 years before cancer diagnosis (mean, 8.8 years). Analyses using conditional logistic regression controlled for BMI, kidney function (estimated glomerular filtration rate, eGFR), smoking status (never, former, or current), history of hypertension, prior sample freeze–thaw cycles, and calendar year of blood draw. Analyses were conducted for eight different PFAS measured at baseline, including PFOA and PFOS. Additional analyses considered PFOA, PFOS, and PFHxS jointly. Analyses considered quartiles of serum concentrations, as well as continuous (log_2-transformed) serum levels. Geometric mean concentrations of PFOA among controls were 4.0 and 4.5 µg/L [ng/mL] for women and men, respectively; those for PFOS were 31.3 and 38.1 µg/L [ng/mL] for women and men, respectively, similar to serum concentrations for the general population at the time.

Steenland et al. (2022) included the cases and controls from Shearer et al. (2021) in a pooled analysis of PFOA and kidney cancer, combined with 103 cases and 511 matched controls from a PFOA-exposed cohort in West Virginia and Ohio previously reported by Barry et al. (2013). This pooled analysis was conducted to derive a dose–response curve between serum PFOA concentration and risk of kidney cancer using two of the largest studies of kidney cancer and PFOA exposure, and to conduct a risk assessment of excess lifetime risk of kidney cancer for specific PFOA serum concentrations and rates of drinking-water consumption.

Rhee et al. (2023a) studied 750 cases and 750 matched controls nested within the PLCO cohort. They looked at associations between a variety of PFAS, including PFOA and PFOS, measured at baseline, and subsequent prostate cancer. There were 750 men with aggressive prostate cancer (defined as stage III or IV or Gleason score ≥ 8, or Gleason score 7 and death from prostate cancer). Cases were diagnosed > 300 days after baseline

blood collection (median, 9 years). Controls were selected from among eligible participants who were alive and cancer-free at the time of the case diagnosis and were individually matched on age at baseline, race or ethnicity, calendar year of baseline blood collection, and characteristics of blood sample (e.g. whether thawed or not). Analyses were further adjusted for BMI, smoking status, family history of prostate cancer, history of diabetes, and serum concentrations of seven other PFAS. All eight PFAS were detected in more than 95% of samples; most PFAS were moderately correlated, with the highest correlation being between PFOA and PFOS (ρ = 0.70). Rhee et al. (2023a) also collected multiple serum samples (at baseline, and at 1- and 5-year follow-up) from a subset of controls (n = 60) and found that the variance between participants was generally markedly higher than the variance within participants; intraclass correlation coefficients across repeats for PFOA and PFOS were 0.73 and 0.85, respectively.

Chang et al. (2023) conducted a nested case–control study of breast cancer among women who were postmenopausal at baseline in the PLCO cohort. There were 621 cases and 621 controls, individually matched on age at baseline, date of blood draw, and menopausal hormone therapy use at baseline, who were alive and cancer-free past the follow-up time of their corresponding matched cases. Prediagnostic serum concentrations of PFOA and PFOS, measured 1 year after baseline, with a median of 5.6 years before case diagnosis, were the exposures of interest. In another study, intensity levels of PFOA and PFOS were assessed using the same untargeted metabolomics platform and were highly correlated with targeted measured serum concentrations of PFOA and PFOS (Spearman correlations, 0.77 and 0.76, respectively). Analyses were conducted for all cases combined by quartile of PFOA and PFOS intensity levels, and by ER (ER+, 435 cases) or PR (PR+, 299 cases) status, and joint ER/PR status. Models were adjusted for age at blood sampling, established breast cancer risk factors (age at menarche, age at first live birth, number of live births, age at menopause, duration of menopausal hormone therapy use, first-degree family history of female breast cancer, personal history of benign breast disease, BMI, smoking status, vigorous physical activity), natural log-transformed intensity levels of PFOA (for the PFOS model) or PFOS (for PFOA models), and variables, whose removal resulted in a ≥ 10% change in the odds ratios (study centre, race or ethnicity, and education).

Zhang et al. (2023) studied data for 360 cases of pancreatic ductal adenocarcinoma (the most common type of pancreatic cancer) and 360 matched controls in a nested case–control study in the PLCO cohort. The same study also involved another 251 cases and 251 controls from the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study, conducted in Finland. The PLCO case and control groups were matched on age, date of blood draw, sex, and race. Blood collected at PLCO baseline was analysed for PFOA and PFOS (median follow-up period, 9 years), using relative intensities rather than absolute concentrations (i.e. based on non-targeted analysis of PFOA and PFOS intensity levels). Previous work has shown that such rankings correlate well with measurements of absolute concentrations (Spearman correlation, 0.76) (Rhee et al., 2023c). Additionally, although untargeted analysis was used by Zhang et al. (2023), in previous PLCO studies, serum PFOA and PFOS concentrations were comparable to those measured among the general population in the NHANES survey in 1999–2000 (Rhee et al., 2023a). Data were analysed using conditional logistic regression, with continuous variables and quintiles, and controlling for smoking, BMI, age at blood draw, and diabetes. It did not appear that each PFAS was adjusted for the other.

[The Working Group noted strengths in all four PLCO nested case–control studies. First, all the studies involved large numbers of cases

and controls; second, they all used measured serum concentrations of PFOA and PFOS before cancer diagnosis, which is used as the exposure metric. Other strengths included consideration of a broad range of confounders, and data on tumour characteristics. Another strength was the mutual control for other PFAS under study (except in Zhang et al., 2023), and the availability of repeat samples in the prostate cancer study to assess reproducibility. Limitations in all four studies included the use of a single measurement to characterize long-term exposure, although the Working Group noted that in Rhee et al. (2023a) repeated measures of PFAS in a subsample indicated good reproducibility within individuals. Another weakness was the relatively low contrasts in exposure, typical of a general population study, making it more difficult to identify potentially corresponding health effect contrasts. While not necessarily a weakness, it was noted that the prostate cancer study by Rhee et al. (2023a) and the breast cancer study by Chang et al. (2023) were restricted to aggressive cancers and postmenopausal cases, respectively. However, for etiological research, it is probably more important to focus on aggressive than indolent prostate cancer, and postmenopausal breast cancer represents the great majority of breast cancer cases. Finally, the Working Group noted that the PLCO cohort had a higher percentage of White participants, e.g. 88–89% in Rhee et al. (2023a) and Chang et al. (2023), compared with the current US population (75%) (United States Census Bureau, 2022).]

2.1.12 Child Health and Development Studies pregnancy cohort

The Child Health and Development Studies (CHDS) pregnancy cohort included 20 754 pregnancies that resulted in 19 044 live births, including 9300 daughters. Between 1959 and 1967, pregnant women in the Oakland area of California, USA, receiving obstetric care through the Kaiser Foundation Health Plan were invited to participate (> 99% of all eligible women enrolled). The researchers obtained access to the medical records of all pregnant women recruited in the cohort, and to those of their children, and collected blood samples from the mothers (mostly, one blood sample per trimester and postpartum). Moreover, all mothers participated in an in-person interview during pregnancy (van den Berg et al., 1988).

To collect information on residence history and update residency and name changes over time, the CHDS cohort was linked to the California Department of Motor Vehicles. Data on the history of residential location of all women recruited in the CHDS cohort were used to identify the population at risk of cancer, corresponding with geographical surveillance by California's cancer registries. Deaths and cases of cancer were identified through linkage of the CHDS with the California Vital Status Records and the California Cancer Registry, respectively. Cases were also identified by self-report in a survey of CHDS daughters conducted in 2010–2013 (Cohn et al., 2020).

A nested breast cancer case–control study was conducted within the CHDS cohort, including 102 cases with breast cancer and 310 controls. Cases were identified through surveillance and self-report until March 2013 and were defined as CHDS daughters with cases of incident invasive or non-invasive breast cancer, which were diagnosed when they were aged < 52 years. Only cases of cancer for which a maternal perinatal blood sample was available for the analyses were selected; this led to the inclusion of 86% of all the cases of breast cancer identified. Three controls were matched to each case on birth year and trimester of maternal blood draw. Controls were selected randomly from among CHDS daughters not known to have received a diagnosis of breast cancer at the age of diagnosis of the corresponding case (Cohn et al., 2020).

After collection, serum samples had been stored at –20 °C, and concentrations of PFAS, including PFOA and PFOS, were measured using LC-MS/MS. The association between maternal PFAS serum levels and the daughter's risk of breast cancer was evaluated using age-matched conditional logistic regression, with PFOA and PFOS serum concentrations analysed as continuous variables after $\log_2$ transformation and adjusting for potential maternal confounders, such as maternal age, race, overweight in early pregnancy, parity, maternal history of breast cancer, maternal serum $\log_2$-transformed dichlorodiphenyldichloroethylene (*p*,*p*′-DDE), maternal serum $\log_2$-transformed dichlorodiphenyltrichloroethane (*o*,*p*′-DDT), and whether the daughter was breastfed (Cohn et al., 2020). Models evaluating PFOS also considered, a priori, inclusion of a PFOS precursor, (*N*-EtFOSAA), and total maternal cholesterol, both $\log_2$-transformed, and their product term (to test for interaction).

[The Working Group noted as a strength of the study that cases were likely to have been accurately determined via the California Cancer Registry.]

[The Working Group also noted that blood PFOA and PFOS concentrations decrease during pregnancy, owing to expanding plasma volume, decreased albumin concentration, and increased glomerular filtration rate. Nevertheless, it has been reported for previous studies that blood PFOA and PFOS concentrations measured during different pregnancy trimesters and postpartum in mothers, as well as measurements of cord blood, are well correlated (Glynn et al., 2012; Kato et al., 2014; Pan et al., 2017; Nielsen et al., 2020). This implies that blood PFOA and PFOS concentrations measured at different times during pregnancy and postpartum can be predictive of fetal exposure during pregnancy. Conversely, Cohn et al. (2020) analysed and compared, in the same study, PFOA and PFOS concentrations measured during pregnancy (22% of the samples) and in the early postpartum period (78% of the samples). This could have introduced a potential non-differential exposure misclassification bias, because not all blood samples were collected at the same time during pregnancy.]

[The Working Group noted that the study included examination of the prenatal exposure window, which is of interest with regard to the etiology of breast cancer in general. However, it was noted that no serum PFAS levels were directly available from study participants, namely, the CHDS daughters, and exposure was notably restricted to prenatal exposure, limiting the generalizability of the results and the possibility for comparison with other studies. Another weakness noted was that no individual information concerning the CHDS daughters was available in the study (Cohn et al., 2020), so that the analyses did not include important confounders. In the 1960s, PFAS contamination was expected to be still low in the USA general population (ATSDR, 2020) and this was reflected by the very low serum PFOA concentrations measured in women of the CHDS cohort, which affects the informativeness and the comparability of the results of the study (Cohn et al., 2020). In contrast, serum PFOS concentrations measured in women of the CHDS cohort were unexpectedly high, considering the time period of blood sampling; no explanation was provided by the authors for these high values. Also affecting generalizability was the restriction to cases diagnosed in daughters younger than 52 years. Additionally, the Working Group noted the lack of information on what percentage of the cohort moved out of the state and could not be followed up. Finally, there was a lack of data on cancer subtypes (e.g. histology, hormone-receptor status), and results were presented based on all cancer subtypes combined, which could mask cancer subtype-specific associations and bias the overall risk estimate towards the null. Overall, on the basis of these limitations, the Working

Group considered this study to be of minimal informativeness.]

2.1.13 The Ronneby Register cohort

Li et al. (2022a) investigated cancer incidence in residents in an area with high-level environmental exposure to, primarily, PFOS and PFHxS, in Sweden. The municipality of Ronneby, on the Baltic coast in the southern part of Sweden, had about 28 000 residents in 2013, and drinking-water was supplied by two waterworks. One of these, situated 2 km from a military airfield, supplied one third of the households of Ronneby municipality (a map of the area is given in Xu et al., 2021). In December 2013, measurements of PFAS in drinking-water from this waterworks revealed sum of PFAS concentrations above 10 000 ng/L [10 ng/mL], whereas the concentration for the other waterworks was below 90 ng/L [0.09 ng/mL] – but still higher than in the drinking-water of the neighbouring municipality of Karlshamn. It was found that PFOS and PFHxS accounted for > 90% of the total PFAS, while the PFOA contamination was relatively limited and strongly overlapping with the concentrations in the reference population. The source of the contamination was the use of PFAS-containing firefighting foam at the airfield from about 1985 until the waterworks was closed, by the end of 2013. No measurements were available before 2013, but the study authors assumed that levels in the drinking-water increased during the years after 1985 and decreased after the end of the exposure to contaminated water, in late 2013 (Li et al., 2018). The Ronneby Register cohort includes 60 507 individuals (men, 53%) who ever lived in Ronneby municipality in the period 1985–2013. Individual exposure was classified by coupling registry information on yearly residential address with information on which addresses had been supplied with contaminated water by the waterworks. Exposed individuals were those who had ever lived in the contaminated district ("ever-high", n = 15 811; 26% of the Ronneby population). This group was subdivided by the calendar period and by the number of years living at an ever-high residence: "early-high" (1985–2004), "late-high" (2005–2013), "short-high" (1–10 years), and "long-high" (≥ 11 years). An internal referent was defined: inhabitants who had ever lived in Ronneby municipality in 1985–2013 but never at addresses receiving contaminated drinking-water. There were [44 696 (74%)] residents with never-high exposure (data derived from Li et al., 2022a, Table 4); the mean age at entry into the cohort was between 30 and 33 years, according to sex and exposure group.

The external reference groups included a regional population (the population of Blekinge County, excluding Ronneby municipality) and a national population (the whole Swedish population). The exposure classification was validated by measurements of several PFAS in the serum of 3084 people from Ronneby municipality (ever-high and never-high), sampled in 2014–2015, and in the serum of 226 people from a neighbouring municipality, sampled in 2016. The ratio of geometric mean levels of PFOS in the late-high group, relative to reference residents, was (239 ng/mL)/(3.9 ng/mL) = 61.3, that for PFHxS was (210 ng/mL)/(0.84 ng/mL) = 250, and that for PFOA was (13 ng/mL)/(1.5 ng/mL) = 8.7. Data on cancer occurrence during the follow-up period 1985–2016 were obtained from the Swedish Cancer Register (using ICD-7 codes). In all, 5702 first-occurring cancers were identified in the Ronneby Register cohort (n = 60 507), with 495 identified in people in the group with the highest exposure, the late-high group, including 374 in people who were in the long-high group. Age-, sex-, and calendar year-standardized incidence ratios (SIRs) were computed for a large number of cancer sites for residents who had never, or had ever, resided at addresses with contaminated water, compared with those residing in uncontaminated areas (external analysis). Internal comparisons based on Cox regression models

were made using the calendar year as the underlying timescale and were adjusted for age and sex. Information on lifestyle and health behaviours was not available, but annual data on highest attained education (from 1990 onwards), residence, work address, and demographic data were obtained from Swedish nationwide registers.

[The strengths of this cohort were the large general population sample with complete ascertainment and follow-up, owing to the use of high-quality Swedish population registers with complete population coverage, and a strong documented exposure contrast. A limitation was the mixed exposure profile, with high levels of PFOS and PFHxS, and somewhat elevated but significantly lower levels of PFOA, as well as the lack of individual serum measurements, or individual water contamination or consumption measurements, hence necessitating an ecological exposure assignment into groups by area and time of residence. Conversely, the group-level exposure assignments may have captured the large exposure contrasts in this population and were supported by a large number of serum measurements. The limited information on potential confounders may be a minor issue, since this is unlikely to be dependent on the water distribution system, which also fits with the sensitivity analysis adjusted for highest attained education (which has been shown to correlate with smoking in Sweden; Eek et al., 2010) showing no change of results. A lack of historical information on area-level contamination of drinking-water with PFAS, particularly during earlier years of the study period was, however, a limitation.]

2.1.14 Dongfeng-Tongji cohort

The Dongfeng-Tongji (DFTJ) cohort is an ongoing prospective study including over 41 000 retired workers recruited from an automotive company in Shiyan, China (Wang et al., 2013). The company is one of the three largest vehicle manufacturers in China and was founded in 1969, so that most first-generation workers had already retired when the DFTJ cohort was initiated. Participants in the DFTJ cohort were recruited in two waves: the first from September 2008 to June 2010, which included 27 009 participants; and the second from April to October 2013, which included 14 120 participants (Feng et al., 2022). The participation rate was approximately 87% during the first wave (Wang et al., 2013) and was not reported for the second wave; however, responders and non-responders reported similar sociodemographic characteristics (Feng et al., 2022). At inclusion, all participants answered face-to-face interviews, underwent physical examinations, and provided a blood sample. For each participant, 10 mL of peripheral venous blood was collected once at inclusion after overnight fasting. Plasma was separated from the blood sample and stored at −80 °C (Wang et al., 2013; Feng et al., 2022).

PFAS plasma levels were low in this cohort: PFOS had the highest median plasma concentrations (10.36 ng/mL), followed by PFOA (1.19 ng/mL).

Cases of incident breast cancer, diagnosed from September 2008 until the end of 2018 (median follow-up 9.6 years), were identified by reviewing participants' medical records or death certificates provided by the five hospitals owned by the automotive company and by the local Center for Disease Control and Prevention.

A case–cohort study was conducted among women included in the DFTJ cohort to investigate the association between plasma levels of six PFAS, including PFOA and PFOS, and breast cancer risk. Women with prevalent cases of cancer at baseline, those with insufficient blood specimens, and those who were lost to follow-up were excluded from the case–cohort study. Among the remaining 18 387 women, 226 were identified as incident breast cancer cases during follow-up. A subcohort of 990 women was randomly selected from the base cohort

(n = 18 387) according to strata determined by age, and among these women, 13 (1.31%) developed breast cancer during follow-up (Feng et al., 2022).

For all women included in the subcohort, the plasma concentrations of six PFAS, including PFOA and PFOS, were measured using LC-MS/MS. The association between PFAS and breast cancer risk was evaluated using Barlow-weighted Cox proportional hazard models adjusted for potential confounders selected a priori, such as age, BMI, smoking, drinking, marital status, education level, occupation type, batch to enter the cohort, parity, menopausal status, history of mastitis, use of hormone replacement therapy, and family history of cancer. PFAS concentrations were natural log-transformed and included one-by-one in separate models for six PFAS, modelled as continuous and categorical variables (in quartile groups identified based on the distribution of each PFAS in the subcohort) (Feng et al., 2022).

[The Working Group noted that this study represents a large cohort of retired Chinese workers with low-level exposure to PFOA, PFOS, and other PFAS compounds. Strengths are high baseline participation, good control for confounders obtained by interviews, limited loss to follow-up, ascertainment of diagnoses by medical records in five company-financed hospitals and death certificates. However, details were not provided on the probable completeness of diagnoses using these methods, nor the percentage of women whose diagnoses were confirmed only via death certificate, which would result in an unknown diagnosis date. Nevertheless, it cannot be predicted in which direction the risk estimates could be affected by the unknown diagnosis date. Other strengths included the availability of prediagnostic serum samples (an average of 9.6 years before diagnosis, but the range of time span from PFAS measurements to diagnosis was not provided). Blood samples were collected only once at baseline. The Working Group noted that there was some evidence, from analyses of repeat samples of PFOA, that single samples may represent long-term averages over a 5–8-year period, with potential misclassification resulting in only minor bias to the null (Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636). However, a concern remained that single PFOA or PFOS samples may not represent lifelong average exposure. Whether the selection of retired workers had an impact on risk estimates was uncertain, but there was no a priori reason to suggest any marked bias due to this selection. No cumulative lifelong exposure metric was available, and the very low exposure contrast for PFOA and PFOS limited the evaluation of exposure–response associations.]

2.1.15 NHANES 1999–2014 cohort

The NHANES is a continuously conducted and nationally representative cross-sectional survey. Participants are selected through a statistical process using census data to be representative of the noninstitutionalized population of the USA and are recruited via mailed letters inviting them to participate in NHANES. Between 1999 and 2014, individuals completed a household interview and a medical examination that included a blood sample collection and an assessment of anthropometric measures. Questionnaires assessed information including demographics, socioeconomic status, alcohol use and smoking history, diet, and medical history. [The Working Group noted that detailed information on the individuals included in the cohort, such as selection and participation rates, was not readily available.]

Among participants with stored blood samples, serum concentrations of PFOA and PFOS were quantified using LC-MS/MS (Wen et al., 2022).

The US National Center for Health Statistics has linked NHANES 1999–2014 cohort participants to the NDI to identify deaths and determine the underlying causes of death using probabilistic matching criteria based on identifiers such as social security numbers and date of birth. Participants were followed for cause-specific mortality until 31 December 2015. If the individual did not match to the NDI, this person was assumed to be alive as of the end of follow-up date. Mortality from all cancers combined was one of the cause-specific death categories included in the files available for public use, and no site-specific cancer mortality data were available. For 11 747 of the cohort participants aged ≥ 18 years at baseline and with blood samples analysed for PFAS, 1251 deaths were observed during the median follow-up of 81 months (interquartile range, IQR, 46–112 months). Of these deaths, 19.8% (248) were from cancer. The medians and 25th and 75th percentiles of serum PFOA and PFOS concentrations at baseline were 3.27 ng/mL (2.00, 5.00) and 11.60 ng/mL (6.40, 22.40), respectively, reflecting general population levels. [The Working Group noted that this study included only a single measure, which may be considered a limitation; however, there was some evidence, from analyses of repeat samples of PFOA, that single samples may represent long-term averages over a 5–8-year period, with potential misclassification resulting in only minor bias to the null (Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636). However, there remained the concern that single PFOA or PFOS samples may not represent average exposure over longer periods.]

Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between PFOA and PFOS categorized in tertiles and overall cancer mortality adjusting for potential confounders (Wen et al., 2022). The confounders included were sex, age, race or ethnicity, smoking status, alcohol intake, physical activities, hypertension, diabetes, healthy eating index, creatinine clearance rate, serum total cholesterol, and serum cotinine. Analyses of PFOA and PFOS were adjusted for other PFAS.

[The Working Group noted some strengths in this study, including probably complete ascertainment of cancer mortality in this large population, which was selected to be a representative sample of the US population, making results generalizable in the USA, relatively good control over potential confounders, and adjustment for other PFAS in analyses of specific PFAS. Weaknesses noted were the unclear timing of the blood sampling relative to diagnosis or treatment; a short follow-up time for some of the participants, which may not reflect the relevant etiological window; and the use of a volunteer-based population that may be healthier than the general population, which may not be fully captured by sampling weights and thus may result in some selection bias. The study focused on all-cancer mortality, without data on cancer incidence or on mortality for specific cancers, making these data of limited informativeness for the Working Group's assessment of individual cancers. The observed estimates of association with cancer mortality would not be applicable to cancer incidence unless the cancer itself had a high rate of fatality.]

2.1.16 Multiethnic Cohort study

Kolonel et al. (2000) described the design and implementation of the Multiethnic Cohort (MEC) study, which was established to study diet and cancer in the USA. The MEC included a community sample of 215 251 citizens (men, 45%) aged 45–75 years who were enrolled during 1993–1996 in Hawaii and California (primarily Los Angeles County) when responding to a mailed 26-page baseline questionnaire on mainly dietary, demographic, and health issues.

The sampling frame was established using drivers' license files, voters' registration files, and Health Care Financing Administration files. The recruitment procedures aimed to obtain a balanced distribution of five specific ethnic groups comprising White, African-American, Latino, Japanese-American, and native Hawaiian people; therefore, less common groups were preferentially sampled. Response proportions spanned 20% to 49%, being lowest in Latino and highest in Japanese-American people. In the final sample, Japanese-American people comprised the largest group (28% in men and 25% in women) followed by White (24–22%), Latino (24–21%), African-American (13–19%) and native Hawaiian (6–7%). The participants represented a more educated subset of the general population. In addition to quantitative information about food and dietary components based upon portion size information, the questionnaire included data on smoking, drinking, obesity, and vigorous physical activity.

Goodrich et al. (2022) performed a case–control study of hepatocellular carcinoma (HCC) nested within the MEC. Incident cancers occurring during the 20 years of follow-up, including non-viral HCC (not of viral etiology), were identified from the early 1990s onwards by the Surveillance, Epidemiology and End Results (SEER) programme of the National Cancer Institute, which includes California. Additional information on health conditions was obtained from Medicare claims and California hospital discharge records (Goodrich et al., 2022). [It was uncertain whether the 50 cases of incident HCC constituted all the HCC cases arising during the follow-up period, given that the authors excluded HCC of viral etiology, and no information was provided about how the 50 controls matched on sex, age, race or ethnicity, and study area were selected.] Plasma concentrations of six PFAS (including PFOA and PFOS) were measured in prediagnostic fasting blood samples collected before diagnosis (median, 7.2 years; range, 0.9–16.4 years).] The unadjusted geometric mean of PFOS was 29.2 µg/L [ng/mL] in both cases and controls. For PFOA, concentrations were 4.21 µg/L [ng/mL] in cases and 4.78 µg/L [ng/mL] in controls, and for PFHxS values were 1.84 µg/L [ng/mL] in cases versus 2.07 µg/L [ng/mL] in controls.

The average age at blood collection was similar for cases (69.7 years) and controls (69.2 years). Men comprised 62% of the sample and 64% were residents of Hawaii. The prevalence of high BMI, high alcohol intake, and diabetes mellitus was much higher among cases than among controls.

Adjusted odds ratios for the association between plasma concentrations of each PFAS and risk of non-viral HCC were computed by conditional logistic regression, which accounted for the matching variables. Sensitivity analyses further adjusting for baseline BMI and baseline diabetes status were performed, but additional covariates (such as other PFAS) were not included in the statistical models. An additional sensitivity analysis considered ordinary logistic regression with covariates that included the matching variables. To account for possible non-linear associations, smoothing splines were inspected, and additional analyses contrasting risk above and below the 85th percentile (which corresponded to the 90th percentile in NHANES for PFOS) were carried out.

Rhee et al. (2023b) performed a nested case–cohort study of RCC within the MEC. The study identified 428 cases of incident RCC, which included all cases with prediagnostic serum samples available and diagnosed before 2018 using record linkages to the Hawaii Tumor Registry and the California Cancer Registry. The 428 controls, who were participants with no RCC diagnosis who were alive at the time of the case diagnosis, were identified using 1:1 matching on sex, race or ethnicity, study centre (Hawaii, California), age at serum collection (± 1 year), date of serum collection (± 1 year), time of serum collection (± 3 hours), and fasting status

(0 to < 6 hours, 6 to < 8 hours, 8 to < 10 hours, and ≥ 10 hours). Concentrations of nine PFAS (including PFOA and PFOS) were assessed in prediagnostic serum samples collected between 1994 and 2006.

Adjusted ORs and 95% CIs were estimated for the association between PFOA and PFOS (log_2-transformed and categorized in quartiles based on the distribution in the controls) and the risk of RCC using conditional logistic regression adjusting for the matching factors as well as BMI, eGFR, smoking status, and hypertension history. Analyses were conducted with further adjustment for other measured PFAS and with stratification by matching factors and other covariates, including race and ethnicity, sex, age at blood draw, calendar year of blood draw, years from blood draw to RCC diagnosis, and eGFR status.

[Strengths of the nested case–control studies conducted within the MEC included prediagnostic measurements of several PFAS compounds in a racially and ethnically diverse population, independent ascertainment of exposure and outcome with high accuracy, a strong focus on possible mechanistic pathways related to PFAS related metabolism, and baseline information on relevant potential confounders including education, socioeconomic level, and health behaviours such as smoking. Regarding the statistical analysis of the HCC study (Goodrich et al., 2022), risk estimates were not adjusted for date of blood sample collection, smoking, alcohol consumption, and other PFAS. Moreover, small numbers in combination with low exposure contrast limited the informativeness of this study. For the RCC study (Rhee et al., 2023b), strengths included the large sample size, adjustment for eGFR and other factors, and the consideration of multiple PFAS for adjustment. Although it was a strength to consider this association across multiple racial and ethnic groups, there was limited statistical power for some of these comparisons.]

2.1.17 Cohort of US Air Force servicemen

Purdue et al. (2023) performed a case–control study nested within a cohort of US Air Force servicemen (with prospectively collected blood specimens) to examine the risk of testicular germ cell tumours (TGCTs; the most common variety) according to adult serum concentrations of selected PFAS, including PFOA and PFOS. The US Air Force was using firefighting foams containing PFOS, PFOA, and other PFAS compounds since the late 1960s until 2018, when the use of long alkyl chain PFAS compounds was discontinued. The US Department of Defense (DoD) has identified over 200 Air Force installations with known or possible release of PFOS and PFOA and, in some airbases, these compounds have been measured in groundwater and drinking-water in amounts exceeding 70 parts per trillion (ppt), the 2016 US EPA lifetime health advisory threshold. The US DoD has since 1985 stored serum samples of members of the Air Force service (and other military branches) collected for the purposes of HIV testing before induction and at periodic medical examinations, overseas assignments, and major overseas deployments. From 2004, all service members had blood samples taken every second year. Samples were stored at –30° C at a central serum repository (Department of Defense Serum Repository, DoDSR), which contains sera from more than 10 million service members (also including US Army and US Navy personnel). DoDSR records have been linked to records of the Defense Medical Surveillance System, providing individual demographic, occupational, and health data.

Purdue et al. (2023) identified TGCT cases by linking DoDSR records with the DoD cancer registry, which contains data on patients diagnosed with cancer at military treatment facilities in the USA. In all, 530 male servicemen with active-duty status, at least one prediagnostic serum sample, no previous history of cancer and

aged < 40 years at the time of TGCT diagnosis were identified from 1988 through 2017. In cases with at least two prediagnostic samples and with the earliest sample collected ≥ 5 years before the TGCT diagnosis, a second prediagnostic sample collected as close to the 5-year prediagnostic lag-time as possible was analysed (n = 187). The median time between collection of selected samples was 4 years (range, 0.1–13.3 years). For each case, one randomly selected male control participant was identified among active-duty Air Force servicemen, with no history of cancer at the time of the case diagnosis, by matching on birth year, race or ethnicity (seven groups), year entering military service, and year of serum sampling. The first serum samples were collected 0.3–0.4 years (median values) after entry into military service and 0–20 years before the diagnosis of TGCT. Serum concentrations of nine PFAS, including linear and branched PFOA and PFOS isomers, were measured by LC-MS/MS. The PFAS serum concentrations of men in the Air Force service were comparable to those of men in the NHANES cohort, albeit slightly higher in earlier years and slightly lower in later years. Fewer than 1% of participants (n = 5) had occupational exposure as a firefighter during military service. Unadjusted and adjusted risk of TGCT was analysed separately for PFOA (sum of linear and branched isomers), PFOS (sum of linear and branched isomers), and other PFAS by conditional logistic regression of matched pairs grouped by quartiles of serum concentrations in controls. Besides matching factors, adjusted analyses accounted for military grade, number of deployments before diagnosis, and the six other PFAS.

[The Working Group noted several strengths of this study, including the nested design, a well-characterized source population, a large, matched dataset, measurements of PFOA and PFOS isomers, two repeated prediagnostic samples collected several years apart in a subset of the population, a reasonable exposure contrast (for PFOS, the upper quartile was > 42.2 ng/mL and the lower quartile was ≤ 18.3 ng/mL), and analyses accounting for effects of other PFAS compounds. Limitations were mainly the loss to follow-up of men leaving the military and missing serum samples for a large proportion of TGCT cases (217 out of 747 cases, 29%) that was not addressed in supplementary analyses. The completeness of TGCT ascertainment was not documented but may be a minor issue since an association between PFAS exposure and completeness of TGCT ascertainment seems unlikely. In most cases, only one serum measurement per person was available, and data on known strong determinants of TGCT (such as cryptorchidism) were lacking, but the association of such determinants with PFAS exposure seems unlikely. The Working Group noted that occupational exposure as a firefighter is classified as *carcinogenic to humans* (Group 1) (IARC, 2023), but the evidence for risk of testicular cancer was *limited*, and very few (n = 5) of the US Air Force servicemen cohort members had been exposed as a military firefighter.]

2.1.18 Finnish Maternity Cohort

The Finnish Maternity Cohort (FMC) is a national registry of women who donated serum during the first trimester of pregnancy. The registry was established in 1983 using residual serum from a national programme to screen for congenital infections (infections transmitted from mother to child during pregnancy) and is estimated to include > 90% of pregnancies among Finnish women during the period 1983–2016 (Pukkala et al., 2007; Holl et al., 2008; Lehtinen et al., 2017). Women donated serum at municipal maternity care units, usually between weeks 10 and 14 of gestation (Madrigal et al., 2024). The registry included each woman's personal identification number and data related to reproductive history, residence at the time of collection,

dates of sample collection and processing, and expected delivery date.

Madrigal et al. (2024) conducted a nested case–control study on the incidence of papillary thyroid cancer, which accounts for approximately 90% of thyroid cancers in Finland (Hakala et al., 2012), by linking the FMC to the nationwide Finnish Population Registry, Cancer Registry, and Medical Birth Register until 2016. The population registry provided information on emigration status and vital status. The cancer registry, which covers all incident cancer cases in Finland since 1953, included date of diagnosis, histology, and stage at diagnosis (Finnish Cancer Registry, 2023). The Medical Birth Register, established in 1987, includes data on gestational age, reproductive history, smoking status, BMI before pregnancy and at the prenatal visit, and information about the delivery and infant or fetus, but not prior history of breastfeeding (Finnish Institute for Health and Welfare, 2023). Information on BMI before pregnancy was largely missing. Madrigal et al. (2024) randomly selected 400 cases of papillary thyroid cancer from among all cases (total number not reported) diagnosed among women in the FMC who provided serum in 1986–2010 during their first pregnancy and for whom this pregnancy had resulted in a full-term live birth with delivery between 1987 and 2010. Cases were restricted to those whose age at sample collection was 18–39 years and who were diagnosed with thyroid cancer ≥ 3 years after delivery. First pregnancies only were used to avoid any changes in PFAS levels related to breastfeeding during a previous pregnancy. Age at cancer diagnosis ranged from 23 to 61 years (mean, 40.9 years). Living, cancer-free controls were individually matched on year of delivery (4–5-year increments) and age at first birth (3-year increments). Serum levels of PFAS and other persistent pollutants were analysed by the Environmental Health Unit Laboratory of the Finnish Institute for Health and Welfare using LC-MS/MS (Koponen et al., 2013; Koponen and Kiviranta, 2019). Analytes included 19 PFAS, 13 polychlorinated biphenyl congeners (PCBs), nine organochlorine pesticides, and three polybrominated diphenyl ethers. The Spearman rank correlation coefficient for levels of PFOA and PFOS was 0.61. Statistical analyses consisted of conditional logistic regression of continuous exposures ($\log_2$-transformed) and of categories (25th, 50th, 75th, and 90th percentiles). For each PFAS detected in > 60% of the controls, including PFOA and PFOS, analyses were conducted with no covariates; with adjustment for any PFAS, PCBs, or organochlorine pesticides correlated (Spearman correlation, 0.3–0.61); and with adjustment for smoking.

[The Working Group noted several strengths of this study, including collection of serum before thyroid cancer diagnosis; adjustment in the analysis for other PFAS, PCBs, and organochlorine pesticides correlated ($\rho = 0.3–0.61$) with the analyte of interest; follow-up of the cohort covering the peak years of thyroid cancer incidence; and the availability of data in the Medical Birth Register on several potential confounders. The Working Group noted that one would expect only minor misclassification of long-term exposure because of reliance on a single prediagnostic sample according to a simulation study (Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636). PFAS concentrations might have been lower than pre-pregnancy levels because of increased plasma volume (Chapman et al., 1998) and glomerular filtration rates (Shankar et al., 2011) in the first trimester; however, a study of PFAS and birth outcomes suggests that little confounding may have occurred (Sagiv et al., 2018). The controls were not matched on the exact year of delivery but on increments of 4–5 years, which might affect comparison of PFAS levels because of temporal trends, although, given the estimated half-lives for PFOA and PFOS, such an effect was thought to be minimal. The Working Group did not

consider that the study had important surveillance bias among women diagnosed under age 40 years, when women may have frequent reproductive health-related visits; given that neither the women nor their medical providers were aware of their PFAS serum levels, these levels are not expected to affect thyroid cancer surveillance, and there were no large differences in stage at diagnosis by age at diagnosis. Analyses were not adjusted for pre-pregnancy BMI (a risk factor for thyroid cancer), which was missing for 85% of the women, nor were there data available on medical or environmental exposure to radiation. Finally, the study population had low-level exposure with a small exposure contrast.]

2.1.19 The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

The Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study was a randomized chemoprevention trial the primary aim of which was to evaluate the effects of supplementation with alpha-tocopherol and beta-carotene on lung cancer incidence (Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994). Secondary aims included evaluating the effects on other major cancers and overall and cause-specific mortality. The participants in the ATBC trial were White male smokers, aged 50–69 years at recruitment, who were identified in the Central Population Register as residing in south-western Finland, who responded to a questionnaire on their smoking history and willingness to participate, and who attended two clinic visits at which they completed a baseline study questionnaire and had trained nurses measure height, weight, blood pressure, heart rate, and visual acuity. The questionnaires included medical, smoking, and occupational history, and dietary habits over the past 12 months. Excluded from the study were people with a previous diagnosis of cancer other than non-melanoma skin cancer or carcinoma in situ; chronic renal insufficiency; cirrhosis of the liver; chronic alcoholism; receiving anticoagulant therapy; other medical conditions that might limit participation for 6 years; and current use of the vitamin supplements under investigation in the trial (Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994). An overnight fasting blood sample was collected at the initial clinic visit, with serum stored at –70° C. Recruitment began in 1985 and continued until 1988 when a total of 29 246 men were randomized to one of four treatment groups in a 2 × 2 factorial design. After late exclusions of 113 men found not to be eligible, the final study population numbered 29 133. Follow-up consisted of three annual clinic visits, with cancer cases ascertained through the Finnish Cancer Registry and deaths through the Central Population Register. The intervention continued until 30 April 1993, with publication of the trial results in 1994 (Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994). After the cessation of the trial, researchers continued to follow the cohort for 20 years, regularly updating data on mortality and cancer incidence.

Zhang et al. (2023) reported on two nested case–control studies on the incidence of pancreatic ductal adenocarcinoma, the most common type of pancreatic cancer. One study was conducted within the ATBC cohort, together with a parallel study conducted within the PLCO cohort (see description of this study above). Within the ATBC study, 251 cases of pancreatic ductal adenocarcinoma were ascertained until December 2011. A total of 251 controls were incidence-density sampled and matched to the cases on age at blood draw (± 5 years) and date of blood draw (within 30 days). Relative serum levels of PFOA and PFOS were measured using untargeted ultra-performance liquid chromatography-tandem mass spectrometry and/or gas chromatography-mass spectrometry. PFOS measurements were available only for 130 cases and controls. Statistical analyses consisted of conditional logistic regression to calculate odds

ratios and 95% confidence intervals per standard deviation increase of $\log_{10}$-transfomed PFOA or PFOS levels and quintiles based on the distribution of the controls, with adjustment for age at blood draw, smoking (years smoked and cigarettes per day), diabetes, and BMI.

[The Working Group noted that the strengths of the ATBC study included prediagnostic blood samples, detailed information on potential confounders collected through questionnaires and, for height and weight, by trained staff, and excellent case ascertainment. In addition, the numbers of cases in the ATBC (n = 251) and PLCO (n = 360) studies reported by Zhang et al. (2023) were large. The Working Group noted that the use of a single blood sample collected at baseline would be expected to result in only minor misclassification of long-term exposure, according to a simulation study (Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636). The Working Group noted that the study limitations included the low-level exposure with a small exposure contrast. The restriction of participants to White male smokers may affect the generalizability of the results. Furthermore, the study relied upon relative quantification of PFOA and PFOS; however, in previous research, relative measures have correlated well with targeted absolute concentration measurements (Rhee et al., 2023c).]

2.1.20 *New York Mount Sinai Hospital Bio*Me *biobank cohort*

Bio*Me* is a biobank linked to medical records within the Institute for Personalized Medicine at the Icahn School of Medicine at Mount Sinai, New York, USA. The collection of plasma samples, medical records, and questionnaire data from patients at Mount Sinai who lived in New York City and the larger metropolitan area started in 2007 and is currently ongoing (Icahn School of Medicine at Mount Sinai, 2023). Participants are enrolled from ambulatory care practices across the Mount Sinai Health System in New York City (Bar-Mashiah et al., 2022). No eligibility criteria were established, to make the cohort as inclusive as possible. As of September 2019, 52 500 patients were enrolled, and about 600 new patients are being enrolled each month (Icahn School of Medicine at Mount Sinai, 2023; van Gerwen et al., 2023). There did not appear to be follow-up of patients other than that conducted through the Mount Sinai hospital or ambulatory network.

van Gerwen et al. (2023) identified 88 cases of thyroid cancer within the Bio*Me* biobank for whom the time between plasma collection and thyroid cancer diagnosis was ≥ 1 year (n = 31; defined as longitudinal cases) or < 1 year (n = 57; defined as cross-sectional cases). The authors did not specify how cases were identified. Of the 88 identified cases of thyroid cancer, 74 were papillary thyroid cancer, as confirmed in pathology reports. Further inclusion or exclusion criteria (e.g. previous cancer) were not specified. Controls were pair-matched to cases on sex, age, race or ethnicity, BMI, smoking status, and calendar year of blood sample collection for PFAS measurement. Eighteen individual PFAS (including PFOA and PFOS) were measured using untargeted methods with liquid chromatography-high resolution mass spectrometry. Analyses were conducted for all thyroid cancer cases, for only papillary thyroid cancer, and for overall cases, stratified by time of blood sample collection in relation to diagnosis (longitudinal cases, n = 31, or cross-sectional cases, n = 57). Median age at sample collection was 43.5 years for cases and controls. Most of the population were women (83%). The mean time between sample collection and cancer diagnosis was 1.5 years for all thyroid cancer cases combined, 4.0 years for the longitudinal cases, and 0.1 years for the cross-sectional cases.

[The Working Group noted that the strengths of the study included the availability

of histological data for the cases and analyses adjusted for age, sex, race, and BMI, and sample storage time, and, for some analyses, adjustment for other specific PFAS compounds. Also, plasma samples were collected ≥ 1 year before diagnosis for a subset, albeit small, of the cases. Limitations included the small sample size, particularly for cases for which plasma was collected > 1 year before diagnosis (longitudinal cases), with the remainder having plasma collected < 1 year before diagnosis or at diagnosis (cross-sectional cases). In addition, the study was based on the use of untargeted assay methods, which limits direct comparisons with other studies. Also, thyroid cancer might be detected among asymptomatic patients who sought medical care for unrelated reasons, which raises a concern for detection bias, given that the cases were recruited in ambulatory practice, especially with such short follow-up. However, the Working Group noted that, since the case and control participants were recruited from within the same network of Mount Sinai ambulatory care practices, a generally comparable medical screening pattern could be assumed among cases and controls; thus, detection bias was unlikely, also considering that patients and practitioners were unaware of PFAS measurements.]

2.1.21 Cancer Prevention Study II LifeLink cohort

The American Cancer Society (ACS) Cancer Prevention Study II (CPS-II) enrolled 1 185 106 participants from 50 US states and the District of Columbia who completed a questionnaire, and mortality was ascertained using the NDI. A subset of this cohort, the CPS-II Nutrition Cohort, started in 1992–1993 by including 184 194 participants aged 50–74 years from 21 states followed with biennial questionnaires for cancer incidence, further verified through medical records or cancer registry files. Between 1998 and 2001, the CPS-II LifeLink Cohort started by recruiting 39 371 members from 20 states from within the CPS-II Nutrition Cohort. Those participants were required to be alive at the time of recruitment into the CPS-II LifeLink Cohort, since participation included a baseline questionnaire and a blood sample collection. Participants in the CPS-II LifeLink Cohort are followed for cancer incidence within the CPS-II Nutrition Cohort (Winquist et al., 2023).

Winquist et al. (2023) performed a study with a case–cohort design within the CPS-II LifeLink Cohort. Participants in the CPS-II LifeLink Cohort were eligible to participate in the case–cohort study if they were men or postmenopausal women who were cancer-free (excluding non-melanoma skin cancer) at the time of blood collection. The median age at the time of enrolment in LifeLink was 71 years for men and 69 years for women. From these eligible participants, the case group was defined as individuals with first primary cancers of kidney (n = 158), bladder (n = 401), prostate (men only, n = 1610), female breast (n = 786), or pancreas (n = 172); or haematopoietic malignancies (n = 635) as of 30 June 2015. The median follow-up time for the members of the subcohort was 14.3 years. The comparison subcohort included 499 women and 500 men (representing 3% of the LifeLink cohort meeting the inclusion criteria). PFOA and PFOS were measured together with other PFAS using LC-MS/MS. Several covariates were available, and the analyses were adjusted for identified cancer risk factors associated with PFAS exposure. Notably, the main models were not adjusted for BMI, because BMI was considered to be on the causal pathway. Of the participants in the comparison cohort, 98% were non-Hispanic White and 79% were aged ≥ 65 years at blood collection. Some participants identified as cases were included in the comparison subcohort (4 kidney cancers, 9 bladder cancers, 11 breast cancers, 58 prostate cancers, 7 pancreatic cancers, 16 haematological malignancies).

[The Working Group noted as strengths the large number of cases and the collection of blood samples before diagnosis. Because of the design as a survivor cohort, and the long time period that had elapsed between enrolment in the CPS-II Nutrition Cohort and enrolment in the LifeLink cohort, it was likely that this study would not have included some persons who may have had cancer related to PFOA or PFOS, especially those who developed cancers earlier in life in a susceptible exposed population. This survivor bias would have biased the results downwards (i.e. towards the null or even towards inverse associations). Indeed, participants in this cohort were cancer-free survivors of the CPS-II Nutrition Cohort whose blood was collected in 1998–2001, when most of them were aged > 65 years. Although using a single sample to measure PFAS is a potential limitation, there is some evidence, from analyses of repeat samples of PFOA, that single samples may represent long-term averages over a 5–8-year period, with potential misclassification resulting in only minor bias to the null (Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636). However, there remains the concern that single PFOA or PFOS samples may not represent average exposure over longer periods, which is particularly relevant here given the older age at blood draw. Thus, it is reasonable to assume that most of the CPS Nutrition Cohort would have been exposed to PFOA or PFOS well before the time of blood collection. The Working Group considered this study to be of minimal informativeness.]

2.1.22 Case–control studies in West Virginia and Ohio

Vieira et al. (2013) conducted two case–control studies of 18 different incident cancers during the years 1996–2005 among residents of 13 counties in Ohio and West Virginia, USA, which included both contaminated and non-contaminated water districts near the same polymer-production plant in Parkersburg, West Virginia, which was the source of contamination in the population studied by Barry et al. (2013). This cohort was described in Section 2.1.5 above. The two case–control studies were included in the same publication (Vieira et al., 2013).

The source population in the study by Vieira et al. was cancer registries of Ohio and West Virginia, and the study included counties outside the contaminated water districts studied by the C8 Science Panel. The source population in Barry et al. was the population living in six contaminated water districts near the plant in Parkersburg, West Virginia, who had participated in the C8 Health Project baseline study of 69 000 residents in the water districts and had provided blood samples in which PFOA was measured.

The final data set consisted of 7869 cases from Ohio and 17 238 cases from West Virginia, from 13 counties, in whom cancer had been diagnosed at age ≥ 15 years, with 18 cancer categories (i.e. bladder, brain, female breast, cervix, colon or rectum, kidney, leukaemia, liver, lung, melanoma of the skin, multiple myeloma, NHL, ovary, pancreas, prostate, testis, thyroid, and uterus).

In the first case–control study conducted by Vieira et al., cases (of the 18 cancers of interest) and controls (controls were all other cancers apart from the cancer of interest, and excluding kidney, pancreatic, testicular, and liver cancers) were compared with regard to residence in a contaminated or non-contaminated water district. This study included cases from both West Virginia and Ohio. Odds ratios were calculated for residence versus non-residence in contaminated water districts, adjusted for age, sex, diagnosis year, smoking status (current, past, and unknown, with never smoker as the referent) and insurance provider (government-insured Medicaid, uninsured, and unknown, with privately insured as the referent). Analyses were done for each of the six contaminated water

districts versus non-contaminated districts (the districts had different degrees of contamination, and serum levels for a large number of residents of each contaminated district were known), and for all six contaminated districts combined.

These same authors also conducted a separate case–control study among Ohio residents only. The Ohio registry provided more residential detail than did the West Virginia registry, enabling geocoding of exact addresses. Exposure in the case–control study in Ohio was based on estimated individual serum levels of PFOA at specific addresses at specific points in time. The individual serum PFOA levels were estimated using linked environmental and toxicokinetics models (Shin et al., 2011a, b). The environmental models estimated air and water concentrations of PFOA between 1951 and 2008, integrating emissions data from the facilities, fate, and transport characteristics of PFOA, and addresses of case and control participants, and then, using estimated water consumption and PFOA serum half-life data, annual serum levels for those drinking the contaminated water were estimated. The authors assumed that the serum levels estimated 10 years before case diagnosis (and analogously for matched controls) were the exposure of interest. Odds ratios were calculated, relative to the unexposed, for the low (3.7–12.8 μg/L [ng/mL]), medium (12.9–30.7 μg/L [ng/mL]), high (30.8–109 μg/L [ng/mL]), and very high (110–655 μg/L [ng/mL]) exposure categories. The second study used the same set of potential confounders as the first study (see above), but additionally considered race.

[The Working Group noted that there was probably some overlap between the cancer cases considered in the study by Vieira et al. (2013) and those in Barry et al. (2013), although the extent of overlap was unknown. The Working Group noted that the strengths of this study were the good case ascertainment via cancer registries, the large number of incident cancers from cancer registries, and the reasonably large number of exposed cases of many specific cancers in people in the contaminated water districts (although small numbers were sometimes an issue for analyses of rarer cancers by category of exposure). The case–control study in Ohio benefited from being able to estimate serum levels for individuals on the basis of a model that was shown to provide a good prediction of the observed levels for 30 000 residents of the six contaminated water districts at one point in time (2005–2006) (Spearman correlation, 0.71; Winquist et al., 2013). The Working Group also noted limitations, including the assignment of an ecological exposure (by water district) in the first case–control study, as well as the use of estimated individual serum levels in the second case–control study (data from Ohio only) based on a model. In this second case–control study, a limitation was also the somewhat arbitrary assumption that the estimated serum levels 10 years before case diagnosis were the most relevant, as well as the assumption that the case and control participants had remained in the same residence for 10 years. Another limitation was the fairly small number of potential confounders available in the analyses. A potential limitation for both studies was the use of people with cancer as the controls, although the authors excluded those cancers thought to be potentially positively associated with PFOA. Use of cancer controls might bias estimates to the null, if any of the included cancers were in fact associated with PFOA. The use of cancer controls also might not reflect the general population with regard to potential confounders such as socioeconomic status and diet, but these potential differences in confounders were considered unlikely to have substantive effects in this population with very high exposure.]

2.2 Cancers of the urinary tract

See Table 2.2.

2.2.1 Kidney cancer

Three occupational cohort studies (Steenland and Woskie, 2012; Consonni et al., 2013; Raleigh et al., 2014), two population-based cohort studies (Barry et al., 2013; Li et al., 2022a), two population-based nested case–control studies (Shearer et al., 2021; Rhee et al., 2023b), one population-based case–cohort study (Winquist et al., 2023) and one population-based case–control study (Vieira et al., 2013) investigated the association between PFOA or PFOS exposure and mortality from and/or relative risk of kidney cancer. Some addressed PFOA exposures in settings where co-exposure to other PFAS compounds beyond background levels was unlikely, indicating that associations, if any, would primarily be due to PFOA (Steenland and Woskie, 2012; Barry et al., 2013; Vieira et al., 2013; Raleigh et al., 2014). Other studies addressing general populations with background exposure to multiple PFAS compounds provided PFAS-specific estimates (Winquist et al., 2023) or estimated PFOA associations after controlling for co-exposure to other PFAS compounds (Shearer et al., 2021; Rhee et al., 2023b).

Raleigh et al. (2014) investigated mortality and cancer incidence in an occupational cohort including 4668 employees working for ≥ 365 days from 1947 through 2002 at an APFO facility in Cottage Grove, Minnesota (in the Minneapolis metropolitan area), USA, and 4359 employees working for ≥ 365 days before 1999 at a tape and abrasives production facility (reference group). Individual cumulative airborne exposure to APFO was estimated. The study updated earlier studies of the same cohort (Gilliland and Mandel, 1993; Lundin et al., 2009) (see Section 2.1.1). There was no indication of increased risk of kidney cancer on the basis of either mortality data (24 deaths across the exposed and reference populations) or incidence data (35 cases).

[The Working Group noted that study strengths were complete ascertainment of the cohort, very limited loss to cancer follow-up, and quantitative cumulative exposure assessment with a large exposure contrast. Co-exposure to TFE (IARC Group 2A; with *inadequate* evidence in humans, but *sufficient* evidence in experimental animals, with evidence that it is a potent carcinogen in rats and mice, IARC, 2016) was addressed explicitly and found to be minimal. The small number of cases created uncertain risk estimates. Non-differential misclassification of exposure may have caused bias towards the null, and risk estimates with reference to unexposed workers should be interpreted with caution.]

Steenland and Woskie (2012) studied cause-specific mortality among 5791 fluoropolymer-production workers (men, 81%) in a polymer-production plant in Parkersburg, West Virginia, USA. The study was an extension by an additional 6 years of the cohort study by Leonard et al. (2008) and with a comprehensive quantitative exposure assessment. The cohort was described in detail earlier (Section 2.1.3). The mean and median estimated PFOA serum concentrations in workers from the Parkersburg plant were 350 ng/mL and 403 ng/mL, respectively, compared with a median of 4 ng/mL in the population of the USA. Mortality rates for exposed workers were compared with those for other workers from the same company in the region and the USA population.

The SMR (with other workers from the same company as the referent) for kidney cancer in the highest quartile of estimated cumulative serum PFOA concentration was 2.66 (95% CI, 1.15–5.24; 8 cases) with no lag, 2.82 (95% CI, 1.13–5.81; 7 cases) after a lag of 10 years, and 3.67 (95% CI, 1.48–7.57; 7 cases) after a lag of 20 years. Exposure–response analyses indicated a positive trend for kidney cancer in analyses with no lag and less consistently with a 10-year lag or a

Table 2.2 Epidemiological studies on exposure to PFOA and PFOS and cancers of the urinary tract

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Raleigh et al. (2014) MN, USA Enrolment, 1947–2002/follow-up, 1947–2008 (mortality), 1988–2008 (incidence) Cohort	9027 (4668 exposed workers, 4359 reference workers); Cottage Grove (MN) PFOA cohort; workers employed for ≥ 1 yr during 1947–2002 at an APFO facility (Cottage Grove; *n* = 4668); reference workers without any exposure to APFO, employed at a tape and abrasives production facility located in the same suburban geographical area and managed by the same company (Saint Paul; *n* = 4359) Exposure assessment method: see Table 2.1	Kidney, mortality	Exposed to APFO (SMR, MN referent):			Age, sex, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. Reference population sharing similar socioeconomic characteristics. *Other limitations*: See Table 2.1. Lacking data on workers who left Minnesota or Wisconsin; small numbers; no accounting for health behaviours.
			Unexposed (Saint Paul plant)	18	1.23 (0.73–1.95)		
			Exposed (Cottage Grove plant)	6	0.53 (0.20–1.16)		
		Kidney, mortality	Estimated cumulative airborne APFO exposure quartile (SMR, MN referent):			Age, sex, calendar period	
			1st quartile ($< 2.6 \times 10^{-5}$ µg/m³-years)	1	0.32 (0.01–1.77)		
			2nd quartile (2.6×10^{-5} to $< 1.4 \times 10^{-4}$ µg/m³-years)	2	0.74 (0.09–2.69)		
			3rd quartile (1.4×10^{-4} to $< 7.3 \times 10^{-4}$ µg/m³-years)	2	0.66 (0.08–2.38)		
			4th quartile ($\geq 7.3 \times 10^{-4}$ µg/m³-years)	1	0.42 (0.01–2.34)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Raleigh et al. (2014) MN, USA Enrolment, 1947–2002/follow-up, 1947–2008 (mortality), 1988–2008 (incidence) Cohort (cont.)		Kidney, incidence	Estimated cumulative airborne APFO exposure quartile (HR):			Age, sex*, year of birth	*Other comments*: *The Working Group assumed that the models were also adjusted for sex, as reported in the methods of Raleigh et al. (2014).
			Unexposed (Saint Paul plant)	19	1		
			1st quartile (< 2.9×10^{-5} µg/m³-years)	4	1.07 (0.36–3.16)		
			2nd quartile (2.9×10^{-5} to < 1.5×10^{-4} µg/m³-years)	4	1.07 (0.36–3.17)		
			3rd quartile (1.5×10^{-4} to < 7.9×10^{-4} µg/m³-years)	4	0.98 (0.33–2.92)		
			4th quartile (≥ 7.9×10^{-4} µg/m³-years)	4	0.73 (0.21–2.48)		
		Urinary bladder, mortality	Exposed to APFO (SMR, MN referent):			Age, sex, calendar period	
			Unexposed (Saint Paul plant)	8	0.62 (0.27–1.22)		
			Exposed (Cottage Grove plant)	8	0.89 (0.38–1.76)		
		Urinary bladder, mortality	Estimated cumulative airborne APFO exposure quartile (SMR, MN referent):			Age, sex, calendar period	
			1st quartile (< 2.6×10^{-5} µg/m³-years)	1	0.40 (0.01–2.25)		
			2nd quartile (2.6×10^{-5} to < 1.4×10^{-4} µg/m³-years)	2	0.93 (0.11–3.38)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Raleigh et al. (2014) MN, USA Enrolment, 1947–2002/follow-up, 1947–2008 (mortality), 1988–2008 (incidence) Cohort (cont.)		Urinary bladder, mortality (cont.)	3rd quartile (1.4×10^{-4} to $< 7.3 \times 10^{-4}$ µg/m³-years)	4	1.61 (0.44–4.13)	Age, sex, calendar period	
			4th quartile ($\geq 7.3 \times 10^{-4}$ µg/m³-years)	1	0.53 (0.01–2.97)		
		Urinary bladder, incidence	Estimated cumulative airborne APFO exposure quartile (HR):			Age, sex*, year of birth	
			Unexposed (Saint Paul Plant)	43	1		
			1st quartile ($< 2.9 \times 10^{-5}$ µg/m³)	7	0.81 (0.36–1.81)		
			2nd quartile (2.9×10^{-5} to $< 1.5 \times 10^{-4}$ µg/m³)	6	0.78 (0.33–1.85)		
			3rd quartile (1.5×10^{-4} to $< 7.9 \times 10^{-4}$ µg/m³)	15	1.50 (0.80–2.81)		
			4th quartile ($\geq 7.9 \times 10^{-4}$ µg/m³)	12	1.66 (0.86–3.18)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Alexander and Olsen (2007) Decatur (AL), USA Enrolment, 1961–1997/follow-up, 1970–2002 (mortality and incidence) Cohort	1588; Decatur (AL) PFOS cohort; production workers in the Alexander et al. (2003) cohort; a questionnaire was administered to living cohort members (response rate, 73.9%) to identify incident cases of bladder cancer; bladder cancer decedents were identified using underlying cause of death from death certificates; analyses excluded 495 living cohort members who did not return the questionnaire Exposure assessment method: see Table 2.1	Urinary bladder, incidence	PFOS exposure category (SIR, US referent):			Age, sex, calendar year	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. Use of incidence data with 74% participation rate in survey; use of cumulative exposure with internal comparisons, good exposure contrast; attempt to validate self-reported cancer for survey respondents. *Other limitations*: See Table 2.1. Occupational cohort with only 11 cases of bladder cancer, 2 in the highest category of exposure; bladder cancer incidence identified by survey of cohort (6 cases) and death certificates (5 deaths); no cancer registry matching; no ability to validate 5 bladder cancers identified by death certificate, mostly male (82%); only partial data on smoking.
			Never exposed	2	0.61 (0.07–2.19)		
			Ever exposed (low or high)	9	1.70 (0.77–3.22)		
			Ever high	6	1.74 (0.64–3.79)		
			Ever low	7	2.26 (0.91–4.67)		
			High for ≥ 1 yr	3	1.12 (0.23–3.27)		
			High or low for ≥ 1 yr	6	1.31 (0.48–2.85)		
		Urinary bladder, incidence	Cumulative PFOS exposure (years of employment in high PFOS-exposed jobs; SIR, US referent):			Age, sex, calendar year	
			0 to < 1	2	1.07 (0.12–3.85)		
			1 to < 5	4	0.95 (0.25–2.43)		
			5 to < 10	3	2.72 (0.55–73.95)		
			≥ 10	2	1.43 (0.16–5.15)		
		Urinary bladder, incidence	Cumulative PFOS exposure (years of employment in high PFOS-exposed jobs; RR):			Age, sex	
			0 to < 1	2	1		
			1 to < 5	4	0.83 (0.15–4.65)		
			5 to < 10	3	1.92 (0.30–12.06)		
			≥ 10	2	1.52 (0.21–10.99)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), 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 workers; Parkersburg (WV, USA), polymer-production PFOA occupational cohort; workers (men, 81%) at a polymer-manufacturing facility who had potential exposure to fluoropolymers with sufficiently detailed work histories Exposure assessment method: see Table 2.1	Kidney, mortality	PFOA-exposed workers (SMR):			Age, sex, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. Ability to evaluate associations with PFOA in a population exposed to levels much higher than in the general population. *Other limitations*: See Table 2.1. Restriction to mortality rates and small numbers of kidney cancer; reverse causation due to reduced glomerular function is an unresolved issue, but there was no excess of kidney disease found in in Steenland et al. (2015), who studied a subset of these workers (n = 3717).
			Other workers referent (same region and company)	12	1.28 (0.66–2.24)		
			US referent	12	1.09 (0.56–1.9)		
		Kidney, mortality	Cumulative serum exposure, no lag (SMR, other workers referent, same region and company):				
			1st quartile (0 to < 904 ppm-years)	1	1.07 (0.02–3.62)		
			2nd quartile (904 to < 1520 ppm-years)	3	1.37 (0.28–3.99)		
			3rd quartile (1520 to < 2700 ppm-years)	0	0.00 (0.00–1.42)		
			4th quartile (≥ 2700 ppm-years)	8	2.66 (1.15–5.24)		
			Trend-test P-value, 0.02				
		Kidney, mortality	Cumulative serum exposure, 10-yr lag (SMR, other workers referent, same region and company):				
			1st quartile (0 to < 798 ppm-years)	2	1.05 (0.13–3.79)		
			2nd quartile (798 to < 1379 ppm-years)	2	0.87 (0.11–3.15)		
			3rd quartile (1379 to < 2384 ppm-years)	1	0.44 (0.01–2.44)		
			4th quartile (≥ 2384 ppm-years)	7	2.82 (1.13–5.81)		
			Trend-test P-value, 0.02				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), 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 (cont.)		Kidney, mortality	Cumulative serum exposure, 20-yr lag (SMR, other workers referent, same region and company):			Age, sex, calendar period	
			1st quartile 1 (0 to < 515 ppm-years)	3	1.34 (0.28–3.91)		
			2nd quartile (515 to < 1057 ppm-years)	1	0.46 (0.01–2.55)		
			3rd quartile (1057 to < 1819 ppm-years)	0	0.00 (0.00–2.03)		
			4th quartile (≥ 1819 ppm-years)	7	3.67 (1.48–7.57)		
			Trend-test *P*-value, 0.003				
		Urinary bladder, mortality	PFOA-exposed workers (SMR):				
			Other workers referent (same region and company)	10	1.08 (0.52–1.99)		
			US referent	10	0.95 (0.46–1.75)		
		Urinary bladder, mortality	Cumulative serum exposure, no lag (SMR, other workers referent, same region and company):				
			1st quartile (0 to < 904 ppm-years)	2	1.24 (0.15–4.47)		
			2nd quartile (904 to < 1520 ppm-years)	6	2.49 (0.97–5.78)		
			3rd quartile (1520 to < 2700 ppm-years)	1	0.39 (0.01–2.17)		
			4th quartile (≥ 2700 ppm-years)	1	0.36 (0.10–2.01)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Steenland et al. (2015) Parkersburg (WV), USA Enrolment, 1948–2002/follow-up, 1951 to interview date in 2008–2011 (incidence) Cohort	3713 workers; a subset of Parkersburg (WV, USA), polymer-production PFOA cohort in Steenland and Woskie (2012); polymer-production workers (men, 80%) who responded (self or next-of-kin) to a questionnaire about health outcomes and who had measured or estimated occupational and residential exposure estimates; 29 incident cases of bladder cancer Exposure assessment method: see Table 2.1	Urinary bladder, incidence	Cumulative PFOA exposure, 10-yr lag (RR): 1st quartile (< 0.8 µg/mL-years) 2nd quartile (0.8 to < 3.44 µg/mL-years) 3rd quartile (3.44 to < 7.04 µg/mL-years) 4th quartile (≥ 7.04 µg/mL-years) Trend-test *P*-value, 0.03	 NR NR NR NR	 1 0.55 (0.12–2.61) 0.47 (0.10–2.21) 0.31 (0.06–1.54)	Age, sex, race, education, BMI, time-varying smoking, time-varying alcohol consumption, year of birth	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. Ability to evaluate associations with PFOA in a population exposed to levels much higher than in the general population. *Other limitations*: See Table 2.1. Few bladder cancers (n = 29).

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
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 Cases: 332 cases of cancer of the urinary bladder 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	Urinary bladder, incidence	Baseline plasma PFOA concentration (IRR):			Age, sex, smoking status, smoking intensity, smoking duration, years of school attendance, occupation associated with bladder cancer risk (rubber industry; textile industry; metal processing; glass industry; truck, bus, taxi drivers; painter, hairdresser; waiter; cook)	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. Large cohort with numerous incident cancers (n = 1240) followed 0–12 yr after baseline enrolment; control of confounders; use of internal comparison. *Other limitations*: See Table 2.1. Low exposure contrast in a population with background exposure levels.
			1st quartile	84	1		
			2nd quartile	82	0.71 (0.46–1.07)		
			3rd quartile	83	0.92 (0.61–1.39)		
			4th quartile	83	0.81 (0.53–1.24)		
			Continuous (per 1 ng/mL increase)	332	1.00 (0.95–1.05)		
		Urinary bladder, incidence	Baseline plasma PFOS concentration (IRR):				
			1st quartile	83	1		
			2nd quartile	84	0.76 (0.50–1.16)		
			3rd quartile	83	0.93 (0.61–1.41)		
			4th quartile	82	0.70 (0.46–1.07)		
			Continuous (per 10 ng/mL increase)	332	0.93 (0.83–1.03)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Barry et al. (2013) Mid-Ohio Valley (OH and WV), USA Enrolment, August 2005 to August 2006/ follow-up, 1952–2011 (incidence) Cohort	32 254 (28 541 community members and 3713 workers); C8 Science Panel Study; included people enrolled in the C8 Health Project who lived, worked, or attended school for ≥ 1 yr between 1950 and 3 December 2004 in a contaminated-water district in the vicinity of a chemical plant using PFOA in manufacturing processes (Parkersburg, WV; polymer-production facility), as well as a subset of those from the original Parkersburg (WV), polymer-production PFOA occupational cohort who worked at the plant between 1948 and 2002 Exposure assessment method: see Table 2.1	Kidney, 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*: See Table 2.1. Large cohort and strong exposure contrast, lagged analyses, adjustment for several covariates. *Other limitations*: See Table 2.1. Self-reported cancer data. Co-exposure to other PFAS in residents not evaluated.
			1st quartile	NR	1		
			2nd quartile	NR	1.23 (0.70–2.17)		
			3rd quartile	NR	1.48 (0.84–2.60)		
			4th quartile	NR	1.58 (0.88–2.84)		
			Continuous (per unit on natural log scale)	105	1.10 (0.98–1.24)		
			Trend-test *P*-value, 0.18				
		Kidney, incidence	Estimated cumulative PFOA serum concentration (ng/mL), 10-yr lag (HR):				
			1st quartile	NR	1		
			2nd quartile	NR	0.99 (0.53–1.85)		
			3rd quartile	NR	1.69 (0.93–3.07)		
			4th quartile	NR	1.43 (0.76–2.69)		
			Continuous (per unit on natural log scale)	105	1.09 (0.97–1.21)		
			Trend-test *P*-value, 0.34				
		Urinary bladder, incidence	Estimated cumulative PFOA serum concentration (ng/mL), no lag (HR):				
			Continuous (per unit on natural log scale)	105	1.00 (0.89–1.12)		
		Urinary bladder, incidence	Estimated cumulative PFOA serum concentration (ng/mL), 10-yr lag (HR):				
			Continuous (per unit on natural log scale)	105	0.98 (0.88–1.10)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Consonni et al. (2013) USA, UK, Italy, Germany, the Netherlands Enrolment, 1950–2002/follow-up, 1950–2008 (mortality) Cohort	5879 male workers (4205 APFO-exposed); the pooled international TFE cohort includes male workers who were ever employed or employed for 6 or 12 mo at one or more of six TFE-production sites in North America and Europe in 1950–2002; the principal occupational exposures were TFE and APFO (facilitating production of PTFE) Exposure assessment method: see Table 2.1	Kidney and other organs in the urinary tract, mortality	Cumulative APFO exposure (SMR, national referent):			Age, calendar period, country	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. 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*: See Table 2.1. Low statistical power to detect less-common cancers; high exposure correlations between TFE monomer and PFOA which precluded evaluation of effects of the individual compounds.
			Ever APFO-exposed	10	1.69 (0.81–3.11)		
			< 16 unit-year	3	1.57 (0.32–4.59)		
			16–138 unit-year	3	1.50 (0.31–4.39)		
			139+ unit-year	4	2.00 (0.54–5.12)		
			Trend-test *P*-value, 0.28				
		Urinary bladder, mortality	SMR (national referent):				
			Ever APFO-exposed	3	0.55 (0.11–1.60)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Shearer et al. (2021) USA Enrolment, 1993–2001; follow-up (from blood draw): median, 8.8 yr (incidence) Nested case–control	Nested within the PLCO cohort (see Table 2.1) Cases: 324; cancer source not reported Controls: 324; density-sampled on calendar time and individually matched on age categories, sex, race and ethnicity, study centre, and year of blood draw Exposure assessment method: see Table 2.1	Kidney (RCC), incidence	Serum PFOA (OR): < 4.0 µg/L ≥ 4.0 to 5.5 µg/L > 5.5 to 7.3 µg/L > 7.3 to 27.2 µg/L Continuous (per unit on $\log_2$ scale) Trend-test *P*-value, 0.007	 47 83 69 125 324	 1 1.47 (0.77–2.80) 1.24 (0.64–2.41) 2.63 (1.33–5.20) 1.71 (1.23–2.37)	Age, sex, race/ ethnicity, study centre, study year of blood draw, BMI, smoking status, history of hypertension, glomerular filtration rate, previous freeze–thaw cycle, calendar year of blood draw	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. High specificity of the outcome. Adjustment for kidney function to exclude reverse causation and for relevant potential confounders. *Other limitations*: See Table 2.1. Exposure assessment at a single time point likely attenuated risk estimates; no lagged analyses and no analyses of risk according to cumulative exposure; external validity is limited by a study population defined by phlebotomy and including mainly non-Hispanic Whites.
		Kidney (RCC), incidence	Serum PFOA (OR): < 4.0 µg/L ≥ 4.0 to 5.5 µg/L > 5.5 to 7.3 µg/L > 7.3 to 27.2 µg/L Continuous (per unit on $\log_2$ scale) Trend-test *P*-value, 0.13	 47 83 69 125 324	 1 1.41 (0.69–2.90) 1.12 (0.52–2.42) 2.19 (0.86–5.61) 1.68 (1.07–2.63)	Age, sex, race/ ethnicity, study centre, study year of blood draw, BMI, smoking status, history of hypertension, glomerular filtration rate, previous freeze–thaw cycle, calendar year of blood draw, PFOS serum concentration, PFHxS serum concentration	

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Shearer et al. (2021) USA Enrolment, 1993–2001; follow-up (from blood draw): median, 8.8 yr (incidence) Nested case–control (cont.)		Kidney (RCC), incidence	Serum PFOA (OR):			Age, sex, race/ethnicity, glomerular filtration rate, BMI, history of hypertension, smoking status, previous freeze–thaw cycle, calendar year of blood draw, study year of blood draw, study centre	
			Time from blood draw, ≥ 8 yr: Continuous (per unit on $\log_2$ scale)	NR	1.66 (1.25–2.19)		
		Kidney (RCC), incidence	Serum PFOS (OR):				
			≤ 26.3 µg/L	60	1		
			> 26.3 to 38.4 µg/L	82	1.67 (0.84–3.30)		
			> 38.4 to 49.9 µg/L	61	0.92 (0.45–1.88)		
			> 49.9 to 154.2 µg/L	121	2.51 (1.28–4.92)		
			Continuous (per unit on $\log_2$ scale)	324	1.39 (1.04–1.86)		
			Trend-test *P*-value, 0.009				
		Kidney (RCC), incidence	Serum PFOS (OR):			Age, sex, race/ethnicity, study centre, study year of blood draw, BMI, smoking status, history of hypertension, glomerular filtration rate, previous freeze–thaw cycle, calendar year of blood draw, PFOA serum concentration, PFHxS serum concentration	
			≤ 26.3 µg/L	60	1		
			> 26.3 to 38.4 µg/L	82	1.24 (0.59–2.57)		
			> 38.4 to 49.9 µg/L	61	0.53 (0.22–1.24)		
			> 49.9 to 154.2 µg/L	121	1.14 (0.45–2.88)		
			Continuous (per unit on $\log_2$ scale)	324	0.92 (0.60–1.42)		
			Trend-test *P*-value, 0.64				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Steenland et al. (2022) USA Enrolment, 1993–2014 (PLCO); August 2005 to August 2006 (C8 Panel study); follow-up, 1993–2014 (PLCO), 1952–2011 (C8 Panel study) Nested case–control	Cases: PLCO, 324; C8 Panel study, 103; all cases of RCC; cases from the PLCO cohort were the same as those identified in Shearer et al. (2021); cases from the C8 study were identified in the C8 panel cohort study (Barry et al., 2013) using the topographical code C64.9 and excluding urothelial carcinomas (e.g. morphology codes 8120, 8130), to capture mostly RCCs Controls: PLCO, 324; C8 panel study, 511; for the PLCO component, controls were the same as those identified in Shearer et al. (2021); for the C8 component, up to 5 controls per case were selected, matched on sex, race, year of birth (within 5 yr); controls were required to have survived past the age at which the case was diagnosed Exposure assessment method: see Table 2.1 for Shearer et al. (2021) and Barry et al. (2013)	Kidney (RCC), incidence	Serum PFOA, 2-piece linear spline (not transformed) model (log odds): Continuous (per ng/mL increase up to the knot (9.5 ng/mL))	427	0.135 (0.071–0.198)	Age, sex, race/ ethnicity, study centre (PLCO), year of blood draw (PLCO), birth year (C8), BMI, hypertension	*Exposure assessment method*: See Table 2.1 for Shearer et al. (2021) and Barry et al. (2013). *Other strengths*: See Table 2.1. Pooled analysis of large and informative studies on kidney cancer. *Other limitations*: See Table 2.1. Cumulative serum levels were not available in the PLCO study.
		Kidney (RCC), incidence	Serum PFOA, 2-piece linear spline (natural log-transformed) model (best-fitting) (log odds): Continuous (per unit increase up to the knot (ln PFOA = 2.55))	427	0.656 (0.333–0.979)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Li et al. (2022a) Ronneby, southern Sweden Enrolment, 1985–2013/follow-up, 1985–2016 (incidence) Cohort	60 507; the Ronneby Register Cohort included all individuals who ever lived in Ronneby municipality in 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 in 1985–2013 (15 811 individuals considered "ever-high"); subsets with long-term exposure (≥ 11 yr) in the latest part of the follow-up period (2005–2013) were considered to be more highly exposed Exposure assessment method: see Table 2.1	Kidney, incidence	Men, 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*: See Table 2.1. Complete registration of a large cohort; no loss to follow-up; long follow-up period. *Other limitations*: See Table 2.1. Mixed PFAS exposure (mainly PFOS, PFHxS and PFOA); no adjustment for known determinants of kidney cancer such as hypertension and overweight; relatively few cases producing uncertain risk estimates.
			Never	46	0.67 (0.49–0.90)		
			Ever	17	0.86 (0.50–1.38)		
		Kidney, incidence	Women, residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Never	43	1.17 (0.84–1.57)		
			Ever	16	1.47 (0.84–2.39)		
		Kidney, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	89	1		
			Ever	33	1.27 (0.85–1.91)		
		Kidney, incidence	Time period of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	89	1		
			Early (1985–2004)	19	1.05 (0.64–1.73)		
			Late (2005–2013)	14	1.85 (1.00–3.40)		
		Kidney, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	89	1		
			Short (1–10 yr)	15	1.11 (0.64–1.92)		
			Long (≥ 11 yr)	18	1.47 (0.87–2.49)		
		Urinary bladder, incidence	Men, residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Never	166	0.94 (0.80–1.09)		
			Ever	57	1.10 (0.84–1.43)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Li et al. (2022a) Ronneby, southern Sweden Enrolment, 1985–2013/follow-up, 1985–2016 (incidence) Cohort (cont.)		Urinary bladder, incidence	Women, residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Age, calendar year	
			Never	35	0.69 (0.48–0.95)		
			Ever	17	1.13 (0.66–1.80)		
		Urinary bladder, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	200	1		
			Ever	74	1.30 (0.99–1.69)		
		Urinary bladder, incidence	Time period of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	200	1		
			Early (1985–2004)	46	1.20 (0.87–1.66)		
			Late (2005–2013)	28	1.50 (0.98–2.29)		
		Urinary bladder, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age, sex	
			Never	200	1		
			Short (1–10 yr)	39	1.23 (0.87–1.73)		
			Long (≥ 11 yr)	35	1.39 (0.95–2.02)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rhee et al. (2023b) CA and HI, USA Enrolment, 1993–1996/follow-up, through 2018 Nested case–control	Nested within the MEC cohort Cases: 428; all RCC cases identified as of 2018 in the MEC study, with available pre-diagnostic serum sample; incident cases identified through linkage with the SEER HI registry and the CA state cancer registry Controls: 428; controls were MEC participants alive at the time of the matched case diagnosis and matched 1:1 to cases on sex, race or ethnicity, study centre, age and date at serum collection, time of serum collection, and fasting status Exposure assessment method: see Table 2.1	Kidney (RCC), incidence	PFOA serum concentration (OR):			Sex, race/ethnicity, study centre, age at serum collection, date of serum collection, time of serum collection, fasting status, smoking status, BMI, history of hypertension, eGFR, PFOS (log_2-transformed), PFHxS (log_2-transformed), PFNA (log_2-transformed), FOSA detected	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. Large sample size; consideration of multiple PFAS adjustment; stratification by race/ethnicity. *Other limitations*: See Table 2.1. Some of the stratified analysis by race/ethnicity have limited statistical power.
			1st quartile (≤ 3.27 µg/L)	107	1		
			2nd quartile (> 3.27 to 4.47 µg/L)	99	1.26 (0.80–1.97)		
			3rd quartile (> 4.47 to 6.22 µg/L)	122	1.26 (0.78–2.05)		
			4th quartile (> 6.22 µg/L)	100	1.04 (0.60–1.81)		
			Continuous (per unit on log_2 scale)	428	0.89 (0.67–1.18)		
			Trend-test *P*-value, 0.75				
		Kidney (RCC), incidence	White participants, PFOA serum concentration (OR):			Sex, study centre, age at serum collection, date of serum collection, time of serum collection, fasting status, smoking status, BMI, history of hypertension, eGFR, PFOS (log_2-transformed), PFHxS (log_2-transformed), PFNA (log_2-transformed), FOSA detected	
			1st quartile (≤ 3.27 µg/L)	19	1		
			2nd quartile (> 3.27 to 4.47 µg/L)	15	2.08 (0.62–6.98)		
			3rd quartile (> 4.47 to 6.22 µg/L)	24	3.63 (0.84–15.8)		
			4th quartile (> 6.22 µg/L)	22	2.94 (0.56–15.5)		
			Continuous (per unit on log_2 scale)	80	2.12 (0.87–5.18)		
			Trend-test *P*-value, 0.48				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rhee et al. (2023b) CA and HI, USA Enrolment, 1993–1996/follow-up, through 2018 Nested case–control (cont.)		Kidney (RCC), incidence	African-American participants, PFOA serum concentration (OR):			Sex, study centre, age at serum collection, date of serum collection, time of serum collection, fasting status, smoking status, BMI, history of hypertension, eGFR, PFOS (log_2-transformed), PFHxS (log_2-transformed), PFNA (log_2-transformed), FOSA detected	
			1st quartile (≤ 3.27 µg/L)	24	1		
			2nd quartile (> 3.27 to 4.47 µg/L)	15	1 (0.23–4.33)		
			3rd quartile (> 4.47 to 6.22 µg/L)	17	1.01 (0.24–4.23)		
			4th quartile (> 6.22 µg/L)	16	1.08 (0.23–5.13)		
			Continuous (per unit on log_2 scale)	72	1.01 (0.51–1.98)		
			Trend-test *P*-value, 0.91				
		Kidney (RCC), incidence	Japanese-American participants, PFOA serum concentration (OR):				
			1st quartile (≤ 3.27 µg/L)	14	1		
			2nd quartile (> 3.27 to 4.47 µg/L)	25	2.62 (0.79–8.69)		
			3rd quartile (> 4.47 to 6.22 µg/L)	37	2.65 (0.77–9.15)		
			4th quartile (> 6.22 µg/L)	31	3.29 (0.84–12.88)		
			Continuous (per unit on log_2 scale)	107	1.00 (0.47–2.13)		
			Trend-test *P*-value, 0.22				

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rhee et al. (2023b) CA and HI, USA Enrolment, 1993–1996/follow-up, through 2018 Nested case–control (cont.)		Kidney (RCC), incidence	Native Hawaiian participants, PFOA serum concentration (OR):			Sex, study centre, age at serum collection, date of serum collection, time of serum collection, fasting status, smoking status, BMI, history of hypertension, eGFR, PFOS (log_2-transformed), PFHxS (log_2-transformed), PFNA (log_2-transformed), FOSA detected	
			1st quartile (≤ 3.27 µg/L)	12	1		
			2nd quartile (> 3.27 to 4.47 µg/L)	10	0.3 (0.04–2.31)		
			3rd quartile (> 4.47 to 6.22 µg/L)	17	0.28 (0.03–2.39)		
			4th quartile (> 6.22 µg/L)	11	0.08 (0.01–0.94)		
			Continuous (per unit on log_2 scale)	50	0.57 (0.21–1.55)		
			Trend-test *P*-value, 0.04				
		Kidney (RCC), incidence	PFOA serum concentration (OR):			Sex, race/ ethnicity, study centre, age at serum collection, date of serum collection, time of serum collection, fasting status, smoking status, BMI, history of hypertension, eGFR, PFOS (log_2-transformed), PFHxS (log_2-transformed), PFNA (log_2-transformed), FOSA detected	
			Calendar year blood drawn, before 2002: Continuous (per unit on log_2 scale)	90	1.49 (0.77–2.87)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rhee et al. (2023b) CA and HI, USA Enrolment, 1993–1996/follow-up, through 2018 Nested case–control (cont.)		Kidney (RCC), incidence	PFOA serum concentration (OR): Calendar year blood drawn, in 2002 or later: Continuous (per unit on $\log_2$ scale)	336	0.80 (0.56–1.13)	Sex, race/ ethnicity, study centre, age at serum collection, date of serum collection, time of serum collection, fasting status, smoking status, BMI, history of hypertension, eGFR, PFOS ($\log_2$-transformed), PFHxS ($\log_2$-transformed), PFNA ($\log_2$-transformed), FOSA detected	
		Kidney (RCC), incidence	PFOS serum concentration (OR): 1st quartile (< 16.65 µg/L)	118	1		
			2nd quartile (16.65 to < 25.05 µg/L)	105	1.05 (0.66–1.66)		
			3rd quartile (25.05 to < 36.40 µg/L)	100	0.99 (0.58–1.68)		
			4th quartile (≥ 36.40 µg/L)	105	0.93 (0.51–1.72)		
			Continuous (per unit on $\log_2$ scale)	428	0.95 (0.74–1.23)		
			Trend-test *P*-value, 0.72				
		Kidney (RCC), incidence	PFOS serum concentration (OR): Calendar year blood drawn, before 2002: Continuous (per unit on $\log_2$ scale)	90	0.77 (0.40–1.48)		
		Kidney (RCC), incidence	PFOS serum concentration (OR): Calendar year blood drawn, in 2002 or later: Continuous (per unit on $\log_2$ scale)	336	0.96 (0.73–1.28)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Winquist et al. (2023) 20 states, USA 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 (kidney cancer, 158, of which 109 were RCC, and urinary bladder, 401); incident cases from the CPS-II Lifelink Cohort (surviving CPS-II Nutrition cohort participants) with a first cancer diagnosis of kidney, urinary bladder detected through self-report or NDI linkage, and verified through medical-record review or cancer registry Controls: 999; a sex-stratified simple random sample of 499 women and 500 men (~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	Kidney, 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. *Other strengths*: See Table 2.1. Large number of cases. *Other limitations*: See Table 2.1. Survivor cohort with blood collected from persons mostly over aged 65, thus the study would not include persons who may have had PFOA- or PFOS-related cancer developed earlier in life, resulting in bias towards the null or even towards inverse associations.
			1st quartile (< 3.900 ng/mL)	39	1		
			2nd quartile (3.900 to < 5.200 ng/mL)	39	0.93 (0.56–1.56)		
			3rd quartile (5.200 to < 7.300 ng/mL)	39	0.83 (0.49–1.40)		
			4th quartile (≥ 7.300 ng/mL)	39	1.20 (0.71–2.04)		
			Continuous (per unit on $\log_2$ scale)	156	1.08 (0.88–1.33)		
		Kidney, incidence	Women, serum PFOA concentration (HR):			Year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			1st quartile (< 3.900 ng/mL)	17	1		
			2nd quartile (3.900 to < 5.200 ng/mL)	13	0.80 (0.34–1.87)		
			3rd quartile (5.200 to < 7.300 ng/mL)	17	1.04 (0.45–2.44)		
			4th quartile (≥ 7.300 ng/mL)	18	1.94 (0.87–4.35)		
			Continuous (per unit on $\log_2$ scale)	65	1.33 (0.97–1.83)		
		Kidney, incidence	Men, serum PFOA concentration (HR):				
			1st quartile (< 3.900 ng/mL)	22	1		
			2nd quartile (3.900 to < 5.200 ng/mL)	26	0.87 (0.43–1.75)		
			3rd quartile (5.200 to < 7.300 ng/mL)	22	0.65 (0.31–1.35)		
			4th quartile (≥ 7.300 ng/mL)	21	0.81 (0.39–1.68)		
			Continuous (per unit on $\log_2$ scale)	91	0.89 (0.66–1.20)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Winquist et al. (2023) 20 states, USA Enrolment, 1998–2001/follow-up, through 30 June 2015 Case–cohort (cont.)		Kidney, incidence	Serum PFOS concentration (HR):			Sex, year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			1st quartile (< 13.000 ng/mL)	35	1		
			2nd quartile (13.000– < 18.000 ng/mL)	39	0.92 (0.54–1.57)		
			3rd quartile (18.000- < 26.000 ng/mL)	42	0.97 (0.58–1.63)		
			4th quartile (≥ 26.000 ng/mL)	40	1.14 (0.67–1.92)		
			Continuous (per unit on $\log_2$ scale)	156	1.03 (0.84–1.26)		
		Kidney, incidence	Women, serum PFOS concentration (HR):			Year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			1st quartile (< 13.000 ng/mL)	19	1		
			2nd quartile (13.000 to < 18.000 ng/mL)	10	0.37 (0.14–0.94)		
			3rd quartile (18.000 to < 26.000 ng/mL)	17	0.76 (0.35–1.66)		
			4th quartile (≥ 26.000 ng/mL)	19	0.93 (0.40–2.15)		
			Continuous (per unit on $\log_2$ scale)	65	1.06 (0.70–1.59)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Winquist et al. (2023) 20 states, USA Enrolment, 1998–2001/follow-up, through 30 June 2015 Case–cohort (cont.)		Kidney, incidence	Men, serum PFOS concentration (HR):			Year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			1st quartile (< 13.000 ng/mL)	16	1		
			2nd quartile (13.000 to < 18.000 ng/mL)	29	1.72 (0.82–3.61)		
			3rd quartile (18.000 to < 26.000 ng/mL)	25	1.39 (0.66–2.93)		
			4th quartile (≥ 26.000 ng/mL)	21	1.33 (0.62–2.85)		
			Continuous (per unit on $\log_2$ scale)	91	1.00 (0.79–1.28)		
		Kidney (RCC), incidence	Serum PFOA concentration (HR):			Sex, year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			1st quartile (< 3.900 ng/mL)	27	1		
			2nd quartile (3.900 to < 5.000 ng/mL)	25	1.00 (0.54–1.87)		
			3rd quartile (5.000 to < 7.400 ng/mL)	28	0.74 (0.40–1.36)		
			4th quartile (≥ 7.400 ng/mL)	27	1.21 (0.65–2.27)		
			Continuous (per unit on $\log_2$ scale)	107	1.06 (0.83–1.35)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Winquist et al. (2023) 20 states, USA Enrolment, 1998–2001/follow-up, through 30 June 2015 Case–cohort (cont.)		Kidney (RCC), incidence	Women, serum PFOA concentration (HR):			Year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			1st quartile (< 3.900 ng/mL)	8	1		
			2nd quartile (3.900 to < 5.000 ng/mL)	8	1.33 (0.42–4.19)		
			3rd quartile (5.000 to < 7.400 ng/mL)	13	1.66 (0.54–5.12)		
			4th quartile (≥ 7.400 ng/mL)	13	3.14 (1.04–9.54)		
			Continuous (per unit on $\log_2$ scale)	42	1.54 (1.05–2.26)		
		Kidney (RCC), incidence	Men, serum PFOA concentration (HR):				
			1st quartile (< 3.900 ng/mL)	19	1		
			2nd quartile (3.900– < 5.000 ng/mL)	17	0.79 (0.36–1.74)		
			3rd quartile (5.000– < 7.400 ng/mL)	15	0.45 (0.20–1.01)		
			4th quartile (≥ 7.400 ng/mL)	14	0.64 (0.28–1.46)		
			Continuous (per unit on $\log_2$ scale)	65	0.80 (0.57–1.11)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Winquist et al. (2023) 20 states, USA Enrolment, 1998–2001/follow-up, through 30 June 2015 Case–cohort (cont.)		Kidney (RCC), incidence	Serum PFOS concentration (HR):			Sex, year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			1st quartile (< 13.000 ng/mL)	25	1		
			2nd quartile (13.000 to < 19.000 ng/mL)	29	0.82 (0.45–1.49)		
			3rd quartile (19.000 to < 26.000 ng/mL)	24	0.96 (0.51–1.80)		
			4th quartile (≥ 26.000 ng/mL)	29	1.13 (0.61–2.07)		
			Continuous (per unit on $\log_2$ scale)	107	1.08 (0.84–1.38)		
		Kidney (RCC), incidence	Women, serum PFOS concentration (HR):			Year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			1st quartile (< 13.000 ng/mL)	11	1		
			2nd quartile (13.000 to < 19.000 ng/mL)	6	0.40 (0.12–1.35)		
			3rd quartile (19.000 to < 26.000 ng/mL)	10	0.89 (0.32–2.46)		
			4th quartile (≥ 26.000 ng/mL)	15	1.29 (0.45–3.74)		
			Continuous (per unit on $\log_2$ scale)	42	1.30 (0.77–2.20)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Winquist et al. (2023) 20 states, USA Enrolment, 1998–2001/follow-up, through 30 June 2015 Case–cohort (cont.)		Kidney (RCC), incidence	Men, serum PFOS concentration (HR):			Year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			1st quartile (< 13.000 ng/mL)	14	1		
			2nd quartile (13.000 to < 19.000 ng/mL)	23	1.25 (0.57–2.74)		
			3rd quartile (19.000 to < 26.000 ng/mL)	14	1.10 (0.46–2.60)		
			4th quartile (≥ 26.000 ng/mL)	14	0.98 (0.42–2.29)		
			Continuous (per unit on $\log_2$ scale)	65	0.97 (0.73–1.29)		
		Urinary bladder, incidence	Serum PFOA concentration (HR):			Sex, year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			1st quartile (< 3.800 ng/mL)	95	1		
			2nd quartile (3.800 to < 5.100 ng/mL)	97	0.84 (0.56–1.26)		
			3rd quartile (5.100 to < 6.700 ng/mL)	99	0.87 (0.58–1.30)		
			4th quartile (≥ 6.700 ng/mL)	105	0.86 (0.58–1.27)		
			Continuous (per unit on $\log_2$ scale)	396	0.93 (0.77–1.13)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Winquist et al. (2023) 20 states, USA Enrolment, 1998–2001/follow-up, through 30 June 2015 Case–cohort (cont.)		Urinary bladder, incidence	Women, serum PFOA concentration (HR):			Year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			1st quartile (< 3.800 ng/mL)	25	1		
			2nd quartile (3.800 to < 5.100 ng/mL)	25	1.23 (0.60–2.52)		
			3rd quartile (5.100 to < 6.700 ng/mL)	12	0.68 (0.27–1.70)		
			4th quartile (≥ 6.700 ng/mL)	20	0.81 (0.37–1.78)		
			Continuous (per unit on $\log_2$ scale)	82	0.91 (0.63–1.31)		
		Urinary bladder, incidence	Men, serum PFOA concentration (HR):				
			1st quartile (< 3.800 ng/mL)	70	1		
			2nd quartile (3.800 to < 5.100 ng/mL)	72	0.80 (0.49–1.32)		
			3rd quartile (5.100 to < 6.700 ng/mL)	87	0.92 (0.57–1.49)		
			4th quartile (≥ 6.700 ng/mL)	85	0.87 (0.54–1.40)		
			Continuous (per unit on $\log_2$ scale)	314	0.93 (0.74–1.17)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Winquist et al. (2023) 20 states, USA Enrolment, 1998–2001/follow-up, through 30 June 2015 Case–cohort (cont.)		Urinary bladder, incidence	Serum PFOS concentration (HR):			Sex, year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			1st quartile (< 13.000 ng/mL)	95	1		
			2nd quartile (13.000 to < 18.000 ng/mL)	92	0.81 (0.54–1.21)		
			3rd quartile (18.000 to < 25.000 ng/mL)	106	1.07 (0.72–1.60)		
			4th quartile (≥ 25.000 ng/mL)	103	0.96 (0.64–1.44)		
			Continuous (per unit on $\log_2$ scale)	396	1.01 (0.86–1.20)		
		Urinary bladder, incidence	Women, serum PFOS concentration (HR):			Year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			1st quartile (< 13.000 ng/mL)	27	1		
			2nd quartile (13.000– < 18.000 ng/mL)	17	0.51 (0.24–1.05)		
			3rd quartile (18.000– < 25.000 ng/mL)	20	0.65 (0.33–1.30)		
			4th quartile (≥ 25.000 ng/mL)	18	0.63 (0.29–1.35)		
			Continuous (per unit on $\log_2$ scale)	82	0.82 (0.58–1.16)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Winquist et al. (2023) 20 states, USA Enrolment, 1998–2001/follow-up, through 30 June 2015 Case–cohort (cont.)		Urinary bladder, incidence	Men, serum PFOS concentration (HR):			Year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	
			1st quartile (< 13.000 ng/mL)	68	1		
			2nd quartile (13.000–< 18.000 ng/mL)	75	0.92 (0.57–1.49)		
			3rd quartile (18.00–< 25.000 ng/mL)	86	1.20 (0.75–1.94)		
			4th quartile (≥ 25.000 ng/mL)	85	1.10 (0.68–1.78)		
			Continuous (per unit on $\log_2$ scale)	314	1.06 (0.78–1.28)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vieira et al. (2013) OH and WV, USA 1996–2005 (incidence) Case–control	Cases: study 1: kidney cancer, 751, and bladder cancer, 1350; study 2: kidney cancer, 246, and bladder cancer, 395; index cancer cases were retrieved from cancer registries covering a community sample with relatively high exposure to PFOA because of contamination of drinking-water from the Parkersburg (WV), polymer-production plant; 18 different cancers were analysed (bladder, brain, female breast, cervix, colon/ rectum, kidney, leukaemia, liver, lung, melanoma of the skin, multiple myeloma, NHL, ovary, pancreas, prostate, testis, thyroid, and uterus)	Kidney, incidence	Study 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*: See Table 2.1. Well-ascertained cases based on cancer registries. *Other comments*: See Table 2.1. Substantial overlap of the study population addressed by a C8 Science Panel Project by Barry et al. (2013).
			Unexposed	657	1		
			Any exposed water district	94	1.1 (0.9–1.4)		
		Kidney, incidence	Study 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	187	1		
			Low (3.7–12.8 µg/L)	11	0.8 (0.4–1.5)		
			Medium (12.9–30.7 µg/L)	17	1.2 (0.7–2.0)		
			High (30.8–109 µg/L)	22	2.0 (1.3–3.2)		
			Very high (110–655 µg/L)	9	2.0 (1.0–3.9)		

Table 2.2 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vieira et al. (2013) OH and WV, USA 1996–2005 (incidence) Case–control (cont.)	Controls: study 1: 23 548 (for kidney), 22 198 (for bladder) other cancers; study 2: 7339 (for kidney), 6944 (for bladder); for each cancer site evaluated, controls were cases of cancer at all other sites, (excluding sites in the kidney, testis, pancreas, and liver, which have been associated with PFOA in studies in experimental animals or humans) Exposure assessment method: See Table 2.1	Urinary bladder, incidence	Study 1. Residence in a PFOA-contaminated water district (OH and WV) (OR):			Age, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	1213	1		
			Any exposed water district	137	0.8 (0.7–1.0)		
		Urinary bladder, incidence	Study 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	326	1		
			Low (3.7–12.8 µg/L)	23	0.9 (0.6–1.4)		
			Medium (12.9–30.7 µg/L)	21	0.9 (0.6–1.4)		
			High (30.8–109 µg/L)	21	1.2 (0.8–2.0)		
			Very high (110–655 µg/L)	4	0.6 (0.2–1.5)		

AL, Alabama; APFO, ammonium perfluorooctanoate; approx., approximately; BMI, body mass index; CA, California; CI, confidence interval; CPS-II, Cancer Prevention Study II; eGFR, estimated glomerular filtration rate; FOSA, perfluorooctane sulfonamide; HI, Hawaii; HR, hazard ratio; IRR, incidence rate ratio; MEC, Multiethnic Cohort; MN, Minnesota; NDI, National Death Index; NR, not reported; OH, Ohio; OR, odds ratio; PFAS, per- and polyfluoroalkyl substances; PFHxS, perfluorohexanesulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; ppm, parts per million; PTFE, polytetrafluoroethylene; RCC, renal cell carcinoma; RR, rate ratio; SEER, Surveillance, Epidemiology, and End Results; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TFE, tetrafluoroethylene; UK, United Kingdom; US, United States; USA, United States of America; WV, West Virginia; yr, year(s).

20-year lag. Numbers were small (1–7 cases in each quartile of exposure with a 10-year lag), but the test for trend across quartiles was significant.

[The Working Group noted that the detailed historical exposure assessment using blood samples to model serum PFOA levels across time was an improvement in the exposure assessment. Results were limited by restriction to mortality rates and by small numbers of fatal kidney cancer. Possible co-exposure to TFE (IARC Group 2A) could not be excluded but seemed of minor importance. Earlier indications that PFOA may be associated with kidney disease and reduced glomerular filtration and thereby introduce reverse causation in studies on PFAS and kidney cancer have not been corroborated in later studies (Dhingra et al., 2016, 2017).]

Barry et al. (2013) evaluated the risk of kidney cancer, among other cancers, in 32 254 adult community residents in the Mid-Ohio Valley, USA, exposed to drinking-water contaminated with PFOA as a result of chemical plant emissions and in workers at a local chemical plant producing PTFE (C8 Health Project). The cohort was described in detail earlier (Section 2.1.5). Briefly, information on cancer occurrence was obtained by interview in 2005–2011 for the period from 1952 onwards. Cumulative exposure to PFOA in community residents was assessed using serum measurements in 2005–2006, historical regional and occupational data from several sources, and PFOA toxicokinetics. The estimated annualized serum PFOA concentrations matched well with measured levels (Spearman correlation, 0.71, comparing predicted levels with 2005–2006 measured levels, Winquist et al., 2013). Cumulative PFOA serum estimates in workers were estimated using a chemical plant-specific JEM.

Estimated cumulative serum PFOA concentration was associated with risk of kidney cancer; the hazard ratio for a one-unit increase in natural log-transformed serum PFOA was 1.10 (95% CI, 0.98–1.24; $P = 0.10$; 105 cases). Quartile analysis also indicated positive trends with increasing exposure. The adjusted hazard ratio for the fourth quartile versus the first was 1.58 (95% CI, 0.88–2.84; linear trend test, $P = 0.18$). Risk estimates based upon 10-year lagged analyses were slightly attenuated in the fourth quartile but not in the third quartile.

[The Working Group noted that this study presented improvements over other cohort studies because of its large study population; the large exposure contrast including both high-level occupational PFOA exposure, environmental PFOA exposure, and PFOA background exposure; the comprehensive exposure modelling using biological measurements in combination with environmental data, also taking PFOA toxicokinetics and variation across time into account; and the statistical analyses adjusting for a number of covariates and including lagged analyses. Although the study almost entirely included residents alive in 2005, the participation in the C8 Health Project was high, and the cohort was largely representative of the target population (Winquist et al., 2013). Moreover, a simulation study did not indicate that failure to include residents who died from kidney cancer before enrolment would bias risk estimates towards null (Barry et al., 2015). Nevertheless, capture of a larger part of the at-risk population would have added additional value to this study.]

Consonni et al. (2013) investigated cause-specific mortality rates in an international occupational cohort of 5879 male TFE workers, of whom 4205 were exposed to APFO. An individual semiquantitative estimate of cumulative TWA exposure to APFO was assigned from a study-specific JEM. The cohort was described in detail earlier (Section 2.1.6). Using national data as the referent, the risk of cancer of the kidney and urinary organs other than bladder (ICD-9 code 189) was elevated (SMR, 1.69; 95% CI, 0.81–3.11) but with no indication of an exposure–response relation (Consonni et al., 2013).

[The Working Group noted that the informativeness of this study was limited because of the small numbers of exposed men with cancer (n = 10), the semiquantitative exposure assessment with few measurements available, and the high correlation between TFE and PFOA exposure. However, exposure to TFE at the Parkersburg facility – the largest facility of the study – was considered to be very low because of strict hygiene controls for this flammable and explosive compound.]

Shearer et al. (2021) conducted a general population-based case–control study, nested within the PLCO cohort, addressing the risk of RCC according to prediagnostic serum concentrations of eight PFAS compounds, including PFOA and PFOS. The PLCO cohort was described in detail earlier (Section 2.1.11). In brief, 324 cases of RCC and 324 individually matched controls with baseline serum samples were enrolled in 1993–2001 from the screening arm of a multicentre randomized cancer screening trial in USA that included approximately 150 000 citizens (approximately half, 74 000, randomly assigned to the screening arm of the trial, provided blood samples at the baseline screening examination; Hayes et al., 2000). The adjusted risk of RCC was increased in individuals with higher PFOA serum concentration. The adjusted odds ratio in the highest exposure quartile (> 7.3–27.2 µg/L [ng/mL]) versus the lowest (< 4.0 µg/L [ng/mL]) was 2.63 (95% CI, 1.33–5.20) and, using a continuous exposure metric, the approximate risk related to a doubling of the serum concentration was 1.71 (95% CI, 1.23–2.37). Several potential confounders were controlled either by matching or by including variables in the models. The estimates of relative risk for PFOA changed little when PFOS and PFHxS were included in multivariable analysis and did not vary by kidney function (P for heterogeneity, 0.97), duration of time since blood sampling (P for heterogeneity, 0.32), and prior freeze–thaw cycles of the specimen (P for heterogeneity, 0.63). There was no indication of risk modification by sex (P for heterogeneity, 0.87) or age (P for heterogeneity, 0.66); although estimates did not differ significantly, associations seemed stronger among those with normal BMI (P for heterogeneity, 0.74), those without a history of hypertension (P for heterogeneity, 0.31), and among former and current smokers (P for heterogeneity, 0.24).

The adjusted risk of RCC was also increased in individuals with higher PFOS serum concentrations with a significant exposure–response trend, but the risk was attenuated when adjusted for PFOA and PFHxS serum concentrations.

[The Working Group noted that this general population study was distinguished from other case–control studies by having PFOA analyses adjusted for other PFAS compounds, by benefiting from blood samples collected on average 8.8 years before diagnosis, and by adjustment for several potential confounders, which added strongly to the reliability of the results. Although using a single sample to measure PFAS was a potential limitation, there is some evidence, from analyses of repeat samples of PFOA, that single samples may represent long-term averages over a 5–8-year period, with potential misclassification resulting in only minor bias to the null (see Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636). Exposure assessment at a single time point precludes analyses of risk according to cumulative exposure in specified exposure windows; however, some insight was obtained by analyses stratified by years from blood collection to diagnosis. Overall, this study within a general population added substantially to the evaluation of risk of kidney cancer after exposure to PFOA and PFOS.]

Steenland et al. (2022) conducted a pooled analysis of two studies on PFOA and RCC, described above (Barry et al., 2013; Shearer et al., 2021). Both studies were based upon quantitative assessment of PFOA serum concentrations and

enabled exposure–response modelling for the purposes of assessment of lifetime excess risk and setting of limit values. The pooled analysis included 427 cases and 835 controls. The best-fitting dose–response model for the pooled data was a two-piece linear spline model with natural log-transformed serum PFOA and a knot at 2.55 (serum PFOA concentration, approximately 12.5 ng/mL). The log odds of RCC increased up to the knot and was flat thereafter. [The Working Group noted that the focus of this paper was on risk assessment and calculation of limit values and on quantitative exposure–response modelling that is important for causal inference.]

Li et al. (2022a) investigated the risk of kidney cancer in a community sample with a high level of exposure in Sweden, with follow-up from 1985 (when PFAS contamination of waterworks started) until the end of 2016 (Section 2.1.13). Exposure was categorized according to period and duration of living in a contaminated area. PFOA constituted only a minor part of the PFAS contamination, which was dominated by PFOS and PFHxS. SIRs, calculated separately for men and women, were adjusted for age and calendar year using regional reference rates. The SIR for kidney cancer for participants who had ever resided in an area with high PFAS contamination was elevated in women, but not in men. Internal comparisons of exposed and unexposed residents, adjusted for age, sex, and calendar year, revealed an increased risk among those who had ever been exposed (HR, 1.27; 95% CI, 0.85–1.91), with slightly higher risk in residents with longer and more recent exposure. [Major strengths included the complete registration of the cohort, no loss to follow-up, and a long follow-up period. Major limitations were the ecological exposure assessment based upon residence without individual estimates related to PFOS exposure, and the relatively few cases of kidney cancer, producing uncertain risk estimates.]

Rhee et al. (2023b) conducted a nested case–control study of prediagnostic serum concentrations of nine PFAS among 428 cases of RCC and 428 individually matched controls within the MEC (see Section 2.1.16). The MEC included more than 215 000 men and women aged 45–75 years at baseline (1993–1996) and represents a very racially, ethnically, and socioeconomically diverse population. Cohort members were living in Hawaii and California (primarily Los Angeles County), USA. Cases were ascertained via cancer registries in California and Hawaii. The controls were individually matched to cases on race, ethnicity, sex, age at serum sample, date of serum sampling, study centre (Hawaii or California), fasting status at time of sample, and time of day of sampling. The controls were not diagnosed with RCC at the time when their matched case was diagnosed. Eleven PFAS were measured, including PFOA, PFOS, PFHxS, and PFNA. Exposure levels were similar to those measured in the general population in NHANES. Analyses were conducted by conditional logistic regression maintaining the matched pairs, were mutually adjusted for all PFAS, and controlled for the matching factors, as well as for smoking status, eGFR, history of hypertension, and BMI. Analyses were carried out modelling the exposure both as categorical (using quartiles) or as continuous (using $\log_2$) serum levels. PFOA and PFOS were correlated (Spearman correlation, $\rho = 0.61$), and PFNA was correlated with both PFOA and PFOS ($\rho = 0.57$ and $\rho = 0.48$, respectively). The legacy PFAS (PFOA, PFOS, PFHxS, and PFNA) were detected in ≥ 97% of study participants. PFOA was not associated with renal cancer in the overall study group, with the OR for quartile 4 versus quartile 1 being 1.04 (95% CI, 0.60–1.81) and the OR for continuous $\log_2$ PFOA being 0.89 (95% CI, 0.67–1.18). However, a positive association was observed for White participants, with an OR per $\log_2$ PFOA concentration of 2.12 (95% CI, 0.87–5.18) and higher ORs for upper quartiles (ranging from 2.1 to 3.6 for quartiles 2 to 4 versus

quartile 1). There was also a suggestive association for those sampled before 2002 (OR per $\log_2$ PFOA concentration, 1.49; 95% CI, 0.77–2.87).

[The Working Group considered this nested case–control study to be informative, given the large sample size, the adjustment for multiple PFAS, the multiple racial or ethnic groups studied, the good cancer ascertainment via registries, and the availability of serum levels before diagnosis. The limitations were mainly the small sample sizes for different racial or ethnic groups.]

Winquist et al. (2023) conducted a case–cohort study within the prospective CPS-II LifeLink Cohort of the ACS, with measurements of PFOA, PFOS, and several other PFAS in prediagnostic serum samples collected during 1998–2001 (Section 2.1.21). Overall, there was no increased risk of kidney cancer or RCC with increasing serum PFOA. In women, serum PFOA concentration was positively associated with RCC (HR per doubling of serum PFOA, 1.54; 95% CI, 1.05–2.26), whereas no association was observed in men. [The Working Group noted several strengths, including the case–cohort design, the large sample size, the good cancer ascertainment via registries and examination by histological subtype, and availability of prediagnostic serum samples. The limitations were mainly the low exposure levels and narrow exposure contrast. There may be a survivor bias downwards for kidney cancer, for which a relatively high proportion of cases are diagnosed before age 65 years, because of the gap between exposure and enrolment.]

Vieira et al. (2013) conducted a case–control study in Ohio and West Virginia, USA, to investigate the risk of 18 cancers, including kidney cancer, in a community sample with relatively high exposure to PFOA due to contamination of drinking-water from the polymer-production plant in Parkersburg, West Virginia, USA (Section 2.1.22). Incident cancers diagnosed in 1996–2005 were identified from cancer registries. The control population was people with other cancers, except cancers of the kidney, testis, liver, or pancreas. Logistic regression was used to estimate odds ratios, which were adjusted for age, sex, diagnosis year, smoking status, and insurance provider. For the Ohio subset with individual-level serum estimates of exposure, the adjusted odds ratios (AOR) for kidney cancer were higher in the highest exposure categories, with indications of a dose–response relation: AOR, 0.8 (95% CI, 0.4–1.5; 11 cases), 1.2 (95% CI, 0.7–2.0; 17 cases), 2.0 (95% CI, 1.3–3.2; 22 cases), and 2.0 (95% CI, 1.0–3.9; 9 cases) versus unexposed for low, medium, high, and very high exposure categories, respectively. Estimates of PFOA annual serum levels 10 years before diagnosis were 3.7–12.8 µg/L [ng/mL], 12.9–30.7 µg/L [ng/mL], 30.8–109 µg/L [ng/mL], and 110–655 µg/L [ng/mL] for these four categories.

For the combined populations of Ohio and West Virginia without individual-level exposure estimates, the odds ratio for kidney cancer was 1.1 (95% CI, 0.9–1.4; 94 exposed cases) for participants exposed to contaminated water districts relative to unexposed participants.

[The Working Group noted that some of the cancer cases were overlapping cases from the study by Barry et al. (2013). Strengths were the large study population with a strong exposure contrast and estimates of individual-level exposure for a subset of the population. Misclassification of exposure was likely to be non-differential, resulting in attenuated risk estimates (if truly deviating from unity). Limitations of the main analysis applying individual-level exposure estimates were mainly related to modelled exposure data.]

The Working Group conducted a random-effects meta-analysis to estimate the rate ratio (RR) per unit (linear) of serum PFOA, by following the same methodology outlined in Bartell and Vieira (2021). Details of the methodology are outlined in Annex 3 (Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.

int/636). The studies by Raleigh et al. (2014) and Consonni et al. (2013) were not included because of the lack of serum measurements. Categorical rate ratios based on contrasting the upper category (usually quartiles) with the referent were used, along with the assumed midpoints of the upper category and referent, to regress the log of the rate ratios on the midpoints to obtain a single linear continuous coefficient that estimates the change in log rate ratio per 10 ng/mL of (linear) PFOA. When including the studies by Steenland and Woskie (2012), Barry et al. (2013), Vieira et al. (2013), Shearer et al. (2021), Rhee et al. (2023b), and Winquist et al. (2023), the meta-analysis described above gave a result for an increase in the meta-rate ratio (meta-RR) per increase of 10 ng/mL of PFOA as 1.15 (95% CI, 0.97–1.37; I^2 = 0.91). In a sensitivity analysis excluding the studies by Steenland and Woskie (2012) and Vieira et al. (2013), given the concern regarding overlap with Barry et al. (2013), this sensitivity analysis gave a result for an increase in the meta-rate ratio per increase of 10 ng/mL PFOA as 1.21 (95% CI, 0.94–1.57; I^2 = 0.95). [The Working Group noted that a general limitation of the meta-analysis was the assumption of a linear exposure–response relation, although it has been observed that in studies with continuous exposure coefficients, (Barry et al., 2013; Shearer et al., 2021; Rhee et al., 2023b; Winquist et al., 2023) a logarithmic transformation of PFOA levels seems to fit the data better than do the untransformed PFOA levels. Other main limitations of the meta-analysis were: (i) the estimate of the linear coefficient using assumed midpoints of only two categories (uppermost and lowest); (ii) the use of average duration of exposure to transform cumulative exposure in the studies by Barry et al., Steenland and Woskie, and Vieira et al. to an assumed average exposure; and (iii) the assumption in the studies by Rhee et al., Shearer et al., and Winquist et al. that a single PFOA measurement is a good estimate of long-term lifetime average exposure (beyond a 5–8-year duration discussed in Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636). Given these limitations, as well as the high heterogeneity across studies with different strengths and weaknesses, the Working Group chose to not rely primarily on the meta-analysis of exposure–response relation to determine the hazard identification for kidney cancer in humans.]

2.2.2 Bladder cancer

See Table 2.2.

Raleigh et al. (2014) studied bladder cancer mortality and incidence among 4668 APFO-exposed workers at an APFO-production facility in Minnesota, USA (see Section 2.1.1 for more details). APFO is the ammonium salt of PFOA; the two substances are usually considered chemically equivalent in aqueous biological media such as the human body (Vierke et al., 2012). Raleigh et al. also studied 4359 unexposed workers at a different plant. Workers at both plants were employed for ≥ 1 year at their respective plants. For bladder cancer mortality, using the Minnesota population as the referent, the SMR for unexposed workers was 0.62 (95% CI, 0.27–1.22; 8 deaths). The SMRs for exposed workers, divided into quartiles of estimated APFO air exposure, were 0.40, 0.93, 1.61, and 0.53, based on 1, 2, 4, and 1 death, respectively. Bladder cancer incidence was ascertained using the Minnesota state cancer registry. Bladder cancer incidence hazard ratios, by quartile of estimated cumulative APFO air exposure, using unexposed workers as the referent, were 0.81 (95% CI, 0.36–1.81; 7 cases), 0.78 (95% CI, 0.33–1.85; 6 cases), 1.50 (95% CI, 0.80–2.81; 15 cases), and 1.66 (95% CI, 0.86–3.18; 12 cases).

Alexander et al. (2003) studied a cohort of 2083 production workers (145 deaths) who were exposed to PFOS at a plant in Decatur, Alabama, USA, that produced speciality films and

fluorochemicals, and who had worked ≥ 1 year at the plant between 1961 and 1997. Based on serum measurements for a sample of workers, a JEM was developed for all workers whereby jobs were classified into three exposure groups. Alexander and Olsen (2007) further followed this PFOS cohort, focusing on bladder cancer incidence; cases were identified using both questionnaire (6 cases) and death certificates (5 cases). Groups with no, low, and high exposure were estimated to have serum PFOS levels of [110–290 ng/mL], [390–890 ng/mL], and [1300–1970 ng/mL], respectively. Among those with any PFOS exposure, the bladder cancer SIR was 1.70 (95% CI, 0.77–3.22; 9 cases) compared with US cancer rates. Using a US population as the referent, the SIRs according to increasing cumulative exposure were 1.07 (95% CI, 0.12–3.85), 0.95 (95% CI, 0.25–2.43), 2.72 (95% CI, 0.55–73.95) and 1.43 (95% CI, 0.16–5.15). Comparing the three groups with the highest cumulative exposure with the group with the lowest cumulative exposure (internal referent, two cases), relative risks by increasing exposure were 0.83 (95% CI, 0.15–4.65; 4 cases), 1.92 (95% CI, 0.30–12.06; 3 cases), and 1.52 (95% CI, 0.21–10.99; 2 cases). A further study of medical care for some of these employees was conducted by Olsen et al. (2004), but this study was limited to certain categories of workers eligible for employer-provided care during the period 1993–1998. [The Working Group considered this study to provide only minimal information for estimating cancer incidence in this cohort.]

Steenland and Woskie (2012) studied cancer mortality among 5791 workers exposed to PFOA at a polymer-production plant in Parkersburg, West Virginia, USA (see Section 2.1.3 for more details). Compared with other non-exposed workers at other plants in the same company, the authors found an SMR for bladder cancer of 1.08 (95% CI, 0.52–1.99; 10 deaths). By quartile of estimated cumulative exposure, SMRs were 1.24 (95% CI, 0.15–4.47; 2 deaths), 2.49 (95% CI, 0.97–5.78; 6 deaths), 0.39 (95% CI, 0.01–2.17; 1 death), and 0.36 (95% CI, 0.10–2.01; 1 death). Steenland et al. (2015) followed a subset ($n = 3713$) of the PFOA-exposed workers in Steenland and Woskie (2012) for bladder cancer incidence. Bladder cancers were found via interview and confirmed via medical records, or via matching to local cancer registries. These authors found, when analysing estimated cumulative serum exposure by quartiles with a 10-year lag and using the lowest quartile as the referent in an internal comparison, RRs of 0.55 (95% CI, 0.12–2.61), 0.47 (95% CI, 0.10–2.21), and 0.31 (95% CI, 0.06–1.54), respectively, based on 29 cases of incident bladder cancer.

Eriksen et al. (2009) conducted a case–cohort study (713, 332, 128, and 67 patients with prostate, bladder, pancreatic, and liver cancer, respectively, and 772 cancer-free participants selected randomly from the full cohort) in a general-population national cohort of 57 053 people in Denmark. Analysis of bladder cancer incidence was done using baseline-measured plasma level of both PFOA and PFOS (Section 2.1.4 for more details). All participants had no previous diagnosis of cancer at the beginning of follow-up. Follow-up for cancer patients ranged from 0 to 12 years (median, 7 years). Analyses of IRRs by quartile of PFOA measured at baseline, using quartile 1 (84 cases) as the referent, were 0.71 (95% CI, 0.46–1.07), 0.92 (95% CI, 0.61–1.39), and 0.81 (95% CI, 0.53–1.24), respectively, based on 82, 83, and 83 cases, respectively. Corresponding RRs for PFOS measured at baseline, using quartile 1 (83 cases) as the referent, were 0.76 (95% CI, 0.50–1.16), 0.93 (95% CI, 0.61–1.41), and 0.70 (95% CI, 0.46–1.07), based on 84, 83, and 82 cases, respectively.

Barry et al. (2013) analysed bladder cancer incidence in a cohort of 32 254 participants with both low and high exposure to drinking-water containing PFOA (with high exposure being similar to the high levels in occupational cohorts), who were living near the plant

in Parkersburg, West Virginia, USA (see Section 2.1.5 for more details). The median PFOA concentration measured in all cohort members in 2005–2006 was 26.1 μg/L [ng/mL], and the mean was 86.6 μg/L [ng/mL] (the US general population concentration was about 4 μg/L [ng/mL] at the time) (Winquist et al., 2013). Approximately 12% of participants in this study had worked in the Parkersburg plant that was the source of the PFOA contamination. Cancer incidence was determined via interview, with confirmation from medical records or from linkage with Ohio and West Virginia cancer registries. Hazard ratios were estimated per unit of increase in natural log-transformed cumulative serum level (a continuous variable), with serum levels over time estimated by a model with good correlation (Spearman correlation, 0.71) to observed serum levels that were available in 2005–2006 for all cohort members (Winquist et al., 2013). Hazard ratios were 1.00 (95% CI, 0.89–1.12) with no lag and 0.98 (95% CI, 0.88–1.10) with a 10-year lag (0 exposure assigned during most recent 10 years), based on 105 cases of incident bladder cancer. [The Working Group noted that among the non-occupational studies with bladder cancer outcomes, the larger studies with the best-characterized individual exposure were those of Eriksen et al. (2009) and Barry et al. (2013). The former was a study of a general population with low background levels of exposure, whereas the latter included both low-exposure participants and participants with very high exposures similar to occupational levels. Hence, the exposure contrasts were much smaller in the former than the latter, but the results of these two larger studies were nonetheless concordant in finding no association with bladder cancer for either PFOA or PFOS (Barry et al. did not study PFOS).]

Consonni et al. (2013) conducted an international cohort study of mortality in male workers at six TFE-production sites who were concomitantly exposed to APFO (or equivalently PFOA, as APFO breaks down to PFOA when soluble). The Spearman correlation between APFO and TFE in this study was 0.72 (see Section 2.1.6 for more details). Restricting the cohort to workers who had ever had exposure to APFO, in the supplemental data, the authors reported a bladder cancer SMR (versus national rates) of 0.55 (95% CI, 0.11–1.60; 3 deaths). [The Working Group noted that the small numbers of cases of incident bladder cancer and of deaths from bladder cancer in each of the three occupational cohorts reported in five papers (Alexander et al., 2003; Alexander and Olsen, 2007; Steenland and Woskie, 2012; Consonni et al., 2013; Steenland et al., 2015) limited the ability to evaluate associations between PFOA and PFOS and bladder cancer. Analyses of bladder cancer incidence in other studies noted below had better statistical precision. However, exposure contrasts between high and no or low exposure were often much reduced in the non-occupational studies.]

Li et al. (2022a) studied bladder cancer incidence in Ronneby, Sweden, among 60 507 residents among whom one third of households had been exposed to relatively high levels of both PFOS and PFOA in drinking-water contaminated by nearby military firefighting operations. [The Working Group noted that, although the authors were unable to estimate separate effects of the two exposures, the PFOS level was more than tenfold that of PFOA, on the basis of a subset of the participants with measured levels of these compounds in serum (see Section 2.1.13 for more details).] For men who had never resided in a high-exposure area, the SIR for bladder cancer incidence (the area surrounding Ronneby was used as the referent) was 0.94 (95% CI, 0.80–1.09; 166 cases), whereas for women it was 0.69 (95% CI, 0.48–0.95; 35 cases). For men ever living in a high-exposure area, the SIR was 1.10 (95% CI, 0.84–1.43; 57 cases), and for women the corresponding estimate was 1.13 (95% CI, 0.66–1.80; 17 cases). When Ronneby residents with ever-high exposure were compared with those with

never-high exposure, the bladder cancer hazard ratio was 1.30 (95% CI, 0.99–1.69). When Ronneby residents with ever-high exposure were further subdivided into "early-high" (lower exposure) and "late-high" (higher exposure), hazard ratios compared with the "never-high" exposure group were 1.20 (95% CI, 0.87–1.66) and 1.50 (95% CI, 0.98–2.29), respectively. [The Working Group noted that the study by Li et al. also had large exposure contrasts but was somewhat weakened by the fact that exposure was assigned ecologically depending on whether or not the participants lived in the Ronneby area.]

Winquist et al. (2023) studied 39 371 surviving participants in the CPS-II Nutrition Cohort (enrolled in 1991–1992) who resided in urban or suburban areas of 20 states in the USA and who had been recruited for participation in the CPS-II LifeLink Cohort. CPS-II LifeLink participants completed a LifeLink cohort baseline questionnaire and provided a blood sample in 1998–2001 (median age: 70 years overall, 71 years for men, 69 years for women) (Section 2.1.21). Using a case–cohort approach, 396 cases of incident bladder cancer were identified and verified among those without previous cancer and compared with a randomly sampled subcohort of 500 men and 499 women. PFOA, PFOS, and several other PFAS compounds were measured in the collected blood samples. In the subsample, PFOS was present at the highest concentrations (median, 18.0 ng/mL), followed by PFOA (median, 5.2 ng/mL); levels were similar to those reported in NHANES. Cases were compared with the subcohort at risk at time of case occurrence via Cox regression. Hazard ratios for bladder cancer incidence were adjusted for sex, year of serum sample collection, age at serum collection; race and education from the 1982 baseline survey; smoking status and alcohol consumption from the 1997 survey (but not adjusted for other PFAS). Overall, for the sexes combined, there were no clear associations between PFOA or PFOS and bladder cancer. The hazard ratios for PFOA quartiles 2 to 4 versus quartile 1 in relation to bladder cancer were 0.84 (95% CI, 0.56–1.26), 0.87 (95% CI, 0.58–1.30), and 0.86 (95% CI, 0.58–1.27), and there was no continuous (using $\log_2$ of serum levels) trend (HR, 0.93; 95% CI, 0.77–1.13; P = 0.478). For PFOS, quartile analyses showed hazard ratios of 0.81 (95% CI, 0.54–1.21), 1.07 (95% CI, 0.72–1.60), and 0.96 (95% CI, 0.64–1.44), and there was no evidence for an association, with a continuous hazard ratio of 1.01 (95% CI, 0.86–1.20; P = 0.890). Sex-specific analyses also showed no clear association for either PFOA or PFOS.

[The study by Winquist et al. (2023) had low exposure contrasts, with a single baseline sample, a moderate number of cases, and good case ascertainment. A weakness was that this was a survivor cohort, with median age at enrolment of approximately 70 years and follow-up starting at time of blood draw approximately 8–9 years after enrolment, which would preclude the identification of bladder cancer cases during this period (eligibility for follow-up after serum sample excluded any prior cancer, fatal or not), resulting in a potential downward bias and minimal informativeness.]

Vieira et al. (2013) conducted two case–control studies of incident bladder cancer among residents of 13 counties in Ohio and West Virginia, USA, including both contaminated and non-contaminated water districts near the same plant in Parkersburg, West Virginia, which was the source of contamination in the population studied by Barry et al. (2013) (see Section 2.1.22). In the first case–control study, cases and controls (all other cancer cases excluding kidney, pancreatic, testicular, and liver cancers), obtained from both Ohio and West Virginia cancer registries, were compared with regard to residence in a contaminated or non-contaminated water district. The bladder cancer OR for exposed residents in a contaminated water district was 0.8 (95% CI, 0.7–1.0; 137 exposed cases) versus residents in non-contaminated water districts. These same authors also conducted a separate

case–control study among Ohio residents; the cases were people with bladder cancer, and the controls were people with other cancers in the Ohio counties, again excluding kidney, pancreatic, testicular, and liver cancers. Exposure in the second study was based on estimated individual annual serum levels of PFOA at specific addresses at specific points in time, 10 years before the diagnosis dates for cases and controls. Relative to the unexposed, ORs for the participants with low, medium, high, and very high-exposure 10 years before diagnosis were 0.9 (95% CI, 0.6–1.4; 23 cases), 0.9 (95% CI, 0.6–1.4; 21 cases), 1.2 (95% CI, 0.8–2.0; 21 cases), and 0.6 (95% CI, 0.2–1.5; 4 cases), respectively, in the second case–control study.

[The Working Group noted that the study by Vieira et al. (2013) included participants with the same large exposure contrasts as in Barry et al. (2013), but it was also somewhat weakened by small numbers in high-exposure groups and assignment of either group-level exposure or broadly estimated individual exposure 10 years before diagnosis.]

2.3 Cancers of the male genital tract

See Table 2.3.

2.3.1 Testicular cancer

Of the studies listed in Table 2.3, associations between PFOA and/or PFOS exposure and testicular cancer were evaluated in two cohort studies (Barry et al., 2013; Li et al., 2022a), one prospective nested case–control study (Purdue et al., 2023), and one cancer registry-based case–control study (Vieira et al., 2013) that probably had some overlap with the Barry et al. (2013) cohort study. Two occupational cohort mortality studies (Steenland and Woskie, 2012; Consonni et al., 2013) reported SMRs based on 1 death from testicular cancer; a third occupational cohort (Raleigh et al., 2014) identified 5 cases of incident testicular cancer among PFOA-exposed workers but did not report estimates of association with testicular cancer. [Given the small numbers of deaths attributable to testicular cancer and lack of risk estimates in the latter studies, the Working Group focused on the investigations by Barry et al. (2013), Li et al. (2022a), Purdue et al. (2023), and Vieira et al. (2013) in the following summary.] In addition, the Working Group conducted an analysis of data from studies carried out in the Veneto region of Italy (an area in which drinking-water is contaminated with PFAS).

Barry et al. (2013) evaluated the risk of testicular cancer in a study of 32 254 community residents and workers exposed to PFOA from a fluoropolymer-production plant in the Mid-Ohio Valley, USA (see the description of the C8 Science Panel study in Section 2.1.5). In analyses that included 17 validated incident testicular cancer cases, the authors observed evidence of an exposure–response association with estimated cumulative PFOA serum concentrations (unlagged analysis: adjusted HR for 1-unit increase in natural log-transformed levels, 1.34; 95% CI, 1.00–1.79). The corresponding hazard ratio in analyses comparing those in the highest and lowest PFOA exposure quartiles was 3.17 (95% CI, 0.75–13.45); in the categorical analysis, $P = 0.04$ for the exposure–response trend based on the within-category midpoints. The patterns of associations were similar, albeit slightly attenuated, in analyses with exposures lagged by 10 years (continuous: HR 1.28; 95% CI, 0.95–1.73; categorical, quartile 4 versus quartile 1: HR, 2.36; 95% CI, 0.41–13.65; P for trend, 0.02). Of the 17 cases of testicular cancer with complete covariate data that were included in these analyses, 15 were reported among community members and 2 among workers; in analyses excluding those employed at the plant, stronger associations were observed (continuous with no lag: HR, 1.73; 95% CI, 1.24–2.40; continuous with 10-year lag: HR, 1.53; 95% CI, 1.09–2.15).

Table 2.3 Epidemiological studies on exposure to PFOA and PFOS and cancers of the male genital tract

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Raleigh et al. (2014) MN, USA Enrolment, 1947–2002/ follow-up, 1947–2008 (mortality), 1988–2008 (incidence) Cohort	9027 men (3716 exposed, 3834 reference); Cottage Grove (MN), PFOA cohort; workers employed for ≥ 1 yr during 1947–2002 at an APFO facility (Cottage Grove; *n* = 4668); reference workers without any exposure to APFO employed at a tape and abrasives production facility located in the same suburban geographical area and managed by the same company (Saint Paul; *n* = 4359) Exposure assessment method: see Table 2.1	Prostate, mortality	Exposed to APFO (SMR, MN referent):			Age, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1. Risk estimates not reported for testicular cancer due to the small number of incident cases among exposed workers (*n* = 5).
			Unexposed (Saint Paul plant)	48	1.03 (0.76–1.37)		
			Exposed (Cottage Grove plant)	24	0.83 (0.53–1.23)		
		Prostate, mortality	Estimated cumulative airborne APFO exposure quartile (SMR, MN referent):				
			1st quartile (< 2.6×10^{-5} µg/ m^3-year)	5	0.66 (0.21–1.54)		
			2nd quartile (2.6×10^{-5} to < 1.4×10^{-4} µg/ m^3-year)	8	1.15 (0.50–2.27)		
			3rd quartile (1.4×10^{-4} to < 7.3×10^{-4} µg/ m^3-year)	3	0.37 (0.08–1.07)		
			4th quartile (≥ 7.3×10^{-4} µg/ m^3-year)	8	1.29 (0.56–2.54)		
		Prostate, mortality	Estimated cumulative airborne APFO exposure quartile (HR):			Age, year of birth	
			Unexposed (Saint Paul plant)	NR	1		
			1st quartile (< 2.9×10^{-5} µg/ m^3-year)	NR	0.34 (0.25–1.60)		
			2nd quartile (2.9×10^{-5} to < 1.5×10^{-4} µg/ m^3-year)	NR	1.12 (0.53–2.37)		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Raleigh et al. (2014) MN, USA Enrolment, 1947–2002/ follow-up, 1947–2008 (mortality), 1988–2008 (incidence) Cohort (cont.)		Prostate, mortality (cont.)	3rd quartile (1.5×10^{-4} to $< 7.9 \times 10^{-4}$ µg/m³-year)	NR	0.36 (0.11–1.17)	Age, year of birth	
			4th quartile ($\geq 7.9 \times 10^{-4}$ µg/m³-year)	NR	1.32 (0.61–2.84)		
		Prostate, incidence	Estimated cumulative airborne APFO exposure quartile (HR):				
			Unexposed (Saint Paul plant)	253	1		
			1st quartile ($< 2.9 \times 10^{-5}$ µg/m³-year)	42	0.80 (0.57–1.11)		
			2nd quartile (2.9×10^{-5} to $< 1.5 \times 10^{-4}$ µg/m³-year)	42	0.85 (0.61–1.19)		
			3rd quartile (1.5×10^{-4} to $< 7.9 \times 10^{-4}$ µg/m³-year)	49	0.89 (0.66–1.21)		
			4th quartile ($\geq 7.9 \times 10^{-4}$ µg/m³-year)	55	1.11 (0.82–1.49)		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), 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), polymer-production occupational PFOA cohort; workers (men, 81%) at a polymer manufacturing facility who had potential exposure to fluoropolymers with sufficiently detailed work histories Exposure assessment method: see Table 2.1	Testis, mortality	PFOA-exposed workers (SMR):			Age, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. Ability to evaluate associations in a high PFOA-exposed population. *Other limitations*: See Table 2.1. Limited statistical power to assess mortality from testicular and prostate cancers.
			Other workers referent (same region and company)	1	1.80 (0.05–10.03)		
			US referent	1	0.74 (0.02–4.12)		
		Prostate, mortality	PFOA-exposed workers (SMR):				
			Other workers referent (same region and company)	21	0.76 (0.47–1.16)		
			US referent	21	0.72 (0.45–1.10)		
		Prostate, mortality	Cumulative serum exposure, no lag (SMR, other workers referent, same region and company):				
			1st quartile (0 to < 904 ppm-years)	6	1.07 (0.39–2.34)		
			2nd quartile (904 to < 1520 ppm-years)	6	0.82 (0.30–1.78)		
			3rd quartile (1520 to < 2700 ppm-years)	5	0.65 (0.21–1.51)		
			4th quartile (≥ 2700 ppm-years)	4	0.57 (0.16–1.46)		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Steenland et al. (2015) Parkersburg (WV), USA Enrolment, 1948–2002/ follow-up, 1951-interview date in 2008–2011 (incidence) Cohort	3713 (2955 male); A subset of Parkersburg (WV), polymer-production PFOA cohort in Steenland and Woskie (2012); polymer-production workers (mean, 80%) who responded (self or next-of-kin) to a questionnaire about health outcomes and who had measured or estimated occupational and residential exposure estimates; 129 incident cases of prostate cancer Exposure assessment method: See Table 2.1	Prostate, incidence	Cumulative PFOA exposure, no lag (RR):			Age, race, education, BMI, time-varying smoking, time-varying alcohol consumption, year of birth	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. Ability to evaluate associations between PFOA and prostate cancer incidence in a high PFOA-exposed population. *Other limitations*: See Table 2.1. Possibility of selection bias given that the investigation included only 62% of the target population; inability to evaluate risk of testicular cancer and other relatively less common malignancies.
			1st quartile (< 3.03 µg/mL-years)	NR	1		
			2nd quartile (3.03 to < 6.16 µg/mL-years)	NR	1.81 (0.69–4.78)		
			3rd quartile (6.16 to < 11.42 µg/mL-years)	NR	2.45 (0.96–6.25)		
			4th quartile (≥ 11.42 µg/ mL-years)	NR	1.88 (0.72–4.88)		
			Trend-test *P*-value, 0.11				
		Prostate, incidence	Cumulative PFOA exposure, 10-yr lag (RR):				
			1st quartile (< 0.8 µg/mL-years)	NR	1		
			2nd quartile (0.8 to < 3.44 µg/mL-years)	NR	1.92 (0.56–6.58)		
			3rd quartile (3.44 to < 7.04 µg/mL-years)	NR	1.89 (0.57–6.34)		
			4th quartile (≥ 7.04 µg/mL-years)	NR	2.15 (0.64–7.26)		
			Trend-test *P*-value, 0.10				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Eriksen et al. (2009) Denmark Enrolment, December 1993 to 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: 713 incident cases of prostate cancer 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	Prostate, incidence	Baseline plasma PFOA concentration (IRR):			Age, years of school attendance, BMI, dietary fat intake, fruit and vegetable intake	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. Large number of prostate cancer cases and non-cases. *Other limitations*: See Table 2.1. Results not reported for different time intervals between serum collection and diagnosis of prostate cancer; lack of mutually adjusted analyses of PFOS and PFOA.
			1st quartile	179	1		
			2nd quartile	178	1.09 (0.78–1.53)		
			3rd quartile	178	0.94 (0.67–1.32)		
			4th quartile	178	1.18 (0.84–1.65)		
			Continuous (per 1 ng/mL increase)	713	1.03 (0.99–1.07)		
		Prostate, incidence	Baseline plasma PFOS concentration (IRR):				
			1st quartile	179	1		
			2nd quartile	178	1.35 (0.97–1.87)		
			3rd quartile	180	1.31 (0.94–1.82)		
			4th quartile	176	1.38 (0.99–1.93)		
			Continuous (per 10 ng/mL increase)	713	1.05 (0.97–1.14)		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Barry et al. (2013) Mid-Ohio Valley (OH and WV) Enrolment, August 2005 to August 2006/ follow-up, 1952 to 2011 (incidence) Cohort	32 254 (28 541 community members and 3713 workers); C8 Science Panel Study; included people enrolled in the C8 Health Project who lived, worked, or attended school for ≥ 1 yr between 1950 and 3 December 2004 in a contaminated-water district in the vicinity of a chemical plant (Parkersburg (WV), polymer-production) using PFOA in manufacturing, as well as a subset of those from the original Parkersburg (WV), polymer production occupational cohort who worked at the plant between 1948 and 2002 Exposure assessment method: see Table 2.1	Testis, incidence	Estimated cumulative PFOA serum concentration (ng/mL), no lag (HR):			Age, time-varying smoking, time-varying alcohol consumption, education, birth year (5-yr calendar intervals)	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. Relatively high participation from those in the C8 Health Project; validation of diagnosed cancers. *Limitations*: See Table 2.1. Limited statistical power to assess risk of testicular cancer.
			1st quartile	NR	1		
			2nd quartile	NR	1.04 (0.26–4.22)		
			3rd quartile	NR	1.91 (0.47–7.75)		
			4th quartile	NR	3.17 (0.75–13.45)		
			Continuous (per unit on natural log scale)	17	1.34 (1.00–1.79)		
			Trend-test *P*-value, 0.04				
		Testis, incidence	Estimated cumulative PFOA serum concentration (ng/mL), 10-yr lag (HR):				
			1st quartile	NR	1		
			2nd quartile	NR	0.87 (0.15–4.88)		
			3rd quartile	NR	1.08 (0.20–5.90)		
			4th quartile	NR	2.36 (0.41–13.65)		
			Continuous (per unit on natural log scale)	17	1.28 (0.95–1.73)		
			Trend-test *P*-value, 0.02				
		Testis, incidence	Community residents: estimated cumulative PFOA serum concentration (ng/mL), no lag (HR):				
			1st quartile	NR	1		
			2nd quartile	NR	0.80 (0.16–3.97)		
			3rd quartile	NR	3.07 (0.61–15.36)		
			4th quartile	NR	5.80 (0.97–34.58)		
			Continuous (per unit on natural log scale)	15	1.73 (1.24–2.40)		
			Trend-test *P*-value, 0.05				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Barry et al. (2013) Mid-Ohio Valley (OH and WV) Enrolment, August 2005 to August 2006/ follow-up, 1952 to 2011 (incidence) Cohort (cont.)		Testis, incidence	Community residents: estimated cumulative PFOA serum concentration (ng/mL), 10-yr lag (HR):			Age, time-varying smoking, time-varying alcohol consumption, education, birth year (5-yr calendar intervals)	
			1st quartile	NR	1		
			2nd quartile	NR	0.98 (0.13–7.14)		
			3rd quartile	NR	1.54 (0.19–12.21)		
			4th quartile	NR	4.66 (0.52–41.63)		
			Continuous (per unit on natural log scale)	15	1.53 (1.09–2.15)		
			Trend-test *P*-value, 0.02				
		Prostate, incidence	Estimated cumulative PFOA serum concentration (ng/mL), no lag (HR):				
			Continuous (per unit on natural log scale)	446	0.99 (0.93–1.04)		
		Prostate, incidence	Estimated cumulative PFOA serum concentration (ng/mL), 10-yr lag (HR):				
			Continuous (per unit on natural log scale)	446	0.99 (0.94–1.05)		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Consonni et al. (2013) USA, UK, Italy, Germany, Netherlands Enrolment, 1950–2002/ follow-up, 1950–2008 Cohort	5879 male workers (APFO-exposed, 4205); the pooled international TFE cohort includes male workers who were ever employed or employed for 6 or 12 mo at one or more of six TFE-production sites in North America and Europe from 1950 to 2002; the principal occupational exposures were TFE and APFO (aiding production of PTFE) Exposure assessment method: see Table 2.1	Testis, mortality	SMR (national referent): Ever APFO-exposed	1	1.35 (0.03–7.49)	Age, calendar period, country	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1. Limited statistical power to assess mortality from testicular and prostate cancers.
		Prostate, mortality	SMR (national referent): Ever APFO-exposed	3	0.24 (0.05–0.70)	Age, calendar period, country	

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rhee et al. (2023a) USA Enrolment, 1993–2001; follow-up (from blood draw), median, 9 yr (incidence) Nested case–control	Nested within the PLCO cohort (see Table 2.1 of Shearer et al., 2021) Cases: 750; aggressive prostate cancer (defined as stage III or IV, Gleason score ≥ 8, or Gleason score 7 and death from prostate cancer) diagnosed > 300 days after blood collection Controls: 750; alive and cancer-free at time of case diagnosis, and individually matched to cases on age at baseline, race/ethnicity, study centre, calendar and study year of blood collection, and prior freeze–thaw cycle Exposure assessment method: see Table 2.1	Prostate (aggressive/ advanced), incidence	Serum PFOA concentration (OR):			Age, race/ ethnicity, study centre, calendar year of blood collection, study year of blood collection, prior freeze–thaw	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			< 2.90 µg/L	194	1		
			2.90 to < 3.80 µg/L	155	0.75 (0.55–1.03)		
			3.80 to < 4.67 µg/L	130	0.65 (0.47–0.91)		
			4.67 to < 6.50 µg/L	149	0.69 (0.49–0.97)		
			≥ 6.50 µg/L	122	0.57 (0.39–0.82)		
			Continuous (per unit increase on $\log_2$ scale)	750	0.82 (0.71–0.96)		
			Trend-test *P*-value, 0.005				
		Prostate (aggressive/ advanced), incidence	Serum PFOA concentration (OR):			Age, race/ ethnicity, study centre, calendar year of blood collection, study year of blood collection, prior freeze–thaw, BMI, smoking status, family history of prostate cancer, history of diabetes, PFOS, PFHxS, PFNA, *N*-EtFOSAA, FOSA, *N*-MeFOSAA, PFHpS	
			< 2.90 µg/L	194	1		
			2.90 to < 3.80 µg/L	155	0.75 (0.53–1.07)		
			3.80 to < 4.67 µg/L	130	0.72 (0.49–1.07)		
			4.67 to < 6.50 µg/L	149	0.67 (0.44–1.03)		
			≥ 6.50 µg/L	122	0.54 (0.32–0.91)		
			Continuous (per unit increase on $\log_2$ scale)	750	0.79 (0.63–0.99)		
			Trend-test *P*-value, 0.02				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rhee et al. (2023a) USA Enrolment, 1993–2001; follow-up (from blood draw), median, 9 yr (incidence) Nested case–control (cont.)		Prostate (aggressive/ advanced), incidence	No. of years from blood draw to diagnosis (OR for a 1-unit increase in serum PFOA on $\log_2$ scale):			Age, race/ ethnicity, study centre, calendar year of blood collection	
			< 1 to 3 yr	115	0.67 (0.51–0.87)		
			> 3 yr	635	0.90 (0.79–1.03)		
		Prostate (aggressive/ advanced), incidence	Serum PFOS concentration (OR):			Age, race/ ethnicity, study centre, calendar year of blood collection, study year of blood collection, prior freeze–thaw	
			< 19.10 µg/L	170	1		
			19.10 to < 25.50 µg/L	145	0.86 (0.62–1.18)		
			25.50 to < 33.50 µg/L	168	0.99 (0.72–1.37)		
			33.50 to < 47.12 µg/L	136	0.80 (0.58–1.12)		
			≥ 47.12 µg/L	131	0.74 (0.51–1.06)		
			Continuous (per unit increase on $\log_2$ scale)	750	0.93 (0.83–1.05)		
			Trend-test *P*-value, 0.08				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Rhee et al. (2023a) USA Enrolment, 1993–2001; follow-up (from blood draw), median, 9 yr (incidence) Nested case–control (cont.)		Prostate (aggressive/ advanced), incidence	Serum PFOS concentration (OR):			Age, race/ ethnicity, study centre, calendar year of blood collection, study year of blood collection, prior freeze–thaw, BMI, smoking status, family history of prostate cancer, history of diabetes, PFOA, PFHxS, PFNA, *N*-EtFOSAA, FOSA, *N*-MeFOSAA, PFHpS	
			< 19.10 µg/L	170	1		
			19.10 to < 25.50 µg/L	145	0.93 (0.64–1.37)		
			25.50 to < 33.50 µg/L	168	1.07 (0.69–1.66)		
			33.50 to < 47.12 µg/L	136	0.88 (0.53–1.46)		
			≥ 47.12 µg/L	131	0.84 (0.45–1.58)		
			Continuous (per unit increase on $\log_2$ scale)	750	0.99 (0.79–1.23)		
			Trend-test *P*-value, 0.34				
		Prostate (aggressive/ advanced), incidence	No. of years from blood draw to diagnosis (OR for a 1-unit increase in serum PFOS on $\log_2$ scale):			Age, race/ ethnicity, study centre, calendar year of blood collection	
			< 1 to 3 yr	115	0.85 (0.70–1.04)		
			> 3 to 5 yr	89	0.94 (0.74–1.18)		
			> 5 to 9 yr	155	0.98 (0.82–1.19)		
			> 9 yr	391	0.95 (0.84–1.09)		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Li et al. (2022a) Ronneby, southern Sweden Enrolment, 1985–2013/ follow-up, 1985–2016 (incidence) Cohort	60 507 (including 31 938 men); the Ronneby Register Cohort included all individuals who ever lived in Ronneby municipality in 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 in 1985–2013 (15 811 individuals with exposure considered "ever-high"); subsets with long-term exposure (≥ 11 yr) in the latest part of the follow-up period (2005–2013) were considered more highly exposed Exposure assessment method: see Table 2.1	Testis, 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*: See Table 2.1. Complete ascertainment of community members in the cohort and follow-up through register-based linkages; high contrast in PFAS exposures within the cohort. *Other limitations*: See Table 2.1. Limited ability to assess potential effects of PFOS and PFOA individually; limited statistical power to assess risk of testicular cancer.
			Never	30	0.85 (0.57–1.21)		
			Ever	14	1.28 (0.70–2.15)		
		Testis, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):				
			Never	31	1		
			Ever	14	1.38 (0.73–2.61)		
		Testis, incidence	Time period of residential exposure to highly PFAS-contaminated drinking-water (HR):				
			Never	31	1		
			Early (1985–2004)	9	1.35 (0.64–2.84)		
			Late (2005–2013)	5	1.46 (0.55–3.83)		
		Testis, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):				
			Never	31	1		
			Short (1–10 yr)	9	1.32 (0.63–2.79)		
			Long (≥ 11 yr)	5	1.51 (0.56–4.03)		
		Prostate, incidence	Residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):				
			Never	712	1.14 (1.05–1.22)		
			Ever	181	0.96 (0.82–1.11)		
		Prostate, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):				
			Never	712	1		
			Ever	181	0.83 (0.71–0.98)		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Li et al. (2022a) Ronneby, southern Sweden Enrolment, 1985–2013/ follow-up, 1985–2016 (incidence) Cohort (cont.)		Prostate, incidence	Time period of residential exposure to highly PFAS-contaminated drinking-water (HR):			Calendar year, age	
			Never	712	1		
			Early (1985–2004)	114	0.88 (0.72–1.08)		
			Late (2005–2013)	67	0.76 (0.59–0.98)		
		Prostate, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):				
			Never	712	1		
			Short (1–10 yr)	95	0.96 (0.78–1.20)		
			Long (≥ 11 yr)	86	0.72 (0.58–0.91)		
Purdue et al. (2023) USA Enrolment, 1988–2017/ follow-up, through 2018 Nested case–control	Nested within a cohort of active-duty US Air Force servicemen (see Table 2.1) Cases: 530 overall (187 with two samples); TGCT diagnosed in the Department of Defence Cancer Registry	Testis, incidence	Serum PFOA (first/only sample) concentration (OR):			Date of birth, race/ethnicity, year entered military service, sample availability, military grade, number of deployments	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			≤ 4.45 ng/mL	161	1		
			4.46–5.87 ng/mL	115	0.7 (0.4–1.0)		
			5.88–7.85 ng/mL	121	0.7 (0.5–1.0)		
			> 7.85 ng/mL	133	0.8 (0.5–1.2)		
			Trend-test *P*-value, 0.46				
		Testis, incidence	Serum PFOA (first/only sample) concentration (OR):			Date of birth, race/ethnicity, year entered military service, sample availability, military grade, number of deployments, other PFAS (PFOS, PFHxS, PFNA, PFDA, PFUnDA, *N*-MeFOSAA)	
			≤ 4.45 ng/mL	161	1		
			4.46–5.87 ng/mL	115	0.7 (0.4–1.0)		
			5.88–7.85 ng/mL	121	0.7 (0.4–1.1)		
			> 7.85 ng/mL	133	0.8 (0.5–1.4)		
			Trend-test *P*-value, 0.86				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Purdue et al. (2023) USA Enrolment, 1988–2017/ follow-up, through 2018 Nested case–control (cont.)	Controls: 530 overall (187 with two samples); one control per case, density-sampled with replacement among eligible US Air Force servicemen on active duty and cancer-free as of the case diagnosis date and matched by date of birth, race/ ethnicity (seven groups), year entering military service, year of baseline serum sample collection, and year of second sample collection (if applicable) Exposure assessment method: see Table 2.1	Testis, incidence	Serum PFOA (second sample) concentration (OR):			Date of birth, race/ethnicity, year entered military service, sample availability, military grade, number of deployments	
			≤ 4.25 ng/mL	55	1		
			4.26–5.65 ng/mL	52	1.0 (0.6–1.8)		
			5.66–7.55 ng/mL	39	0.7 (0.4–1.4)		
			> 7.55 ng/mL	41	0.7 (0.4–1.5)		
			Trend-test *P*-value, 0.35				
		Testis, incidence	Serum PFOA (second sample) concentration (OR):			Date of birth, race/ethnicity, year entered military service, sample availability, military grade, number of deployments, other PFAS (PFOS, PFHxS, PFNA, PFDA, PFUnDA, *N*-MeFOSAA)	
			≤ 4.25 ng/mL	55	1		
			4.26–5.65 ng/mL	52	1.0 (0.5–2.0)		
			5.66–7.55 ng/mL	39	0.6 (0.3–1.4)		
			> 7.55 ng/mL	41	0.6 (0.2–1.6)		
			Trend-test *P*-value, 0.22				
		Testis, incidence	Serum PFOS (first/only sample) concentration (OR):			Date of birth, race/ethnicity, year entered military service, sample availability, military grade, number of deployments	
			≤ 18.3 ng/mL	131	1		
			18.4–29.3 ng/mL	116	1.0 (0.6–1.5)		
			29.4–42.2 ng/mL	153	1.4 (0.8–2.3)		
			> 42.2 ng/mL	130	1.2 (0.7–2.0)		
			Trend-test *P*-value, 0.64				

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Purdue et al. (2023) USA Enrolment, 1988–2017/ follow-up, through 2018 Nested case–control (cont.)		Testis, incidence	Serum PFOS (first/only sample) concentration (OR): ≤ 18.3 ng/mL 18.4–29.3 ng/mL 29.4–42.2 ng/mL > 42.2 ng/mL Trend-test *P*-value, 0.15	 131 116 153 130	 1 1.2 (0.7–1.9) 1.9 (1.0–3.4) 1.8 (0.9–3.6)	Date of birth, race/ethnicity, year entered military service, sample availability, military grade, number of deployments, other PFAS (PFOA, PFHxS, PFNA, PFDA, PFUnDA, *N*-MeFOSAA)	
		Testis, incidence	Serum PFOS (second sample) concentration (OR): ≤ 13.2 ng/mL 13.3–21.2 ng/mL 21.3–33.5 ng/mL > 33.5 ng/mL Trend-test *P*-value, 0.02	 42 38 50 57	 1 1.1 (0.6–1.9) 1.9 (0.9–4.1) 2.6 (1.1–6.4)	Date of birth, race/ethnicity, year entered military service, sample availability, military grade, number of deployments	

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Purdue et al. (2023) USA Enrolment, 1988–2017/ follow-up, through 2018 Nested case–control (cont.)		Testis, incidence	Serum PFOS (second sample) concentration (OR):			Date of birth, race/ethnicity, year entered military service, sample availability, military grade, number of deployments, other PFAS (PFOA, PFHxS, PFNA, PFDA, PFUnDA, *N*-MeFOSAA)	
			≤ 13.2 ng/mL	42	1		
			13.3–21.2 ng/mL	38	1.5 (0.7–3.3)		
			21.3–33.5 ng/mL	50	2.8 (1.1–7.0)		
			> 33.5 ng/mL	57	4.6 (1.4–15.1)		
			Trend-test *P*-value, 0.009				
		Testis (seminoma), incidence	Serum PFOS (first/only sample) concentration (OR):				
			Below median	NR	1		
			Above median	NR	1.8 (1.0–3.3)		
		Testis (seminoma), incidence	Serum PFOS (second sample) concentration (OR):				
			Below median	NR	1		
			Above median	NR	2.8 (1.2–6.3)		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), 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 study within the CPS-II Lifelink Cohort (see Table 2.1) Cases: 3762 overall (1610 prostate cancers); incident cases from the CPS-II Lifelink Cohort (surviving CPS-II Nutrition cohort participants) with first cancer diagnosis of prostate (men only) 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 (~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	Prostate, incidence	Serum PFOA concentration (HR):			Year of serum sample collection, age at serum collection, race, education, smoking status, alcohol consumption	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			1st quartile (< 4.000 ng/mL)	398	1		
			2nd quartile (4.000 to < 5.300 ng/mL)	391	0.82 (0.60–1.11)		
			3rd quartile (5.300 to < 6.900 ng/mL)	405	0.93 (0.68–1.27)		
			4th quartile (≥ 6.900 ng/mL)	405	0.83 (0.61–1.14)		
			Continuous (per unit on $\log_2$ scale)	1599	0.93 (0.79–1.08)		
		Prostate, incidence	Serum PFOS concentration (HR):				
			1st quartile (< 14.000 ng/mL)	389	1		
			2nd quartile (14.000 to < 19.000 ng/mL)	392	0.94 (0.70–1.26)		
			3rd quartile (19.000 to < 26.000 ng/mL)	410	1.11 (0.81–1.50)		
			4th quartile (≥ 26.000 ng/mL)	408	1.08 (0.80–1.46)		
			Continuous (per unit on $\log_2$ scale)	1599	1.00 (0.88–1.14)		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vieira et al. (2013) OH and WV, USA 1996–2005 (incidence) Case–control	Cases: study 1: 134 cancers of the testis, 3678 cancers of the prostate; Study 2: 61 cancers of the testis, 1155 cancers of the prostate; index cancer cases were retrieved from cancer registries covering a community sample with relatively high exposure to PFOA because of contamination of drinking-water from the Parkersburg (WV), polymer-production plant Controls: NR; for each cancer site evaluated, controls were cases of cancer at all other sites among men, with the exclusion of four cancers of a priori interest (kidney, testis, pancreas, and liver) that have been associated with PFOA in studies in experimental animals or humans Exposure assessment method: see Table 2.1	Testis, incidence	Study 1: residence in a PFOA-contaminated water district (OH and WV) (OR):			Age, diagnosis year, insurance provider, smoking status	*Exposure assessment critique*: See Table 2.1 *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1. *Other comments*: Substantial overlap with Barry et al. (2013).
			Unexposed	116	1		
			Any exposed water district	18	1.0 (0.6–1.8)		
			Little Hocking	8	5.1 (1.6–15.6)		
			Lubeck	2	0.9 (0.2–4.5)		
			Tuppers Plains	2	0.4 (0.1–2.0)		
			Belpre	1	0.6 (0.1–5.0)		
			Pomeroy	0	NC		
			Mason	5	0.5 (0.2–1.5)		
		Testis, incidence	Analysis 2: individual-level annual PFOA serum exposure, assuming 10-yr residency and latency (OH only) (OR):			Age, race, diagnosis year, insurance provider, smoking status	
			Unexposed	50	1		
			Low (3.7–12.8 µg/L)	1	0.2 (0.0–1.6)		
			Medium (12.9–30.7 µg/L)	3	0.6 (0.2–2.2)		
			High (30.8–109 µg/L)	1	0.3 (0.0–2.7)		
			Very high (110–655 µg/L)	6	2.8 (0.8–9.2)		
		Prostate, incidence	Analysis 1: Residence in a PFOA-contaminated water district (OH and WV) (OR):			Age, diagnosis year, insurance provider, smoking status	
			Unexposed	3244	1		
			Any exposed water district	434	0.9 (0.8–1.1)		
			Little Hocking	36	1.4 (0.9–2.3)		
			Lubeck	78	1.2 (0.9–1.6)		
			Tuppers Plains	56	0.8 (0.6–1.1)		
			Belpre	56	0.8 (0.6–1.1)		
			Pomeroy	12	1.3 (0.6–2.6)		
			Mason	196	0.9 (0.7–1.0)		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vieira et al. (2013) OH and WV, USA 1996–2005 (incidence) Case–control (cont.)		Prostate, incidence	Analysis 2: individual-level annual PFOA serum exposure, assuming 10-yr residency and latency (OH only) (OR):			Age, race, diagnosis year, insurance provider, smoking status	
			Unexposed	941	1		
			Low (3.7–12.8 µg/L)	71	1.1 (0.8–1.5)		
			Medium (12.9–30.7 µg/L)	65	0.8 (0.6–1.0)		
			High (30.8–109 µg/L)	47	0.8 (0.5–1.1)		
			Very high (110–655 µg/L)	31	1.5 (0.9–2.5)		
Hardell et al. (2014) Örebro County, Sweden 2007–2011 Case–control	Cases: 201; patients with prostate cancer admitted for treatment at the University Hospital in Örebro between 2007 and 2011 Controls: 186; cancer-free controls from Örebro County who were identified from the Swedish population registry and matched to cases on age Exposure assessment method: quantitative measurements; analytical method was state-of-the-art; a single blood sample was collected during the same time period for cases and matched controls; blood was collected before	Prostate, incidence	Serum PFOA concentration (OR):			Age, BMI, year of sampling	*Exposure assessment critique*: Key strengths were that whole blood levels represent the combined exposure through all exposure pathways; measurement error low. Key limitations were that if prostate cancer alters ADME of PFAS there could be possible differential exposure misclassification, as blood collection of cases was at or after diagnosis; single samples at time of case hospitalization may not reflect exposure at crucial windows in cancer development.
			≤1.9 ng/mL (median for controls)	93	1		
			> 1.9 ng/mL	108	1.1 (0.7–1.7)		
		Prostate, incidence	Serum PFOS concentration (OR):				
			≤8.3 ng/mL (median for controls)	92	1		
			> 8.3 ng/mL	109	1.0 (0.6–1.5)		
		Prostate (Gleason score, 7–10), incidence	Serum PFOA concentration (OR):				
			≤1.9 ng/mL (median for controls)	56	1		
			> 1.9 ng/mL	67	1.2 (0.7–1.8)		
		Prostate (Gleason score, 7–10), incidence	Serum PFOS concentration (OR):				
			≤8.3 ng/mL (median for controls)	53	1		
			> 8.3 ng/mL	70	1.1 (0.7–1.9)		
		Prostate (PSA level ≥ 11), incidence	Serum PFOA concentration (OR):				
			≤1.9 ng/mL (median for controls)	39	1		
			> 1.9 ng/mL	52	1.3 (0.8–2.1)		

Table 2.3 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description Exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hardell et al. (2014) Örebro County, Sweden 2007–2011 Case–control (cont.)	treatment, during hospitalization to receive treatment or at general practitioners	Prostate (PSA level ≥ 11), incidence	Serum PFOS concentration (OR):			Age, BMI, year of sampling	*Other strengths*: Availability of information on disease aggressiveness (Gleason score and PSA) and family history of prostate cancer. *Other limitations*: Lack of adjustment for other PFAS; relatively small sample size.
			≤8.3 ng/mL (median for controls)	47	1		
			> 8.3 ng/mL	44	0.8 (0.4–1.3)		
		Prostate, incidence	Heredity and serum PFOA concentration (OR):				
			No heredity, ≤ 1.9 ng/mL	77	1		
			Heredity, ≤ 1.9 ng/mL	16	1.1 (0.5–2.6)		
			No heredity, > 1.9 ng/mL	84	1.0 (0.6–1.5)		
			Heredity, > 1.9 ng/mL	24	2.6 (1.2–6.0)		
		Prostate, incidence	Heredity and serum PFOS concentration (OR):			Age, BMI, year of sampling	
			No heredity, ≤ 8.3 ng/mL	72	1		
			Heredity, ≤ 8.3 ng/mL	20	1.2 (0.6–2.5)		
			No heredity, > 8.3 ng/mL	89	0.9 (0.5–1.4)		
			Heredity, > 8.3 ng/mL	20	2.7 (1.04–6.8)		

ADME, absorption, distribution, metabolism, and excretion; APFO, ammonium perfluorooctanoate; approx., approximately; BMI, body mass index; CI, confidence interval; CPS-II, Cancer Prevention Study II; *N*-EtFOSAA, 2-(*N*-ethyl-perfluorooctane sulfonamido) acetic acid; FOSA, perfluorooctane sulfonamide; HR, hazard ratio; IRR, incidence rate ratio; *N*-MeFOSAA, 2-(*N*-methyl-perfluorooctane sulfonamido) acetic acid; MN, Minnesota; mo, month(s); NC, not calculated; NDI, National Death Index; NR, not reported; OH, Ohio; OR, odds ratio; PFAS, per- and polyfluoroalkyl substances; PFDA, perfluorodecanoic acid; PFHpS, perfluoroheptanesulfonic acid; PFHxS, perfluorohexanesulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PFUnDA, perfluoroundecanoic acid; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; ppm, part per million; PSA, prostate-specific antigen; PTFE, polytetrafluoroethylene; RR, rate ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TGCT, testicular germ cell tumour; TFE, tetrafluoroethylene; UK, United Kingdom; US, United States; USA, United States of America; WV, West Virginia; yr, year(s).

[The Working Group considered this study to be highly informative for the relation between PFOA and testicular cancer. Its primary strengths included the detailed characterization of estimated serum PFOA levels over time, the high response rate among participants in the C8 Health Project, and the validation of diagnosed testicular cancers through state registries and medical chart review. However, the small number of confirmed cases of testicular cancer was a limitation.]

Li et al. (2022a) investigated the incidence of testicular cancer in the Ronneby community cohort in Sweden, which had high exposures to PFAS (primarily PFOS and PFHxS, but also PFOA to some extent) from contaminated drinking-water (Section 2.1.13). Based on 14 observed cases of incident testicular cancer among residents in areas with contaminated drinking-water, elevated but imprecise risks were observed relative to regional rates (SIR, 1.28; 95% CI, 0.70–2.15) and relative to those in the Ronneby municipality among people who had never resided in contaminated water districts (HR, 1.38; 95% CI, 0.73–2.61). In analyses of people residing in districts with contaminated water during the later years when levels of PFAS contamination were higher (versus those never residing in districts with contaminated water), the hazard ratio was 1.46 (95% CI, 0.55–3.83). For those with a longer duration of residence in contaminated districts, the hazard ratio was 1.51 (95% CI, 0.56–4.03). The risk estimates for exposure in later years and for longer duration of residence were both based on analyses with 5 exposed cases.

[The strengths of this study included the complete ascertainment of community members in the cohort and follow-up through register-based linkages, and the high contrast in PFAS exposures within the cohort. However, the PFAS exposure profile and exposure assessment approach in this investigation – which characterized the potential for PFAS exposure overall rather than for specific PFAS and did not account for individual-level factors such as water consumption or use of bottled water or water filtration – limited the ability to isolate potential effects of PFOS and PFOA individually and also probably resulted in non-differential exposure misclassification, which typically might be expected to attenuate the reported risk estimates. The Working Group also noted that the findings from this study may not be directly comparable to those for PFOA in Barry et al. (2013), given that PFAS exposure in this study was dominated by PFOS and PFHxS. PFOA serum levels (in samples collected 1–2 years after cessation of exposure) were lower in this population than in the C8 Science Panel study. Finally, with only 14 exposed cases of testicular cancer, the study had limited statistical power to evaluate associations with this malignancy.]

Purdue et al. (2023) conducted a nested case–control study of prediagnostic serum PFAS concentrations and risk of TGCT among US Air Force servicemen, using sera collected between 1988 and 2017 and stored in the DoD Serum Repository (Section 2.1.17). The study included 530 cases of TGCT among servicemen aged < 40 years and on active duty at diagnosis and 530 individually matched controls; of these, 187 cases and 187 matched controls also had measured PFAS concentrations from a second prediagnostic serum sample collected a median of 4 years after the first sample. In analyses conditioned on matching factors and adjusted for military grade and number of deployments, serum PFOA concentrations were not associated with TGCT risk on the basis of measurements in the first or only samples in the study population overall (fourth versus first quartile, OR, 0.8; 95% CI, 0.5–1.2; *P* for trend, 0.46) or the second samples from 187 case–control sets (OR, 0.7; 95% CI, 0.4–1.5; *P* for trend, 0.35); the results were similar after additionally adjusting for other PFAS. For PFOS, although no association with TGCT risk was seen in analyses of the

first or only samples (fourth versus first quartile, OR, 1.2; 95% CI, 0.7–2.0; *P* for trend, 0.64), the authors observed an exposure–response association with PFOS concentrations in the second samples (OR, 2.6; 95% CI, 1.1–6.4; *P* for trend, 0.02). After adjustment for other PFAS, the corresponding risk estimates for the fourth versus first quartiles of PFOS concentrations in the first/only and second serum samples were 1.8 (95% CI, 0.9–3.6; *P* for trend, 0.15) and 4.6 (95% CI, 1.4–15.1; *P* for trend, 0.009), respectively. Associations with seminomas (which are typically diagnosed at older ages than are nonseminomas) were observed for PFOS (e.g. above versus below median PFOS concentrations with adjustment for other PFAS: first or only sample, OR, 1.8; 95% CI, 1.0–3.3; second sample, OR, 2.8; 95% CI, 1.2–6.3).

[The Working Group considered this study to be highly informative because of a number of strengths, including its large sample size, the measurements of PFOA and PFOS in prediagnostic samples, the availability of repeated samples during potential etiologically relevant time periods from a subset of cases and controls, the ability to adjust for other PFAS, and the identification of cases in an age range during which most TGCTs are diagnosed. With respect to the timing of the repeated sample collections in this study, the Working Group noted that the first or only samples were often collected shortly after entering military service (a median of 0.3 and 0.4 years after enlistment for cases and controls, respectively) and probably reflected exposure patterns before military service. In contrast, the second samples (when available or selected) were typically collected after several years of service and may be more representative of PFAS levels during active duty, although PFOA and PFOS levels were still generally similar to those for comparably aged men in the US population overall. Participants with second samples also tended to be older and were more likely to be diagnosed with seminoma (which is consistent with the typical age distributions of TGCT subtypes). As such, it is possible that the association with PFOS observed in the analyses of second samples may reflect patterns of risk related to exposure during military service, during different etiological time windows, and/or for seminomas in particular. A limitation of this study was the lack of information provided on associations with PFOA for histological subtypes of TGCT, which precluded an assessment of potential differences in the relation between PFOA and seminoma and nonseminoma tumours in this population.]

A single non-nested case–control study evaluated testicular cancer risk in relation to exposure to PFOA. A case–control study by Vieira et al. (2013) using data from cancer registries in Ohio and West Virginia evaluated various malignancies, including testicular cancer, among Mid-Ohio Valley residents with exposure to PFOA-contaminated drinking-water (Section 2.1.22). In analyses based on ecological exposure assignment for residence in areas of West Virginia and Ohio with contaminated water (all participants in the study), the investigators found no association with testicular cancer overall (adjusted OR, 1.0; 95% CI, 0.6–1.8; 18 cases in districts with contaminated water). An elevated OR was observed in the water district with the highest levels of PFOA exposure (Little Hocking: adjusted OR, 5.1; 95% CI, 1.6–15.6; 8 exposed cases). In analyses based on estimated serum PFOA concentrations among Ohio participants (not available for West Virginia participants), an elevated risk of testicular cancer was observed among those in the highest category of exposure compared with unexposed individuals, although the confidence interval was wide and included the null value (adjusted OR, 2.8; 95% CI, 0.8–9.2; 6 exposed cases).

[The Working Group noted that the cancer cases included in Vieira et al. (2013) overlapped with those in the study by Barry et al. (2013), although the degree of overlap was unknown. It was also noted that in the analyses of more

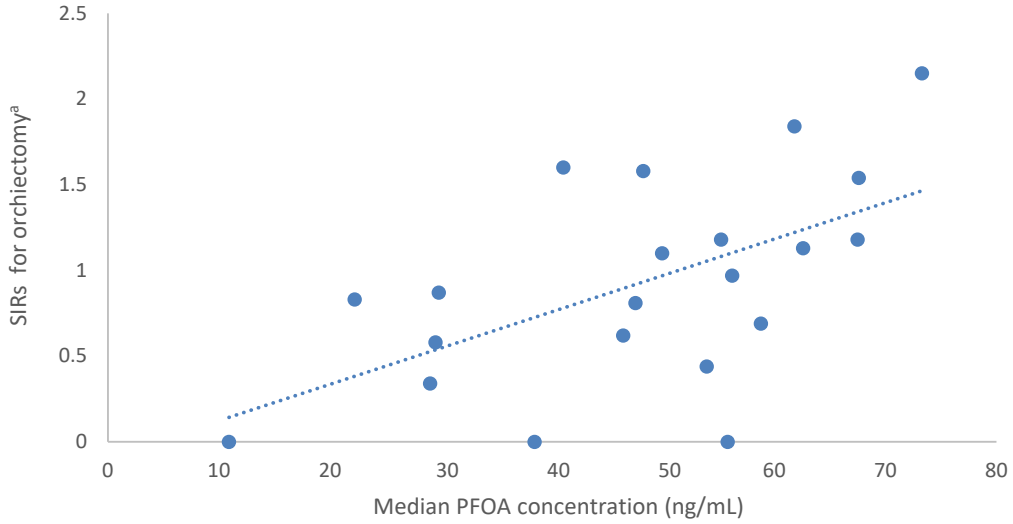
detailed estimates of serum PFOA concentrations (only available for Ohio participants), the testicular cancer cases from Little Hocking may have been overrepresented in the highest exposure category (as this district had the highest levels of PFOA contamination). The degree of overlap was not reported, but the risk estimates from the two analyses may not be independent.]

In the Veneto region of Italy, an area with water contaminated with PFAS (overwhelmingly PFOA) from a local manufacturing plant, residents were invited to participate in a surveillance programme (participation rate, 63.5%) to address public concern about their exposure. Some of the participants lived in areas of the region with less-contaminated water. Among adults aged 14–39 years at recruitment, more than 18 000 people (9230 men) participating in this programme provided serum (Pitter et al., 2020). The median serum PFOA concentration was 44.4 ng/mL. An epidemiological investigation evaluated the frequency of orchiectomies in this region between 1997 and 2014 (Sistema Epidemiologico Regionale, 2016). Orchiectomy was used as a proxy for a diagnosis of testicular cancer (sensitivity and positive predictive values of 91.7% (95% CI, 88.0–95.4%) and 92.8% (95% CI, 89.3–96.2%), respectively, in this region). Orchiectomies were ascertained using information in hospital discharge records, which included address of residence and the main medical procedures from hospital stays and were completed for the purpose of reimbursement from the Italian national health system. SIRs for orchiectomy were estimated for the 21 municipalities separately, comparing the observed orchiectomies (n = 70 overall) versus expected numbers based on regional rates in 5-year age groups (Sistema Epidemiologico Regionale, 2016). The Working Group combined the serum PFOA data and orchiectomy rates by municipality (Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636); as shown in Fig. 2.1, a strong correlation (Spearman correlation, 0.57; P = 0.006) was observed between serum PFOA concentrations and rates of orchiectomy (standardized on age by 5-year age groups from 15–54 years to the overall regional rate) by municipality. The Working Group also conducted a Poisson regression of observed orchiectomies on median PFOA levels across 21 municipalities, using the log of expected events as an offset, and correcting for dispersion. The RR for each unit (ng/mL) increase of PFOA was 1.018 (95% CI, 1.006–1.031; P = 0.003).

[The Working Group considered the findings from these data from a region with high PFOA exposure to be informative because of the large number of serum measurements in the population, high PFOA levels, and good ascertainment of orchiectomy, which was shown to be an excellent surrogate for diagnosis of testicular cancer in this region. The ecological design and small numbers of orchiectomies by municipality and resulting imprecise SIR values were limitations.]

A review by Bartell and Vieira (2021) included a meta-analysis of associations between PFOA and testicular cancer from the Vieira et al. (2013) study and those reported in Barry et al. (2013); they found a 3% increase in the risk of testicular cancer for each 10 ng/mL increase in estimated serum PFOA concentration (random-effects meta-RR, 1.03; 95% CI, 1.02–1.04). Results from a fixed-effects meta-analysis were similar. [The Working Group considered the informativeness of this meta-analysis to be reduced because of the unknown degree of overlap between the studies by Vieira et al. (2013) and Barry et al. (2013), and because the study by Purdue et al. (2023) was not available that time. If there were substantial overlap between the studies by Vieira et al. (2013) and Barry et al. (2013), then the resulting meta-RRs could be overestimated. Another meta-analysis by Seyyedsalehi and Boffetta (2023) was not considered because it also did not include the Purdue et al. (2023) study and did not contribute any other information.]

Fig. 2.1 Serum PFOA concentrations and orchiectomy rates by municipality, in Veneto, Italy



PFOA, perfluorooctanoic acid; SIR, standardized incidence ratio.
[a] Age-standardized to the regional Veneto population.
Pearson correlation coefficient, 0.58; $P = 0.006$.
Note that SIRs were plotted because they followed approximately normal distribution.

2.3.2 Prostate cancer

As summarized in Table 2.3 and below, there have been six investigations of prostate cancer incidence, mortality, or both in cohorts with occupational (Steenland and Woskie, 2012; Consonni et al., 2013; Raleigh et al., 2014; Steenland et al., 2015) or high environmental (Barry et al., 2013; Li et al., 2022a) exposure to PFOA and/or PFOS, and three investigations of serum PFOA and PFOS concentrations and risk of prostate cancer nested within general population cohorts (Eriksen et al., 2009; Rhee et al., 2023a; Winquist et al., 2023). Prostate cancer was also evaluated in two case–control studies (Vieira et al., 2013; Hardell et al., 2014). As described above and in Section 2.1.22, the study by Vieira et al. (2013) included individuals in the Mid-Ohio Valley with high exposure to PFOA, and the population overlapped with that of the cohort study by Barry et al. (2013). Hardell et al. (2014) conducted a population-based case–control study of serum PFAS concentrations and prostate cancer in a population with background levels of exposure in Sweden. Beyond these studies, an occupational cohort of 652 PFOS-exposed employees at a fluorochemical-production facility evaluated prostate cancer (5 exposed cases) identified from health claims data (Olsen et al., 2004). [The Working Group considered the study by Olsen et al. (2004) to be uninformative, given the small number of exposed cases and the focus on prevalent (rather than incident) cancers as the outcome; as such, it was not included in Table 2.3 or in the summary below.]

Raleigh et al. (2014) examined prostate cancer incidence and mortality among 3716 male workers at an APFO-production facility in Cottage Grove, Minnesota, USA (Section 2.1.1). They found no evidence of excess prostate cancer mortality on the basis of 24 deaths among PFOA-exposed workers (relative to Minnesota state rates: SMR, 0.83; 95% CI, 0.53–1.23), and no associations were observed in exposure–response analyses with unexposed workers as the reference group. Exposure–response analyses of

prostate cancer incidence (on the basis of 188 cases among PFOA-exposed workers) were similarly null.

Steenland and Woskie (2012) evaluated prostate cancer mortality among 5791 workers exposed to PFOA at a fluoropolymer-production plant in Parkersburg, West Virginia, USA, in the Mid-Ohio Valley (Section 2.1.3). In analyses based on 21 deaths among PFOA-exposed workers, the authors found no evidence of excess prostate cancer mortality relative either to workers from other plants within the same company in the same region (SMR, 0.76; 95% CI, 0.47–1.16) or to the general US population (SMR, 0.72; 95% CI, 0.45–1.10), and no associations were observed in exposure–response analyses of estimated cumulative PFOA exposure. In a subsequent analysis of prostate cancer incidence that included 129 cases among a subset of 2955 male workers from this cohort, Steenland et al. (2015) observed elevated but imprecise estimates of prostate cancer rates among those with higher estimated cumulative PFOA exposure. Relative to those in the lowest quartile, the rate ratios in the second, third, and fourth quartiles were 1.81 (95% CI, 0.69–4.78), 2.45 (95% CI, 0.96–6.25), and 1.88 (95% CI, 0.72–4.88), respectively, and the *P* for trend was 0.11. Similar patterns were observed in analyses lagged by 10 years.

[The Working Group noted that the small numbers of deaths from prostate cancer in Raleigh et al. (2014) and Steenland and Woskie (2012) limited the ability to evaluate associations with prostate cancer mortality in both studies. Analyses of prostate cancer incidence by Steenland et al. (2015) and Raleigh et al. (2014) – which included 129 and 188 cases, respectively – had somewhat better statistical power.]

Eriksen et al. (2009) conducted a prospective case–cohort study nested within a cohort of older Danish adults with background levels of exposure to PFOA and PFOS. Samples were collected at cohort enrolment between 1993 and 1997, and prediagnostic plasma concentrations of PFOA and PFOS were measured for 713 cases of prostate cancer and 680 non-cases (Section 2.1.4). For PFOS, the authors observed about 30–40% increased risks of prostate cancer in the three upper quartiles compared with the lowest quartile (e.g. fourth versus first quartile, incidence rate ratio, IRR, 1.38; 95% CI, 0.99–1.93); in regression analyses in which plasma PFOS concentration was included as a continuous variable, the IRR corresponding to a 10 ng/mL increase in plasma PFOS levels was 1.05 (95% CI, 0.97–1.14). For PFOA, an exposure–response pattern was not apparent in analyses based on quartiles of measured levels; a modest increase in risk was observed when PFOA was modelled continuously (per 1 ng/mL increase, IRR, 1.03; 95% CI, 0.99–1.07).

[The Working Group noted that the main strengths of this study were the large number of cases of prostate cancer and non-cases, a well-defined national cohort with complete ascertainment of incident cancer cases, data on a wide range of potential confounding factors, and a reasonable exposure contrast in a population with plasma PFOA and PFOS concentrations consistent with background levels of exposure. The measurements of PFOA and PFOS were conducted using samples collected a median of 7 years before cancer diagnosis; however, the authors did not report results for different time intervals between serum collection and diagnosis of prostate cancer to assess potential etiologically relevant periods of exposure. Also, the investigators observed a strong correlation between plasma PFOA and PFOS concentrations (Spearman correlation, 0.70) but did not evaluate prostate cancer risk in analyses with mutual adjustment for both chemicals, limiting the ability to assess the associations with each of these exposures independently.]

Barry et al. (2013) evaluated the risk of incident prostate cancer among community members and workers in the C8 Science Panel study (Section 2.1.5). A total of 446 validated prostate

cancer cases were included in the analyses; the investigators found no evidence of an exposure–response association with estimated cumulative PFOA serum concentrations (unlagged analysis: adjusted HR corresponding to a unit increase in natural log-transformed levels, 0.99; 95% CI, 0.93–1.04). The corresponding risk estimate from an analysis with a 10-year lag period was similar (HR, 0.99; 95% CI, 0.94–1.05).

[The Working Group noted that the strengths of the study by Barry et al. (2013) included the detailed enumeration of the cohort, ascertainment or confirmation of cancer diagnoses, and relatively large numbers of incident prostate cancer cases.]

Consonni et al. (2013) evaluated prostate cancer mortality in a pooled international cohort of 4773 male workers who had ever been exposed to TFE (Section 2.1.6). Among those who had ever been exposed to APFO (n = 4205), the investigators observed reduced mortality from prostate cancer in analyses based on 3 observed deaths (using national reference rates: SMR, 0.24; 95% CI, 0.05–0.70).

[The Working Group noted that the small numbers of deaths from prostate cancer in this occupational cohort limited the ability to evaluate associations with prostate cancer mortality.]

Rhee et al. (2023a) conducted a nested case–control study of aggressive prostate cancer (750 cases, 750 matched controls) in relation to prediagnostic serum PFAS concentrations (including PFOA and PFOS) within the PLCO Cancer Screening Trial cohort (Section 2.1.11). Aggressive prostate cancer was defined as having stage III or IV disease, Gleason score ≥ 8, or Gleason score 7 and death from prostate cancer. The study included cases with serum samples collected > 300 days before prostate cancer diagnosis (a median of 9 years from blood collection to diagnosis). Controls were selected from among participants who were alive and cancer-free as of the case diagnosis date and were individually matched to cases on age at baseline, race or ethnicity, study centre, calendar year and study year of blood collection, and previous freeze–thaw cycles. For a subset of 60 controls, the investigators measured PFAS concentrations in sera collected at three time points up to 6 years apart. In overall logistic regression analyses of PFOA conditioned on matching factors, the investigators observed an inverse association with aggressive prostate cancer (per doubling in serum PFOA concentration, OR for a 1-unit increase in PFOA serum concentration on the $\log_2$ scale, 0.82; 95% CI, 0.71–0.96). This association remained apparent in analyses adjusted for prostate cancer risk factors (BMI, smoking status, family history of prostate cancer, history of diabetes) and other PFAS – PFOS, PFHxS, PFNA, *N*-EtFOSAA, perfluorooctane sulfonamide (FOSA), 2-*N*-methyl-perfluorooctane sulfonamido acetate (*N*-MeFOSAA), and perfluoroheptanesulfonic acid (PFHpS). However, in analyses restricted to cases diagnosed > 3 years after blood collection, the association was less apparent (OR_{log2}, 0.90; 95% CI, 0.79–1.03). For PFOS, a modest inverse association was observed in analyses conditioned on matching factors but not adjusted for other covariates (OR_{log2}, 0.93; 95% CI, 0.83–1.05), whereas no association was observed after adjustment for prostate cancer risk factors and other PFAS (OR_{log2}, 0.99; 95% CI, 0.79–1.23). Analyses of serial samples collected up to 6 years apart from a subset of controls demonstrated good within-subject agreement in measurements of PFOA and PFOS over time, with overall intraclass correlation coefficients of 0.73 (95% CI, 0.62–0.81) and 0.85 (95% CI, 0.78–0.90) for PFOA and PFOS, respectively (Rhee et al., 2023a).

[The Working Group identified several strengths of this study that contributed to its informativeness, including its large sample size, measurements of serum PFOA and PFOS concentrations in prediagnostic samples, and the ability to adjust for measured concentrations of other PFAS and other potential confounding factors.]

In the Ronneby community cohort (Section 2.1.13), Li et al. (2022a) identified 181 cases of prostate cancer among residents in areas with PFAS-contaminated drinking-water. The investigators found that prostate cancer incidence rates among men who resided in exposed areas were similar to regional rates (SIR, 0.96; 95% CI, 0.82–1.11) and that risk for these men was lower than that for men in the Ronneby municipality who had never resided in contaminated water districts (HR, 0.83; 95% CI, 0.71–0.98). Inverse associations with prostate cancer risk were also observed among those residing in contaminated districts during the later years (HR, 0.76; 95% CI, 0.59–0.98; 67 exposed cases) and those with longer duration of residence in contaminated districts (HR, 0.72; 95% CI, 0.58–0.91; 86 exposed cases).

[The Working Group noted that the strengths of the study (Li et al., 2022a) included the detailed enumeration of the cohort, ascertainment and confirmation of cancer diagnoses, and relatively large numbers of incident prostate cancer cases. However, a limitation of the exposure assessment in the study by Li et al. (2022a) was the inability of their analysis to distinguish between the potential effects of PFOS and PFHxS.]

Winquist et al. (2023) evaluated prostate cancer in their case–cohort investigation in the ACS CPS-II LifeLink Cohort (see Section 2.1.21). In analyses with 1599 selected prostate cancer cases, they found no associations with prostate cancer risk for either PFOA or PFOS; when $\log_2$-transformed levels were modelled continuously, the observed hazard ratios were 0.93 (95% CI, 0.79–1.08) and 1.00 (95% CI, 0.88–1.14) for PFOA and PFOS, respectively. Analyses based on quartiles of PFOA and PFOS were similarly null. [The Working Group noted several strengths of this study, including its large sample size, measurements of serum PFOA and PFOS concentrations in prediagnostic samples, and the ability to adjust for other potential confounding factors. Limitations included the relatively low exposure contrast in the study population.]

In addition to the cohort-based studies summarized above, the Working Group also reviewed two case–control studies of PFOA and/or PFOS exposure and prostate cancer (Vieira et al., 2013; Hardell et al., 2014).

Vieira et al. (2013) evaluated prostate cancer in their case–control studies on multiple cancer types among Mid-Ohio Valley residents exposed to PFOA from contaminated drinking-water. In analyses with 434 PFOA-exposed cases in West Virginia and Ohio, they found no association with prostate cancer (adjusted OR, 0.9; 95% CI, 0.8–1.1); a modest increased risk was observed in the water district with the highest levels of PFOA exposure (adjusted OR, 1.4; 95% CI, 0.9–2.3; 36 exposed cases). Among Ohio participants, an elevated but imprecise OR was also observed among those in the highest category of PFOA exposure compared with unexposed individuals (adjusted OR, 1.5; 95% CI, 0.9–2.5; 31 exposed cases).

[The Working Group noted that the degree of overlap in the cancer cases included in the studies by Vieira et al. (2013) and Barry et al. (2013) was unknown, and as such the results of the two studies cannot necessarily be interpreted independently.]

Hardell et al. (2014) conducted a case–control study of serum PFAS concentrations (including PFOA and PFOS) and prostate cancer in Örebro County, Sweden. The study included 201 cases and 186 population-based controls, with blood samples collected in the period 2007–2011. Samples were collected from cases after diagnosis of prostate cancer but before initiating treatment. The investigators found no associations with PFOA or PFOS in overall analyses and among those with markers indicative of more advanced disease (Gleason score 7–10, or prostate-specific antigen, PSA ≥ 11). However, for participants who reported a family history of disease (prostate cancer in a first-degree relative)

and had serum concentrations above the median (24 cases), increased risks were observed for both PFOA (OR, 2.6; 95% CI, 1.2–6.0) and PFOS (OR, 2.7; 95% CI, 1.04–6.8) relative to participants with no family history and serum concentrations at or below the median for the respective chemicals.

[The Working Group noted several limitations of this study. Samples were collected from cases after diagnosis of prostate cancer, and it was possible that the measurements of serum PFOA and PFOS concentrations may have been influenced by disease status, which could have resulted in differential exposure misclassification between cases and controls, possibly biasing risk estimates either towards or away from the null value. It was also possible that PFAS concentrations at the time of diagnosis may not have reflected exposure levels during an etiologically relevant time period. However, the sample collections occurred before cases were treated, so any potential treatment-related effects on PFAS levels were not a concern in this study. Other limitations included the non-participation of some selected cases and matched controls (response rates were 79% and 54%, respectively), the lack of adjustment for other PFAS in the statistical analyses, and the relatively small sample size, particularly for analyses stratified by family history of prostate cancer.]

2.4 Cancers of the breast and thyroid gland

2.4.1 Cancer of the breast

See Table 2.4.

(a) Cohort and nested case–control studies

There were 12 cohort or nested case–control studies that contributed evidence on PFOA and PFOS exposure and the risk of breast cancer in women. Three of these studies were occupational cohorts (Alexander et al., 2003; Steenland and Woskie, 2012; Raleigh et al., 2014). [The Working Group noted that these occupational cohorts included few women and thus had extremely limited power with which to consider associations with breast cancer, resulting in limited inference from those studies.] Two studies (Barry et al., 2013; Li et al., 2022a) considered how environmental exposure to high levels of PFAS in the contaminated environment from nearby industrial or occupational sources was related to breast cancer risk using modelled exposure assessment. The remaining studies included two nested case–control studies focused on PFAS measurements during pregnancy in relation to subsequent risk of breast cancer in the individual (Ghisari et al., 2017) and the offspring (Cohn et al., 2020), as well as blood measurements in nested substudies within larger population-based cohorts (Hurley et al., 2018; Mancini et al., 2020a; Feng et al., 2022; Chang et al., 2023; Winquist et al., 2023).

Raleigh et al. (2014) evaluated cancer incidence and mortality in an occupational cohort that included 4668 workers (of whom 952 were women) who had worked for ≥ 1 year and were exposed to APFO at a factory in Cottage Grove, Minneapolis, USA, between 1947 and 2002, and a comparison group of 4359 employees (of whom 526 were women) who were unexposed workers at a factory in Saint Paul (see Section 2.1.1). Individual inhalation exposure was estimated using a JEM, and information on cancer incidence and mortality was obtained via linkages to registries, with follow-up until 2008. Women represented only 21% of the workers at the Cottage Grove facility and 12% at the Saint Paul facility. There were 26 deaths (11 exposed, 15 unexposed) from breast cancer (25 among women) and 62 cases (34 exposed, 28 unexposed) of incident breast cancer. There was little evidence to suggest that increased APFO exposure was associated with a higher SMR for breast cancer relative to population mortality rates or with an increased hazard ratio for incident breast cancer cases, although this was based on few cases. [The Working Group noted that very

Table 2.4 Epidemiological studies on exposure to PFOA or PFOS and cancers of the breast and thyroid gland

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Raleigh et al. (2014) MN, USA Enrolment, 1947–2002/ follow-up, 1947–2008 (mortality), 1988–2008 (incidence) Cohort	9027 (952 exposed women, 526 reference women); Cottage Grove (MN) PFOA cohort; workers employed for ≥ 1 yr in 1947–2002 at an APFO facility (Cottage Grove; *n* = 4668); reference workers without any exposure to APFO employed at a tape and abrasives production facility located in the same suburban geographical area and managed by the same company (Saint Paul; *n* = 4359) Exposure assessment method: see Table 2.1	Breast, mortality	Exposed to APFO (SMR, MN referent):			Age, sex, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. Unlikely TFE co-exposure; Reference population sharing similar socioeconomic characteristics. *Other limitations*: See Table 2.1. Lacking data on workers that left Minnesota or Wisconsin. Small numbers especially for women (12% of the cohort).
			Unexposed (Saint Paul plant)	15	1.39 (0.78–2.29)		
			Exposed (Cottage Grove plant)	11	0.82 (0.41–1.47)		
		Breast, mortality	Estimated cumulative airborne APFO exposure quartile (SMR, MN referent):				
			1st quartile ($< 2.6 \times 10^{-5}$ µg/m³-years)	5	0.80 (0.26–1.86)		
			2nd quartile (2.6×10^{-5} to $< 1.4 \times 10^{-4}$ µg/m³-years)	3	0.88 (0.18–2.56)		
			3rd quartile (1.4×10^{-4} to $< 7.3 \times 10^{-4}$ µg/m³-years)	2	0.73 (0.09–2.62)		
			4th quartile ($\geq 7.3 \times 10^{-4}$ µg/m³-years)	1	1.02 (0.03–5.69)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Raleigh et al. (2014) MN, USA Enrolment, 1947–2002/ follow-up, 1947–2008 (mortality), 1988–2008 (incidence) Cohort (cont.)		Breast, incidence	Estimated cumulative airborne APFO exposure quartile (HR):			Age, [sex], year of birth	
			Unexposed (Saint Paul plant)	28	1		
			1st quartile (< 2.9×10^{-5} µg/ m^3-years)	8	0.36 (0.16–0.79)		
			2nd quartile (2.9×10^{-5} to < 1.5×10^{-4} µg/ m^3-years)	8	0.65 (0.29–1.42)		
			3rd quartile (1.5×10^{-4} to < 7.9×10^{-4} µg/ m^3-years)	14	1.47 (0.77–2.80)		
			4th quartile (≥ 7.9×10^{-4} µg/ m^3-years)	4	0.85 (0.29–2.46)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), 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 ≥ 365 days before 31 December 1997 Exposure assessment method: see Table 2.1	Thyroid, mortality	Employed in APFO-exposed job (SMR, MN referent): Never Ever probable/ never definite Ever definite	 1 0 0	 2.16 (0.05–12.00) 0 (0.00–8.45) 0 (0.00–42.96)	Age, sex, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: Occupational cohort with relatively high exposures. *Other limitations*: Small cohort with limited number of deaths; potential healthy-worker effect due to external comparison of rates with general population; limited information on covariates.
Alexander et al. (2003) Decatur (AL), USA Enrolment, 1961–1997/ follow-up, 1961–1998 (mortality) Cohort	2083 (241 exposed and 112 unexposed women); Decatur (AL) PFOS cohort; production workers (men, 83%) who worked ≥ 365 days in a plant producing speciality films and fluorochemicals, one of the main ones being perfluorooctane-sulfonyl (POSF). Exposure assessment method: See Table 2.1	Breast, mortality	PFOS exposure group (SMR, AL referent): All jobs Only non-exposed Ever low, never high Ever high	 2 2 0 0	 1.57 (0.19–5.66) 5.11 (0.62–18.45) 0 0	Sex, age, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1 *Other limitations*: Occupational cohort with few breast cancer deaths (n = 2); outcome assessment limited to mortality; mostly men (83%).

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), 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 Cohort	5791 (women, 19%); Parkersburg (WV), polymer-production PFOA cohort; workers (men, 81%) at a polymer-manufacturing facility who had potential exposure to fluoropolymers and had sufficiently detailed work histories Exposure assessment method: see Table 2.1	Breast, mortality	PFOA-exposed workers (SMR):			Age, sex, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: Occupational cohort with few breast cancer deaths (n = 4); outcome assessment limited to mortality; mostly men (81%).
			Other workers referent (same region and company)	4	0.65 (0.13–1.90)		
			US referent	4	0.79 (0.21–2.02)		
		Breast, mortality	Cumulative serum exposure, no lag (SMR, other workers referent, same region and company), women only:				
			1st quartile (0 to < 904 ppm-years)	2	1.49 (0.18–5.39)		
			2nd quartile (904 to < 1520 ppm-years)	0	0.00 (0.00–3.56)		
			3rd quartile (1520 to < 2700 ppm-years)	1	0.87 (0.02–4.83)		
			4th quartile (≥ 2700 ppm-years)	0	0.00 (0.00–3.42)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Leonard et al. (2008) Parkersburg (WV), USA Enrolment, 1948–2002/ follow-up, 1948–2002 (mortality) Cohort	6027 workers; Parkersburg (WV), polymer-production occupational PFOA cohort; workers (men, 81%) at a polymer-manufacturing facility who had potential exposure to fluoropolymers and had sufficiently detailed work histories; most recent follow-up for some cancer sites Exposure assessment method: records	Thyroid, mortality	Workers in the Parkersburg (WV), polymer-production plant (SMR): Referent US population Referent WV population Referent other workers (same region and company)	 3 3 3	 [3.120 (0.644–9.119)] [2.856 (0.589–8.347)] [6.286 (1.297–18.369)]	Sex, age, calendar period	*Exposure assessment critique*: See Table 2.1. *Other strengths*: Occupational cohort with relatively high exposures; complete cohort ascertainment and follow-up; use of local reference groups increased comparability with respect to socioeconomic factors and health behaviours. *Other limitations*: 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.

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Barry et al. (2013) Mid-Ohio Valley (OH and WV) Enrolment, August 2005-August 2006/follow-up, 1952 to 2011 (incidence) Cohort	32 254 (women, 17 360; community, 16 602; and occupational, 758); C8 Science Panel Study included people enrolled in the C8 Health Project who lived, worked, or attended school for ≥ 1 yr between 1950 and 3 December 2004 in a contaminated-water district in the vicinity of a chemical plant (Parkersburg (WV), polymer production) using PFOA in manufacturing, as well as a subset of those from the original Parkersburg (WV), polymer-production occupational cohort who worked at the plant between 1948 and 2002 Exposure assessment method: see Table 2.1	Breast, 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*: Wide range of PFOA exposure levels; availability of detailed information on potential confounding factors; relatively high participation rates; validation of cancer diagnoses through medical chart review. *Other limitations*: Mostly retrospective with relatively few validated cases for prospective analyses.
			Continuous (per unit on natural log scale)	559	0.94 (0.89–1.00)		
		Breast, incidence	Estimated cumulative PFOA serum concentration (ng/mL), 10-yr lag (HR):				
			Continuous (per unit on natural log scale)	559	0.93 (0.88–0.99)		
		Thyroid, incidence	Estimated cumulative PFOA serum concentration (ng/mL), no lag (HR):				
			1st quartile	NR	1		
			2nd quartile	NR	1.54 (0.77–3.12)		
			3rd quartile	NR	1.48 (0.74–2.93)		
			4th quartile	NR	1.73 (0.85–3.54)		
			Continuous (per unit on natural log scale)	86	1.10 (0.95–1.26)		
			Trend-test *P*-value, 0.25				
		Thyroid, incidence	Excluding person-time before estimated date first known to have lived or worked in the contaminated-water districts: estimated cumulative PFOA serum concentration (ng/mL), no lag (HR):				
			Continuous (per unit on natural log scale)	NR	1.06 (0.92–1.23)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Barry et al. (2013) Mid-Ohio Valley (OH and WV) Enrolment, August 2005-August 2006/follow-up, 1952 to 2011 (incidence) Cohort (cont.)		Thyroid, 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)	
			1st quartile	NR	1		
			2nd quartile	NR	2.06 (0.93–4.56)		
			3rd quartile	NR	2.02 (0.90–4.52)		
			4th quartile	NR	1.51 (0.67–3.39)		
			Continuous (per unit on natural log scale)	86	1.04 (0.89–1.20)		
			Trend-test *P*-value, 0.57				
		Thyroid, incidence	Excluding person-time before estimated date first known to have lived or worked in the contaminated-water districts: estimated cumulative PFOA serum concentration (ng/mL), 10-yr lag (HR):				
			Continuous (per unit on natural log scale)	NR	1.02 (0.87–1.19)		
		Thyroid, incidence	Community residents: estimated cumulative PFOA serum concentration (ng/mL), no lag (HR):				
			1st quartile	NR	1		
			2nd quartile	NR	1.54 (0.73–3.26)		
			3rd quartile	NR	1.71 (0.81–3.59)		
			4th quartile	NR	1.40 (0.66–2.97)		
			Continuous (per unit on natural log scale)	78	1.04 (0.89–1.23)		
			Trend-test *P*-value, 0.46				

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Barry et al. (2013) Mid-Ohio Valley (OH and WV) Enrolment, August 2005-August 2006/follow-up, 1952 to 2011 (incidence) Cohort (cont.)		Thyroid, incidence	Community residents: 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)	
			1st quartile	NR	1		
			2nd quartile	NR	2.09 (0.91–4.82)		
			3rd quartile	NR	1.92 (0.82–4.50)		
			4th quartile	NR	1.42 (0.60–3.37)		
			Continuous (per unit on natural log scale)	78	1.00 (0.84–1.20)		
			Trend-test *P*-value, 0.56				
		Thyroid, incidence	Workers: estimated cumulative PFOA serum concentration (ng/mL), no lag (HR):				
			1st quartile	NR	1		
			2nd quartile	NR	4.64 (0.42–50.8)		
			3rd quartile	NR	9.70 (0.67–141.2)		
			4th quartile	NR	14.72 (0.85–253.9)		
			Continuous (per unit on natural log scale)	8	1.93 (1.00–3.71)		
			Trend-test *P*-value, 0.04				
		Thyroid, incidence	Workers: estimated cumulative PFOA serum concentration (ng/mL), 10-yr lag (HR):				
			1st quartile	NR	1		
			2nd quartile	NR	1.65 (0.09–31.5)		
			3rd quartile	NR	4.52 (0.10–198.4)		
			4th quartile	NR	5.85 (0.13–257.1)		
			Continuous (per unit on natural log scale)	8	1.12 (0.61–2.05)		
			Trend-test *P*-value, 0.01				

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Ghisari et al. (2017) Denmark Enrolment, 1996–2002/ follow-up, through 2010 Nested case–control	Nested within the Danish National Birth Cohort (see Table 2.1) Cases: 178; nulliparous women at the time of blood draw during pregnancy followed for breast cancer, selected from ~100 000 pregnant women Controls: 233; nulliparous women at the time of blood draw during pregnancy frequency-matched on age Exposure assessment method: see Table 2.1	Breast (pre-menopausal), incidence	Serum PFOA (ng/mL) (RR):			Age at blood draw, BMI before pregnancy, total gravidities, oral contraceptive use, age at menarche, smoking status during pregnancy, alcohol intake during pregnancy, physical activity, education	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations* See Table 2.1.
			Continuous (per unit on natural log scale)	158	1.17 (0.63–2.17)		
		Breast (pre-menopausal), incidence	Serum PFOS (ng/mL) (RR):				
			Continuous (per unit on natural log scale)	158	1.15 (0.64–2.08)		
		Breast (pre-menopausal), incidence	CYP19 (C > T) genotype (RR per unit natural log transformed PFOA, ng/mL):				
			CC	35	7.24 (1.00–52)		
			CT	59	0.79 (0.26–2.38)		
			TT	34	0.55 (0.14–2.24)		
		Breast (pre-menopausal), incidence	CYP19 (C > T) genotype (RR per unit natural log transformed PFOS, ng/mL):				
			CC	35	6.42 (1.08–38.3)		
			CT	59	1.16 (0.44–3.10)		
			TT	34	0.45 (0.10–1.97)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hurley et al. (2018) CA, USA Enrolment, 1995–1996/ follow-up, 1 January 2006 to 1 August 2014 (incidence) Nested case–control	Nested within the California Teachers Study (See Table 2.1) Cases: 902; California Teachers Study; female public-school teachers and other professionals with a diagnosis of invasive breast cancer, age < 80 yr at diagnosis with no prior history of breast cancer, who provided a blood specimen and answered a questionnaire, who were continuous residents of CA; participation rate, 65% Controls: 858; women drawn from probability sample of at-risk cohort members, frequency-matched on age, race/ethnicity, and residence; participation rate, 55% Exposure assessment method: see Table 2.1	Breast, incidence	Serum PFOA (ng/mL) (OR):			Age at baseline, race/ethnicity, region of residence, date of blood draw, (date of blood draw)^2, season of blood draw, total smoking pack-years, BMI, family history of breast cancer, age at first full-term pregnancy, pork consumption[a], and menopausal status at blood draw	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. [a] This is the standard covariate set used for all analyses. Additional covariates are indicated as required.
			1st tertile	331	1		
			2nd tertile	298	0.901 (0.705–1.152)		
			3rd tertile	273	0.925 (0.715–1.197)		
			Continuous (per unit $\log_{10}$ scale)	902	0.733 (0.496–1.081)		
			Trend-test *P*-value, 0.54				
		Breast, incidence	Serum PFOS (ng/mL) (OR):				
			1st tertile	318	1		
			2nd tertile	297	0.883 (0.691–1.129)		
			3rd tertile	287	0.898 (0.695–1.161)		
			Continuous (per unit $\log_{10}$ scale)	902	0.934 (0.683–1.277)		
			Trend-test *P*-value, 0.41				
		Breast, post-menopausal at blood draw, incidence	Serum PFOA (ng/mL) (OR):			Standard covariates[a]	
			1st tertile	306	1		
			2nd tertile	287	0.889 (0.689–1.147)		
			3rd tertile	266	0.912 (0.699–1.189)		
			Continuous (per unit $\log_{10}$ scale)	859	0.715 (0.476–1.073)		
			Trend-test *P*-value, 0.49				
		Breast (post-menopausal at blood draw), incidence	Serum PFOS (ng/mL) (OR):			Standard covariates[a]	
			1st tertile	293	1		
			2nd tertile	284	0.843 (0.653–1.088)		
			3rd tertile	282	0.860 (0.661–1.118)		
			Continuous (per unit $\log_{10}$ scale)	859	0.885 (0.641–1.223)		
			Trend-test *P*-value, 0.26				

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hurley et al. (2018) CA, USA Enrolment, 1995–1996/ follow-up, 1 January 2006 to 1 August 2014 (incidence) Nested case–control (cont.)		Breast (pre-menopausal at blood draw), incidence	Serum PFOA (ng/mL) (OR):			Age at baseline, race/ethnicity, region of residence, date of blood draw, (date of blood draw)^2, season of blood draw, dietary fat, total red meat consumption	
			1st tertile	25	1		
			2nd tertile	11	0.888 (0.239–3.302)		
			3rd tertile	7	0.669 (0.143–3.119)		
			Continuous (per unit $\log_{10}$ scale)	43	0.177 (0.023–1.342)		
			Trend-test *P*-value, 0.62				
		Breast (pre-menopausal at blood draw), incidence	Serum PFOS (ng/mL) (OR):			Age at baseline, race/ethnicity, region of residence, season of blood draw, total red meat consumption	
			1st tertile	25	1		
			2nd tertile	13	1.796 (0.493–6.546)		
			3rd tertile	5	1.208 (0.163–8.944)		
			Continuous (per unit $\log_{10}$ scale)	43	0.900 (0.166–4.876)		
			Trend-test *P*-value, 0.57				
		Breast (ER+ or PR+), incidence	Serum PFOA (ng/mL) (OR):			Age at baseline, race/ethnicity, region of residence, date of blood draw, (date of blood draw)^2, season of blood draw, total smoking pack-years, BMI, family history of breast cancer, age at first full-term pregnancy, menopausal status at blood draw, pork consumption	
			1st tertile	266	1		
			2nd tertile	247	0.918 (0.707–1.191)		
			3rd tertile	230	0.952 (0.725–1.251)		
			Continuous (per unit on $\log_{10}$ scale)	743	0.779 (0.513–1.183)		
			Trend-test *P*-value, 0.71				
		Breast (ER+ or PR+), incidence	Serum PFOS (ng/mL) (OR):				
			1st tertile	250	1		
			2nd tertile	247	0.937 (0.721–1.218)		
			3rd tertile	246	0.967 (0.737–1.270)		
			Continuous (per unit on $\log_{10}$ scale)	743	1.054 (0.744–1.493)		
			Trend-test *P*-value, 0.81				

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Hurley et al. (2018) CA, USA Enrolment, 1995–1996/ follow-up, 1 January 2006 to 1 August 2014 (incidence) Nested case–control (cont.)		Breast (ER– and PR–), incidence	Serum PFOA (ng/mL) (OR):			Age at baseline, race/ethnicity, region of residence, date of blood draw, (date of blood draw)^2, season of blood draw, physical activity	
			1st tertile	43	1		
			2nd tertile	35	0.846 (0.510–1.403)		
			3rd tertile	29	0.792 (0.460–1.365)		
			Continuous (per unit on $\log_{10}$ scale)	107	0.528 (0.239–1.165)		
			Trend-test *P*-value, 0.39				
		Breast (ER– and PR–), incidence	Serum PFOS (ng/mL) (OR):				
			1st tertile	47	1		
			2nd tertile	32	0.628 (0.378–1.041)		
			3rd tertile	28	0.615 (0.357–1.059)		
			Continuous (per unit on $\log_{10}$ scale)	107	0.573 (0.323–1.016)		
			Trend-test *P*-value, 0.06				

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mancini et al. (2020a) France Enrolment, 1990/follow-up, through 2013 (incidence) Nested case–control	Nested within E3N cohort (see Table 2.1) Cases: 194; incident postmenopausal breast cancers among women with serum (≥ 3 aliquots) collected before diagnosis, a completed dietary questionnaire in 1993, and randomly selected from 240 eligible breast cancers Controls: 194; density-sampled at time of case occurrence and matched by age within 2 yr, menopausal status at blood collection, BMI at blood collection, and year of blood collection Exposure assessment method: see Table 2.1	Breast (post-menopausal), incidence	Serum PFOA (OR): 1st quartile (1.3–4.8 ng/mL) 2nd quartile (4.8–6.8 ng/mL) 3rd quartile (6.8–8.8 ng/mL) 4th quartile (8.8–21.4 ng/mL) Trend-test *P*-value, 0.43	 85 118 91 94	 1 1.69 (0.89–3.21) 0.88 (0.43–1.80) 0.92 (0.43–1.98)	Age at blood draw, BMI at blood draw, menopausal status at blood draw, year of blood draw, total serum lipids, BMI, smoking status, physical activity (MET-h/week), education level, history of benign breast disease, family history of breast cancer, parity/age at first full-term pregnancy, total breastfeeding duration, age at menarche, age at menopause, use of oral contraceptives, current use of MHT, adherence to Western diet, adherence to Mediterranean diet	*Exposure assessment critique*: See Table 2.1. *Other strengths*: Adjustment for breast cancer risk factors; pathology reports for > 93% of cases. *Other limitations*: Limited statistical power, especially to explore differences by subtype.
		Breast (post-menopausal), incidence	Serum PFOS (OR): 1st quartile (5.8–13.6 ng/mL) 2nd quartile (13.6–17.3 ng/mL) 3rd quartile (17.3–22.5 ng/mL) 4th quartile (22.5–85.3 ng/mL) Trend-test *P*-value, 0.25	 80 109 99 100	 1 1.94 (1.00–3.78) 2.03 (1.02–4.04) 1.72 (0.88–3.36)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mancini et al. (2020a) France Enrolment, 1990/follow-up, through 2013 (incidence) Nested case–control (cont.)		Breast (post-menopausal, ER+), incidence	Serum PFOA (OR): 1st quartile (1.3–4.8 ng/mL) 2nd quartile (4.8–6.8 ng/mL) 3rd quartile (6.8–8.8 ng/mL) 4th quartile (8.8–21.4 ng/mL) Trend-test *P*-value, 0.64	 NR NR NR NR	 1 1.72 (0.88–3.36) 1.34 (0.66–2.73) 1.42 (0.68–2.95)	Age at blood draw, BMI at blood draw, menopausal status at blood draw, year of blood draw, total serum lipids, BMI, smoking status, physical activity (MET-h/week), education level, history of benign breast disease, family history of breast cancer, parity/age at first full-term pregnancy, total breastfeeding duration, age at menarche, age at menopause, use of oral contraceptives, current use of MHT, adherence to Western diet, adherence to Mediterranean diet	
		Breast (post-menopausal, ER+), incidence	Serum PFOS (OR): 1st quartile (5.8–13.6 ng/mL) 2nd quartile (13.6–17.3 ng/mL) 3rd quartile (17.3–22.5 ng/mL) 4th quartile (22.5–85.3 ng/mL) Trend-test *P*-value, 0.04	 NR NR NR NR	 1 1.85 (0.90–3.82) 2.22 (1.05–4.69) 2.33 (1.11–4.90)		
		Breast (post-menopausal, ER–), incidence	Serum PFOA (OR): 1st quartile (1.3–4.8 ng/mL) 2nd quartile (4.8–6.8 ng/mL) 3rd quartile (6.8–8.8 ng/mL) 4th quartile (8.8–21.4 ng/mL) Trend-test *P*-value, 0.59	 NR NR NR NR	 1 7.73 (1.46–41.08) 3.18 (0.55–18.47) 3.98 (0.67–23.52)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mancini et al. (2020a) France Enrolment, 1990/follow-up, through 2013 (incidence) Nested case–control (cont.)		Breast (post-menopausal, ER–), incidence	Serum PFOS (OR):			Age at blood draw, BMI at blood draw, menopausal status at blood draw, year of blood draw, total serum lipids, BMI, smoking status, physical activity (MET-h/week), education level, history of benign breast disease, family history of breast cancer, parity/age at first full-term pregnancy, total breastfeeding duration, age at menarche, age at menopause, use of oral contraceptives, current use of MHT, adherence to Western diet, adherence to Mediterranean diet	
			1st quartile (5.8–13.6 ng/mL)	NR	1		
			2nd quartile (13.6–17.3 ng/mL)	NR	15.40 (1.84–129.19)		
			3rd quartile (17.3–22.5 ng/mL)	NR	4.74 (0.45–49.62)		
			4th quartile (22.5–85.3 ng/mL)	NR	7.07 (0.73–68.03)		
			Trend-test *P*-value, 0.72				
		Breast (post-menopausal), PR+), incidence	Serum PFOA (OR):				
			1st quartile (1.3–4.8 ng/mL)	NR	1		
			2nd quartile (4.8–6.8 ng/mL)	NR	1.40 (0.67–2.93)		
			3rd quartile (6.8–8.8 ng/mL)	NR	1.28 (0.59–2.77)		
			4th quartile (8.8–21.4 ng/mL)	NR	1.54 (0.70–3.69)		
			Trend-test *P*-value, 0.37				
		Breast (post-menopausal, PR+), incidence	Serum PFOS (OR):				
			1st quartile (5.8–13.6 ng/mL)	NR	1		
			2nd quartile (13.6–17.3 ng/mL)	NR	1.84 (0.82–4.14)		
			3rd quartile (17.3–22.5 ng/mL)	NR	2.47 (1.07–5.65)		
			4th quartile (22.5–85.3 ng/mL)	NR	2.76 (1.21–6.30)		
			Trend-test *P*-value, 0.02				

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Mancini et al. (2020a) France Enrolment, 1990/follow-up, through 2013 (incidence) Nested case–control (cont.)		Breast (post-menopausal, PR–), incidence	Serum PFOA (OR): 1st quartile (1.3–4.8 ng/mL) 2nd quartile (4.8–6.8 ng/mL) 3rd quartile (6.8–8.8 ng/mL) 4th quartile (8.8–21.4 ng/mL) Trend-test *P*-value, 0.90	 NR NR NR NR	 1 3.44 (1.30–9.10) 1.80 (0.62–5.19) 1.69 (0.56–3.12)	Age at blood draw, BMI at blood draw, menopausal status at blood draw, year of blood draw, total serum lipids, BMI, smoking status, physical activity (MET-h/week), education level, history of benign breast disease, family history of breast cancer, parity/age at first full-term pregnancy, total breastfeeding duration, age at menarche, age at menopause, use of oral contraceptives, current use of MHT, adherence to Western diet, adherence to Mediterranean diet	
		Breast (post-menopausal, PR–), incidence	Serum PFOS (OR) 1st quartile (5.8–13.6 ng/mL) 2nd quartile (13.6–17.3 ng/mL) 3rd quartile (17.3–22.5 ng/mL) 4th quartile (22.5–85.3 ng/mL) Trend-test *P*-value, 0.93	 NR NR NR NR	 1 3.47 (1.29–9.15) 1.82 (0.61–5.45) 1.71 (0.57–5.10)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Chang et al. (2023) USA Enrolment, 1993–2001/ follow-up, through November 2013 Nested case–control	Nested within PLCO cohort Cases: 621; all incident invasive breast cancer cases diagnosed up to and including November 2013 among women who were postmenopausal and not using hormone therapy at baseline (unless they were hormone receptor-negative cases) Controls: 621; controls were selected using incidence density sampling, all were postmenopausal, still alive and cancer-free at the time of case diagnosis with matching by age at baseline, date of blood draw and baseline MHT use Exposure assessment method: see Table 2.1	Breast (post-menopausal), incidence	Serum PFOA (OR):			Age at baseline, date of blood draw, MHT use at baseline, age at blood draw, study centre, race/ ethnicity, education, age at menarche, age at first live birth and number of births, age at menopause, duration of MHT use, first degree family history of female breast cancer, personal history of benign breast disease, BMI, smoking status, vigorous physical activity[a], PFOS (natural log transformed)	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Limitations*: See Table 2.1. [a] This is the standard covariate set used for all analyses. Additional covariates are indicated as required.
			1st quartile	147	1		
			2nd quartile	148	0.91 (0.64–1.30)		
			3rd quartile	162	1.07 (0.73–1.55)		
			4th quartile	164	1.01 (0.66–1.55)		
			Trend-test *P*-value, 0.83				
		Breast (post-menopausal), incidence	Serum PFOS (OR):			Standard covariates[a] and PFOA (natural log transformed)	
			1st quartile	145	1		
			2nd quartile	158	1.21 (0.84–1.74)		
			3rd quartile	167	1.39 (0.96–1.99)		
			4th quartile	151	1.17 (0.77–1.79)		
			Trend-test *P*-value, 0.58				
		Breast (post-menopausal, ER+/PR+), incidence	Serum PFOA (OR):			Standard covariates[a] and PFOS (natural log transformed)	
			1st quartile	NR	1		
			2nd quartile	NR	1.14 (0.66–1.97)		
			3rd quartile	NR	0.99 (0.55–1.80)		
			4th quartile	NR	0.81 (0.40–1.62)		
			Trend-test *P*-value, 0.41				

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Chang et al. (2023) USA Enrolment, 1993–2001/ follow-up, through November 2013 Nested case–control (cont.)		Breast (post-menopausal, ER+/PR+), incidence	Serum PFOS (OR): 1st quartile 2nd quartile 3rd quartile 4th quartile Trend-test *P*-value, 0.08	 NR NR NR NR	 1 1.46 (0.84–2.54) 2.19 (1.21–3.98) 1.89 (0.97–3.69)	Standard covariates[a] and PFOA (natural log transformed)	
		Breast (post-menopausal, ER–/PR–), incidence	Serum PFOA (OR) 1st quartile 2nd quartile 3rd quartile 4th quartile Trend-test *P*-value, 0.21	 NR NR NR NR	 1 0.90 (0.38–2.10) 2.23 (0.90–5.54) 1.62 (0.62–4.23)	Standard covariates[a] and PFOS (natural log transformed)	
		Breast (post-menopausal, ER–/PR–), incidence	Serum PFOS (OR): 1st quartile 2nd quartile 3rd quartile 4th quartile Trend-test *P*-value, 0.34	 NR NR NR NR	 1 1.01 (0.38–2.63) 1.12 (0.48–2.62) 0.60 (0.19–1.83)	Standard covariates[a] and PFOA (natural log transformed)	
		Breast (post-menopausal, ER+), incidence	Serum PFOA (OR): 1st quartile 2nd quartile 3rd quartile 4th quartile Trend-test *P*-value, 0.96	 NR NR NR NR	 1 1.07 (0.68–1.66) 1.01 (0.64–1.61) 1.03 (0.61–1.75)	Standard covariates[a] and PFOS (natural log transformed)	
		Breast (post-menopausal, ER–), incidence	Serum PFOA (OR): 1st quartile 2nd quartile 3rd quartile 4th quartile Trend-test *P*-value, 0.19	 NR NR NR NR	 1 0.84 (0.36–1.95) 2.08 (0.85–5.07) 1.63 (0.63–4.20)	Standard covariates[a] and PFOS (natural log transformed)	

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Chang et al. (2023) USA Enrolment, 1993–2001/ follow-up, through November 2013 Nested case–control (cont.)		Breast (post-menopausal, ER+), incidence	Serum PFOS (OR):			Standard covariates[a] and PFOA (natural log transformed)	
			1st quartile	NR	1		
			2nd quartile	NR	1.26 (0.81–1.95)		
			3rd quartile	NR	1.59 (1.01–2.50)		
			4th quartile	NR	1.29 (0.77–2.15)		
			Trend-test *P*-value, 0.39				
		Breast (post-menopausal, ER–), incidence	Serum PFOS (OR):			Standard covariates[a] and PFOA (natural log transformed)	
			1st quartile	NR	1		
			2nd quartile	NR	0.98 (0.39–2.47)		
			3rd quartile	NR	1.13 (0.49–2.62)		
			4th quartile	NR	0.52 (0.18–1.55)		
			Trend-test *P*-value, 0.20				
		Breast (post-menopausal, PR+), incidence	Serum PFOA (OR):			Standard covariates[a] and PFOS (natural log transformed)	
			1st quartile	NR	1		
			2nd quartile	NR	1.14 (0.66–1.96)		
			3rd quartile	NR	1.02 (0.57–1.83)		
			4th quartile	NR	0.77 (0.39–1.52)		
			Trend-test *P*-value, 0.31				
		Breast (post-menopausal, PR–), incidence	Serum PFOA (OR):			Standard covariates[a] and PFOS (natural log transformed)	
			1st quartile	NR	1		
			2nd quartile	NR	0.90 (0.47–1.70)		
			3rd quartile	NR	2.05 (1.06–3.94)		
			4th quartile	NR	1.48 (0.75–2.93)		
			Trend-test *P*-value, 0.15				
		Breast (post-menopausal, PR+), incidence	Serum PFOS (OR):			Standard covariates[a] and PFOA (natural log transformed)	
			1st quartile	NR	1		
			2nd quartile	NR	1.55 (0.90–2.67)		
			3rd quartile	NR	2.34 (1.29–4.23)		
			4th quartile	NR	1.79 (0.92–3.48)		
			Trend-test *P*-value, 0.14				

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Chang et al. (2023) USA Enrolment, 1993–2001/ follow-up, through November 2013 Nested case–control (cont.)		Breast (post-menopausal, PR–), incidence	Serum PFOS (OR): 1st quartile 2nd quartile 3rd quartile 4th quartile Trend-test *P*-value, 0.15	 NR NR NR NR	 1 1.00 (0.52–1.92) 0.91 (0.50–1.64) 0.61 (0.29–1.31)	Standard covariates[a] and PFOA (natural log transformed)	
Cohn et al. (2020) Oakland (CA), USA Enrolment, at birth between 1959 and 1967/ follow-up, birth to March 2013 (incidence) Nested case–control	Nested within the CHDS cohort (see Table 2.1) Cases: 102; offspring in the Child Health and Development Studies pregnancy cohort who had incident invasive or non-invasive breast cancer diagnosed by age 52 yr and who had a maternal perinatal blood sample and complete information on potential confounders and effect modifiers Controls: 310; 3 per case, density-sampled on case age and matched on birth year and trimester of maternal blood draw Exposure assessment method: see Table 2.1	Breast, incidence	Log_2 maternal serum PFOS (OR): Continuous (for 4th quartile median vs 1st quartile median (difference of 3.15 ng/mL))	 102	 0.3 (0.1–0.9)	Age, birth year, trimester of maternal blood draw, maternal age at pregnancy, maternal history of breast cancer, African-American, primipara, maternal overweight at first prenatal visit, maternal serum log_2(*p,p′*-DDE), maternal serum log_2(*o,p′*-DDT), daughter breastfed, log_2(*N*-EtFOSAA), log_2(total cholesterol), log_2(*N*-EtFOSAA) × log_2 (total cholesterol)	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Li et al. (2022a) Ronneby, southern Sweden Enrolment, 1985–2016/ follow-up, 1985–2016 (incidence) Cohort	60 507 (28 569 women: 20 933 never high, 7636 ever high exposure); the Ronneby Register Cohort included 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 in 1985–2013 (15 811 individuals considered "ever-high"); subsets with long-term exposure (≥ 11 yr) in the latest part of the follow-up period (2005–2013) were considered more highly exposed Exposure assessment method: see Table 2.1	Breast, incidence	Women, 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-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.
			Never	525	0.80 (0.73–0.87)		
			Ever	156	0.75 (0.64–0.88)		
		Breast, incidence	Women, residential exposure to highly PFAS-contaminated drinking-water (HR):				
			Never	525	1		
			Ever	156	0.95 (0.79–1.13)		
		Breast, incidence	Women, time period of residential exposure to highly PFAS-contaminated drinking-water (HR):				
			Never	525	1		
			Early (1985–2004)	102	0.94 (0.76–1.16)		
			Late (2005–2013)	54	0.96 (0.72–1.29)		
		Breast, incidence	Women, duration of residential exposure to highly PFAS-contaminated drinking-water (HR):				
			Never	525	1		
			Short (1–10 yr)	89	1.01 (0.80–1.26)		
			Long (≥ 11 yr)	67	0.87 (0.67–1.13)		
		Thyroid, incidence	Men, residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):			Calendar year, age, sex	
			Never	14	1.33 (0.73–2.23)		
			Ever	3	0.89 (0.18–2.61)		
		Thyroid, incidence	Women, residential exposure to highly PFAS-contaminated drinking-water (SIR, Blekinge county excluding Ronneby referent):				
			Never	32	1.38 (0.94–1.95)		
			Ever	16	2.08 (1.19–3.38)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Li et al. (2022a) Ronneby, southern Sweden Enrolment, 1985–2016/ follow-up, 1985–2016 (incidence) Cohort (cont.)		Thyroid, incidence	Residential exposure to highly PFAS-contaminated drinking-water (HR):				
			Never	46	1		
			Ever	19	1.36 (0.79–2.33)		
		Thyroid, incidence	Time period of residential exposure to highly PFAS-contaminated drinking-water (HR):				
			Never	46	1		
			Early (1985–2004)	11	1.20 (0.62–2.33)		
			Late (2005–2013)	8	1.69 (0.77–3.73)		
		Thyroid, incidence	Duration of residential exposure to highly PFAS-contaminated drinking-water (HR):				
			Never	46	1		
			Short (1–10 yr)	12	1.35 (0.71–2.56)		
			Long (≥ 11 yr)	7	1.38 (0.60–3.18)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Feng et al. (2022) Shiyan, China Enrolment, September 2008 to June 2010 and April to October 2013/follow-up, 2008 to 2018 (incidence) Case–cohort	Nested within the Dongfeng-Tongji cohort (see Table 2.1) Cases: 226; incident breast cancer drawn from 18 387 female retirees of an auto facility who provided a specimen; total of 226 breast cancer diagnoses included 13 diagnoses among women in the subcohort Comparison cohort: 990 (including 13 cases); subcohort of women randomly selected according to age strata. The 13 cases included among the 990 in the comparison cohort served as controls until time of cancer diagnosis Exposure assessment method: see Table 2.1	Breast, incidence	Plasma PFOA concentration (HR):			Calendar time, age, BMI, smoking, drinking, marital status, education level, occupation, batch to enter cohort, parity, menopausal status, history of mastitis, use of HRT, family history of cancer	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1.
			1st quartile (< 0.84 ng/mL)	53	1		
			2nd quartile (0.84–1.18 ng/mL)	48	0.88 (0.56–1.39)		
			3rd quartile (1.19–1.79 ng/mL)	58	1.28 (0.80–2.04)		
			4th quartile (≥ 1.80 ng/mL)	67	1.69 (1.05–2.70)		
			Continuous (per unit on natural log scale)	226	1.35 (1.03–1.78)		
		Breast, incidence	Plasma PFOS concentration (HR):				
			1st quartile (< 6.39 ng/mL)	53	1		
			2nd quartile (6.39–10.35 ng/mL)	48	0.75 (0.47–1.19)		
			3rd quartile (10.36–15.66 ng/mL)	67	1.05 (0.66–1.67)		
			4th quartile (≥ 15.67 ng/mL)	58	0.87 (0.54–1.39)		
			Continuous (per unit on natural log scale)	226	0.88 (0.66–1.16)		
		Breast (post-menopausal), incidence	Plasma PFOA concentration (HR):				
			Low (< 1.19 ng/mL)	90	1		
			High (≥ 1.19 ng/mL)	115	1.53 (1.06–2.20)		
			Continuous (per unit on natural log scale)	205	1.34 (1.01–1.77)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Feng et al. (2022) Shiyan, China Enrolment, September 2008 to June 2010 and April to October 2013/follow-up, 2008 to 2018 (incidence) Case–cohort (cont.)		Breast (post-menopausal), incidence	Plasma PFOS concentration (HR): Low (< 10.36 ng/mL) High (≥ 10.36 ng/mL) Continuous (per unit on natural log scale)	 84 121 205	 1 1.13 (0.80–1.58) 0.91 (0.71–1.17)	Calendar time, age, BMI, smoking, drinking, marital status, education level, occupation, batch to enter cohort, parity, history of mastitis, age at menopause, use of HRT, family history of cancer	
Madrigal et al. (2024) Finland Enrolment, 1986–2010/ follow-up, through 2016 Nested case–control	Nested within the Finnish Maternity Cohort (see Table 2.1) Cases: 400; National registry of nulliparous women who donated serum during the first trimester of pregnancy. 400 cases were randomly selected from cases diagnosed among women who donated serum for their first pregnancy and had a live, full-term birth delivered between 1987–2010, and who had no prior diagnosis of cancer at enrolment	Thyroid (papillary), incidence	PFOA serum concentration (OR): ≤ 2.82 ng/mL > 2.82 to 3.77 ng/mL > 3.77 to 4.85 ng/mL > 4.85 to 6.75 ng/mL > 6.75 ng/mL Continuous (per unit on $\log_2$ scale) Trend-test *P*-value, 0.31	 94 105 98 78 25 400	 1 1.10 (0.73–1.64) 0.99 (0.65–1.50) 1.30 (0.80–2.11) 0.54 (0.27–1.08) 0.90 (0.68–1.19)	Calendar year of delivery, age at first birth, PFOS, *N*-EtFOSAA, PFHpS detected	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1; data available in the Medical Birth Registry included many host factors and potential confounders. *Other limitations*: See Table 2.1; data on host factors and potential confounders were collected during the pregnancy only.

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Madrigal et al. (2024) Finland Enrolment, 1986–2010/ follow-up, through 2016 Nested case–control (cont.)	Controls: 400; individually matched on year of delivery (4–5-yr increments) and age at first birth (3-yr increments) Exposure assessment method: see Table 2.1	Thyroid (papillary), incidence	PFOA serum concentration (OR):			Calendar year of delivery, age at first birth, smoking status at the time of pregnancy	
			≤ 2.82 ng/mL	94	1		
			> 2.82 to 3.77 ng/mL	105	1.13 (0.76–1.69)		
			> 3.77 to 4.85 ng/mL	98	1.05 (0.70–1.57)		
			> 4.85 to 6.75 ng/mL	78	1.40 (0.89–2.21)		
			> 6.75 ng/mL	25	0.63 (0.34–1.14)		
			Continuous (per unit on $\log_2$ scale)	400	0.95 (0.75–1.20)		
			Trend-test *P*-value, 0.48				
		Thyroid (papillary), incidence	Age < 40 yr, PFOA serum concentration (OR):			Calendar year of delivery, age at first birth	
			Continuous (per unit on $\log_2$ scale)	185	1.37 (0.92–2.03)		
		Thyroid (papillary), incidence	Age < 40 yr, PFOA serum concentration (OR):			Calendar year of delivery, age at first birth, PFOS, *N*-EtFOSAA, PFHpS	
			Continuous (per unit on $\log_2$ scale)	185	1.20 (0.71–2.01)		
		Thyroid (papillary), incidence	Age ≥ 40 yr, PFOA serum concentration (OR):			Calendar year of delivery, age at first birth	
			Continuous (per unit on $\log_2$ scale)	215	0.77 (0.57–1.04)		
		Thyroid (papillary), incidence	Age ≥ 40 yr, PFOA serum concentration (OR):			Calendar year of delivery, age at first birth, PFOS, *N*-EtFOSAA, PFHpS detected, *N*-EtFOSAA detected	
			Continuous (per unit on $\log_2$ scale)	215	0.70 (0.45–1.08)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Madrigal et al. (2024) Finland Enrolment, 1986–2010/ follow-up, through 2016 Nested case–control (cont.)		Thyroid (papillary), incidence	PFOS serum concentration (OR):			Calendar year of delivery, age at first birth, PFOA, *N*-EtFOSAA, PFHpS detected, total PCBs, hexachlorobenzene, β-HCH, chlordane metabolites, DDT metabolites	
			≤ 11.49 ng/mL	98	1		
			> 11.49 to 15.76 ng/mL	94	0.98 (0.61–1.57)		
			> 15.76 to 22.63 ng/mL	119	1.28 (0.76–2.18)		
			> 22.63 to 27.95 ng/mL	54	0.95 (0.50–1.82)		
			> 27.95 ng/mL	35	0.86 (0.38–1.95)		
			Continuous (per unit on $\log_2$ scale)	400	1.14 (0.81–1.59)		
			Trend-test *P*-value, 0.74				
		Thyroid (papillary), incidence	PFOS serum concentration (OR):			Calendar year of delivery, age at first birth, smoking status at the time of pregnancy	
			≤ 11.49 ng/mL	98	1		
			> 11.49 to 15.76 ng/mL	94	0.98 (0.62–1.54)		
			> 15.76 to 22.63 ng/mL	119	1.23 (0.75–2.00)		
			> 22.63 to 27.95 ng/mL	54	0.92 (0.52–1.62)		
			> 27.95 ng/mL	35	0.87 (0.45–1.65)		
			Continuous (per unit on $\log_2$ scale)	400	1.04 (0.81–1.33)		
			Trend-test *P*-value, 0.61				
		Thyroid (papillary), incidence	Age < 40 yr, PFOS serum concentration (OR):			Calendar year of delivery, age at first birth	
			Continuous (per unit on $\log_2$ scale)	185	1.34 (0.92–1.96)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Madrigal et al. (2024) Finland Enrolment, 1986–2010/ follow-up, through 2016 Nested case–control (cont.)		Thyroid (papillary), incidence	Age < 40 yr, PFOS serum concentration (OR): Continuous (per unit on $\log_2$ scale)	185	1.14 (0.68–1.93)	Calendar year of delivery, age at first birth, PFOA, *N*-EtFOSAA, total PCBs, hexachlorobenzene, β-HCH, chlordane metabolites, DDT metabolites	
		Thyroid (papillary), incidence	Age ≥ 40 yr, PFOS serum concentration (OR): Continuous (per unit on $\log_2$ scale)	215	0.86 (0.61–1.20)	Calendar year of delivery, age at first birth	
		Thyroid (papillary), incidence	Age ≥ 40 yr, PFOS serum concentration (OR): Continuous (per unit on $\log_2$ scale)	215	1.01 (0.60–1.71)	Calendar year of delivery, age at first birth, PFOA, *N*-EtFOSAA, total PCBs, hexachlorobenzene, β-HCH, chlordane metabolites, DDT metabolites	

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
van Gerwen et al. (2023) Mount Sinai, New York, USA Enrolment 2008–2021 Nested case–control	Nested within Bio*Me* cohort (see Table 2.1). Cases: 88 adult patients diagnosed with thyroid cancer using ICD codes 193 (9th Revision) and C73 (10th Revision) within Bio*Me*, a medical record-linked biobank within the Institute for Personalized Medicine at the Icahn School of Medicine at Mount Sinai Controls: 88 healthy (non-cancer) participants, pair-matched on sex, age (± 5 yr), race/ethnicity, BMI, smoking status ("Have you ever smoked ≥ 100 cigarettes in your entire life", yes/no), and calendar year of sample collection Exposure assessment method: see Table 2.1	Thyroid, incidence and prevalence	Plasma PFOA concentration (OR):			Age, BMI, sex, race, storage time of plasma sample	*Exposure assessment critique*: See Table 2.1. *Other strengths*: See Table 2.1. *Other limitations*: See Table 2.1. *Other comments*: Analyses were repeated for the time between plasma sample collection and thyroid cancer diagnosis: < 1 yr (cross-sectional group) and ≥ 1 yr (longitudinal group).
			Continuous (per unit on $\log_2$ scale)	88	0.99 (0.63–1.56)		
			Continuous (per IQR increase)	88	0.99 (0.53–1.83)		
		Thyroid, incidence and prevalence	Plasma PFOA concentration (OR):			Age, BMI, sex, race, storage time of plasma sample, other PFAS	
			Continuous (per unit on $\log_2$ scale)	88	0.74 (0.31–1.72)		
			Continuous (per IQR increase)	88	0.66 (0.20–2.08)		
		Thyroid, incidence	Longitudinal study population (diagnosed ≥ 1 yr after sample collection), plasma PFOA concentration (OR):			Age, BMI, sex, race, storage, time of plasma sample	
			Continuous (per unit on $\log_2$ scale)	31	1.52 (0.77–2.98)		
		Thyroid, prevalence	Cross-sectional study population (diagnosed < 1 yr after sample collection), plasma PFOA concentration (OR):				
			Continuous (per unit on $\log_2$ scale)	57	0.84 (0.49–1.40)		
		Thyroid, incidence and prevalence	Plasma sb-PFOS (branched PFOS) concentration (OR):			Age, BMI, sex, race, storage time of plasma sample	
			Continuous (per unit on $\log_2$ scale)	88	1.32 (0.99–1.81)		
			Continuous (per IQR increase)	88	1.73 (0.97–3.24)		
		Thyroid, incidence and prevalence	Plasma sb-PFOS (branched PFOS) concentration (OR):			Age, BMI, sex, race, storage time of plasma sample, other PFAS	
			Continuous (per unit on $\log_2$ scale)	88	1.21 (0.43–3.55)		
			Continuous (per IQR increase)	88	1.47 (0.18–12.26)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
van Gerwen et al. (2023) Mount Sinai, New York, USA Enrolment 2008–2021 Nested case–control (cont.)		Thyroid, incidence	Longitudinal study population (diagnosed ≥ 1 yr after sample collection), plasma sb-PFOS (branched PFOS) concentration (OR):			Age, BMI, sex, race, storage time of plasma sample	
			Continuous (per unit on $\log_2$ scale)	31	3.09 (1.73–6.13)		
		Thyroid, prevalence	Cross-sectional study population (diagnosed < 1 yr after sample collection), plasma sb-PFOS (branched PFOS) concentration (OR):				
			Continuous (per unit on $\log_2$ scale)	57	1.13 (0.83–1.56)		
		Thyroid, incidence and prevalence	Plasma *n*-PFOS (linear PFOS) concentration (OR):				
			Continuous (per unit on $\log_2$ scale)	88	1.56 (1.17–2.15)		
			Continuous (per IQR increase)	88	2.32 (1.34–4.26)		
		Thyroid, incidence and prevalence	Plasma *n*-PFOS (linear PFOS) concentration (OR):			Age, BMI, sex, race, storage time of plasma sample, other PFAS	
			Continuous (per unit on $\log_2$ scale)	88	2.80 (1.32–6.45)		
			Continuous (per IQR increase)	88	7.09 (1.69–34.54)		
		Thyroid, incidence	Longitudinal study population (diagnosed ≥ 1 yr after sample collection), plasma *n*-PFOS (linear PFOS) concentration (OR):			Age, BMI, sex, race, storage time of plasma sample	
			Continuous (per unit on $\log_2$ scale)	31	2.67 (1.59–4.88)		
		Thyroid, prevalence	Cross-sectional study population (diagnosed < 1 yr after sample collection), plasma *n*-PFOS (linear PFOS) concentration (OR):				
			Continuous (per unit on $\log_2$ scale)	57	1.45 (1.07–2.01)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
van Gerwen et al. (2023) Mount Sinai, New York, USA Enrolment 2008–2021 Nested case–control (cont.)		Thyroid (papillary), incidence and prevalence	Plasma PFOA concentration (OR):				
			Continuous (per unit on $\log_2$ scale)	74	1.03 (0.63–1.68)		
			Continuous (per IQR increase)	74	1.03 (0.55–1.96)		
		Thyroid (papillary), incidence and prevalence	Plasma sb-PFOS (branched PFOS) concentration (OR):				
			Continuous (per unit on $\log_2$ scale)	74	1.30 (0.95–1.83)		
			Continuous (per IQR increase)	74	1.61 (0.91–2.97)		
		Thyroid (papillary), incidence and prevalence	Plasma *n*-PFOS (linear PFOS) concentration (OR):				
			Continuous (per unit on $\log_2$ scale)	74	1.56 (1.13–2.21)		
			Continuous (per IQR increase)	74	2.22 (1.24–4.20)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Winquist et al. (2023) 20 states, USA Enrolment, 1998–200/ follow-up, through 30 June 2015 Case–cohort	Case–cohort within the CPS-II Lifelink Cohort Cases: 3762 overall (786 female breast); incidence cases from the CPS-II Lifelink Cohort (surviving CPS-II Nutrition cohort participants) with first cancer diagnosis of kidney, bladder, breast (females only), prostate (males only), or pancreatic cancer, leukaemia, or lymphoma, detected through self-report or NDI linkage and verified through medical records review or cancer registry; all participants with incident cancers	Breast (post-menopausal), incidence	Women, serum PFOA concentration (HR):			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 (< 3.700 ng/mL)	193	1		
			2nd quartile (3.700 to < 5.000 ng/mL)	196	0.80 (0.56–1.15)		
			3rd quartile (5.000 to < 6.900 ng/mL)	189	0.75 (0.52–1.09)		
			4th quartile (≥ 6.900 ng/mL)	202	0.82 (0.57–1.17)		
			Continuous (per unit on $\log_2$ scale)	780	0.96 (0.82–1.12)		
		Breast (post-menopausal), incidence	Women, serum PFOS concentration (HR):				
			1st quartile (< 12.000 ng/mL)	160	1		
			2nd quartile (12.000 to < 17.000 ng/mL)	195	0.66 (0.45–0.97)		
			3rd quartile (17.000 to < 24.000 ng/mL)	211	0.84 (0.57–1.23)		
			4th quartile (≥ 24.000 ng/mL)	214	0.70 (0.48–1.01)		
			Continuous (per unit on $\log_2$ scale)	780	0.87 (0.75–1.01)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Winquist et al. (2023) 20 states, USA Enrolment, 1998–200/ follow-up, through 30 June 2015 Case–cohort (cont.)	Comparison cohort: 999; a sex-stratified simple random sample of 499 women and 500 men (~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						
Vieira et al. (2013) OH and WV, USA 1996–2005 (incidence) Case–control	Cases: study 1: 4057 female breast, 343 thyroid cancer; study 2: 1260 female breast, 94 thyroid; cancer cases were retrieved from cancer registries covering a community sample with relatively high exposure to PFOA because of contamination of drinking-water from the Parkersburg (WV), polymer-production plant	Breast, incidence	Analysis 1. Residence in a PFOA-contaminated water district (OH and WV) (OR)			Age, diagnosis year, insurance provider, smoking status	*Exposure assessment critique*: See Table 2.1. *Other strengths*: ascertainment of cases from cancer registries; large exposure contrast. *Other limitations*: use of other types of cancer as controls; lack of adjustment for several potential confounding variables; lack of information concerning tumour hormone-receptor status.
			Females: Unexposed	3621	1		
			Any exposed water district	436	1.0 (0.9–1.1)		
		Breast, incidence	Analysis 2. Individual-level annual PFOA serum exposure, assuming 10-yr residency and latency (OH only) (OR)			Age, race, diagnosis year, insurance provider smoking status	
			Females: Unexposed	1037	1		
			Low (3.7–12.8 µg/L)	72	0.9 (0.7–1.2)		
			Medium (12.9–30.7 µg/L)	77	1.1 (0.8–1.5)		
			High (30.8–109 µg/L)	45	0.7 (0.5–1.0)		
			Very high (110–655 µg/L)	29	1.4 (0.9–2.3)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Vieira et al. (2013) OH and WV, USA 1996–2005 (incidence) Case–control (cont.)	Controls: NR; for each cancer site evaluated, controls were cases of cancer at all other sites among women, with the exclusion of four cancers of a priori interest (kidney, testis, pancreas, and liver) that have been associated with PFOA in studies in experimental animals or humans Exposure assessment method: see Table 2.1	Thyroid, incidence	Analysis 1: residence in a PFOA-contaminated water district (OH and WV) (OR):			Age, sex, diagnosis year, insurance provider, smoking status	
			Unexposed	303	1		
			Any exposed water district	40	1.1 (0.7–1.5)		
			Little Hocking	3	0.8 (0.3–2.7)		
			Lubeck	7	1.2 (0.6–2.6)		
			Tuppers Plains	2	0.3 (0.1–1.4)		
			Belpre	5	0.9 (0.4–2.2)		
			Pomeroy	0	NC		
			Mason	23	1.4 (0.9–2.2)		
		Other (specify), thyroid, incidence	Analysis 2: individual-level annual PFOA serum exposure, assuming 10-yr residency and latency (OH only) (OR):				
			Unexposed	79	1		
			Low (3.7–12.8 µg/L)	5	0.9 (0.4–2.3)		
			Medium (12.9–30.7 µg/L)	5	0.9 (0.4–2.3)		
			High (30.8–109 µg/L)	3	0.7 (0.2–2.1)		
			Very high (110–655 µg/L)	2	0.8 (0.2–3.5)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wielsøe et al. (2017) Greenland Enrolment, 2000–2003/ follow-up, 2011–2014 Case–control	Cases: 77 cases of breast cancer; recruited at diagnosis at Dronning Ingrids Hospital in Nuuk (where all breast cancer cases in Greenland are registered) during two time periods: 2000–2003 and 2011–2014; all cases were among women of Greenland Inuit descent	Breast, incidence	Serum PFOA concentration (OR):			Age, BMI, cotinine levels, parity, breastfeeding	*Exposure assessment critique*: Key strengths were that serum levels represent the combined exposure through all exposure pathways; measurement error low. Key limitations were that if breast cancer alters ADME of PFAS there could be possible differential exposure misclassification, as blood was collected after diagnosis (also see Bonefeld-Jorgensen et al., 2011); single samples at time of case hospitalization may not reflect exposure at crucial windows in cancer development.
			1st tertile	14	1		
			2nd tertile	26	1.86 (0.80–4.31)		
			3rd tertile	37	2.64 (1.17–5.97)		
			Continuous (per unit increase)	77	1.26 (1.01–1.58)		
		Breast, incidence	Serum PFOS concentration (OR):				
			1st tertile	8	1		
			2nd tertile	25	3.13 (1.20–8.15)		
			3rd tertile	44	5.50 (2.19–13.84)		
			Continuous (per unit increase)	77	1.02 (1.01–1.03)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Wielsøe et al. (2017) Greenland Enrolment, 2000–2003/ follow-up, 2011–2014 Case–control (cont.)	Controls: 81 controls for the participants recruited during 2000–2003 were selected from two cross-sectional studies on healthy persons with POPs serum measurements in the same period; the controls recruited during 2011–2014 were patients with nonmalignant diagnoses at the Dronning Ingrids hospital; controls were frequency-matched on age and geographical living area to cases; all controls were in people of Greenland Inuit descent Exposure assessment method: quantitative serum measurements; analytical method was state-of-the-art; a single blood sample was collected; blood was collected at the hospital before treatment						*Other strengths*: cases confirmed by a positive histological sample. *Other limitations*: exclusion of cases and controls from the final analyses not clearly explained; some of the controls were hospital patients with nonmalignant abnormalities in the uterus, ovaries and breasts; small sample size and limited statistical power; cross-sectional design; no information about the delay between diagnosis and the collection of blood or if treatment occurred before blood collection; unexplained elevation in median PFOS level for cases recruited in early time period.

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tsai et al. (2020) Taiwan, China 2014–2016 Case–control	Cases: 120 patients aged 25–80 yr at diagnosis, recruited at NTUH Controls: 119 controls aged 25–80 yr and without any history of malignancy; recruited through advertisements on posters and flyers at NTUH and in the community; controls received a small financial compensation (~US$ 6.30) after completing the study Exposure assessment method: quantitative serum measurements; analytical method was state-of-the-art; a single blood sample was collected during approx. the same time period for cases and matched controls; blood was collected at the hospital before treatment	Breast, incidence	Serum PFOA concentration (OR):			Age, history of pregnancy, oral contraception use, abortion, BMI, menopause, education level	*Exposure assessment critique*: Key strengths were that plasma levels represent the combined exposure through all exposure pathways; although blood samples were collected after diagnosis, a strength was that they were collected before treatment; measurement error low. Key limitations were that if breast cancer alters ADME of PFAS there could be possible differential exposure misclassification as plasma collected after diagnosis; single samples at time of case hospitalization may not reflect exposure at crucial windows in cancer development.
			Continuous (per unit increase on natural log scale)	120	0.89 (0.59–1.34)		
		Breast, incidence	Serum PFOS concentration (OR):				
			Continuous (per unit increase on natural log scale)	120	1.07 (0.64–1.79)		
		Breast, incidence	Serum PFOA concentration (OR per unit increase on natural log scale):			History of pregnancy, oral contraception use, abortion, BMI, menopause, education level	
			Age ≤ 50 yr	60	1.14 (0.66–1.96)		
			Age > 50 yr	60	0.78 (0.40–1.51)		
		Breast, incidence	Serum PFOS concentration (OR per unit increase on natural log scale):				
			Age ≤ 50 yr	60	2.34 (1.02–5.38)		
			Age > 50 yr	60	0.62 (0.29–1.29)		
		Breast (ER–), incidence	Serum PFOA concentration (OR per unit increase on natural log scale):				
			Age ≤ 50 yr	11	0.42 (0.17–1.06)		
			Age > 50 yr	12	1.08 (0.33–3.59)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Tsai et al. (2020) Taiwan, China 2014–2016 Case–control (cont.)		Breast (ER –), incidence	Serum PFOS concentration (OR per unit increase on natural log scale):			History of pregnancy, oral contraception use, abortion, BMI, menopause, education level	*Other strengths*: cases confirmed by positive histological samples; controls included participants without any history of malignancy; models adjusted for important confounding variables; available information on tumour hormone-receptor status. *Other limitations*: small sample size and limited statistical power; cross sectional design; strategy for recruiting controls could have induced a control selection bias if people positively responding to advertisement had a healthier lifestyle and a higher medical awareness compared with the source population for cases.
			Age ≤ 50 yr	11	0.23 (0.05–1.15)		
			Age > 50 yr	12	0.66 (0.20–2.22)		
		Breast (ER+), incidence	Serum PFOA concentration (OR per unit increase on natural log scale):				
			Age ≤ 50 yr	49	1.41 (0.77–2.56)		
			Age > 50 yr	48	0.70 (0.35–1.42)		
		Breast (ER+), incidence	Serum PFOS concentration (OR per unit increase on natural log scale):				
			Age ≤ 50 yr	49	3.25 (1.29–8.23)		
			Age > 50 yr	48	0.53 (0.24–1.18)		

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Itoh et al. (2021) Japan Enrolment, May 2001 to September 2005 Case–control	Cases: 401 women aged 20–74 yr with new invasive breast cancer, admitted to any of the four hospitals included in the study; of 412 eligible patients, 405 (98%) agreed to participate Controls: 401 selected among individuals attending two of the hospitals for medical check-ups during the study period; they were confirmed to not have cancer and were matched with cases by age (within 3 yr) and residential area (urban or rural); two of the control participants refused to provide blood specimens and two refused to allow their samples to be used in the present analysis	Breast, incidence	Serum PFOA concentration (OR): 1st quartile (0.72–3.98 ng/mL) 2nd quartile (4.00–5.57 ng/mL) 3rd quartile (5.57–7.62 ng/mL) 4th quartile (7.64–62.98 ng/mL) Trend-test *P*-value, 0.0001	 167 100 82 52	 1 0.45 (0.25–0.80) 0.39 (0.20–0.73) 0.21 (0.10–0.45)	Age and residential area (urban or rural), BMI, height, menopausal status and age at menopause, age at first childbirth, family history of breast cancer, smoking status, physical activity, age at menarche, number of births, breastfeeding duration, alcohol intake, isoflavone intake, and education level	*Exposure assessment critique*: Key strengths were that serum levels represent the combined exposure through all exposure pathways. Measurement error low. Key limitations were that if breast cancer alters ADME of PFAS there could be possible differential exposure misclassification; no information available concerning the delay between diagnosis and blood sample used for PFAS measurements and if cases had received cancer treatment before blood sample; single samples at time of case hospitalization may not reflect exposure at crucial windows in cancer development; minimal information on potential carcinogenic co-exposures.

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Itoh et al. (2021) Japan Enrolment, May 2001 to September 2005 Case–control (cont.)	Exposure assessment method: quantitative serum measurements; analytical method state-of-the-art; a single serum sample was collected during hospitalization for cases of invasive cancer and matched non-cancer controls in the hospital for medical check-up	Breast, incidence	Serum PFOA concentration (OR): 1st quartile (0.72–3.98 ng/mL) 2nd quartile (4.00–5.57 ng/mL) 3rd quartile (5.57–7.62 ng/mL) 4th quartile (7.64–62.98 ng/mL) Trend-test *P*-value, 0.001	 167 100 82 52	 1 0.37 (0.19–0.73) 0.39 (0.18–0.84) 0.20 (0.08–0.51)	Age and residential area (urban or rural), BMI, height, menopausal status and age at menopause, age at first childbirth, family history of breast cancer, smoking status, physical activity, age at menarche, number of births, breastfeeding duration, alcohol intake, isoflavone intake, and education level, serum total concentrations of PCBs (lipid-adjusted), fish and shellfish intake, vegetable intake, and calendar year of blood sampling	*Other strengths*: cases were histologically confirmed invasive breast cancer; high response rate reduced the possibility of selection bias; large sample size; detailed information on diet, available information on tumour hormone-receptor status; analysis examined impact of individual isomers and combinations of isomers, including the sum of 6 PFOS isomers and the sum of 2 PFOA isomers as well as combinations of PFSAs and PFCAs.

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Itoh et al. (2021) Japan Enrolment, May 2001 to September 2005 Case–control (cont.)		Breast, incidence	Serum PFOS concentration (OR): 1st quartile (1.13–10.25 ng/mL) 2nd quartile (10.29–14.27 ng/mL) 3rd quartile (14.27–19.24 ng/mL) 4th quartile (19.28–377.33 ng/mL) Trend-test *P*-value, < 0.0001	 183 85 86 47	 1 0.41 (0.22–0.77) 0.37 (0.19–0.71) 0.14 (0.07–0.31)	Age and residential area (urban or rural), BMI, height, menopausal status and age at menopause, age at first childbirth, family history of breast cancer, smoking status, physical activity, age at menarche, number of births, breastfeeding duration, alcohol intake, isoflavone intake, and education level	*Other limitations*: potential selection bias for controls; lack of information and adjustment for socioeconomic status; cross sectional design; no adjustment for education; use of medical check-up examinees as controls may have caused selection bis due to a higher medical awareness and different socioeconomic status compared to the source population for cases.

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Itoh et al. (2021) Japan Enrolment, May 2001 to September 2005 Case–control (cont.)		Breast, incidence	Serum PFOS concentration (OR)			Age and residential area (urban or rural), BMI, height, menopausal status and age at menopause, age at first childbirth, family history of breast cancer, smoking status, physical activity, age at menarche, number of births, breastfeeding duration, alcohol intake, isoflavone intake, and education level, serum total concentrations of PCBs (lipid-adjusted), fish and shellfish intake, vegetable intake, and calendar year of blood sampling	
			1st quartile (1.13–10.25 ng/mL)	183	1		
			2nd quartile (10.29–14.27 ng/mL)	85	0.38 (0.18–0.82)		
			3rd quartile (14.27–19.24 ng/mL)	86	0.31 (0.14–0.69)		
			4th quartile (19.28–377.33 ng/mL)	47	0.15 (0.06–0.39)		
			Trend-test *P*-value, 0.0001				

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Itoh et al. (2021) Japan Enrolment, May 2001 to September 2005 Case–control (cont.)		Breast (pre-menopausal), incidence	Serum PFOA concentration (OR):			Age and residential area (urban or rural), BMI, height, age at first childbirth, family history of breast cancer, smoking status, physical activity, age at menarche, number of births, breastfeeding duration, alcohol intake, isoflavone intake, education level	
			Low (0.7–4.5 ng/mL)	NR	1		
			Middle (4.5–6.7 ng/mL)	NR	0.72 (0.38–1.37)		
			High (6.73–62.98 ng/mL)	NR	0.66 (0.28–1.54)		
			Trend-test *P*-value, 0.26				
		Breast (pre-menopausal), incidence	Serum PFOS concentration (OR):				
			Low (1.1–11.5 ng/mL)	NR	1		
			Middle (11.5–17.0 ng/mL)	NR	0.52 (0.27–1.01)		
			High (17.1–377.33 ng/mL)	NR	0.28 (0.09–0.85)		
			Trend-test *P*-value, 0.007				
		Breast (post-menopausal), incidence	Serum PFOA concentration (OR):			Age and residential area (urban or rural), BMI, height, age at menopause, age at first childbirth, family history of breast cancer, smoking status, physical activity, age at menarche, number of births, breastfeeding duration, alcohol intake, isoflavone intake, education level, years after menopause	
			Low (0.7–4.5 ng/mL)	NR	1		
			Middle (4.5–6.7 ng/mL)	NR	0.61 (0.34–1.07)		
			High (6.73–62.98 ng/mL)	NR	0.41 (0.23–0.75)		
			Trend-test *P*-value, 0.005				

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Itoh et al. (2021) Japan Enrolment, May 2001 to September 2005 Case–control (cont.)		Breast (post-menopausal), incidence	Serum PFOS concentration (OR):			Age and residential area (urban or rural), BMI, height, age at menopause, age at first childbirth, family history of breast cancer, smoking status, physical activity, age at menarche, number of births, breastfeeding duration, alcohol intake, isoflavone intake, education level, years after menopause	
			Low (1.1–11.5 ng/mL)	NR	1		
			Middle (11.5–17.0 ng/mL)	NR	0.60 (0.33–1.09)		
			High (17.1–377.33 ng/mL)	NR	0.35 (0.19–0.66)		
			Trend-test *P*-value, 0.001				
		Breast (ER– and PR–), incidence	Serum PFOA concentration (OR):			Age and residential area (urban or rural), BMI, height, menopausal status and age at menopause, age at first childbirth, family history of breast cancer, smoking status, physical activity, age at menarche, number of births, breastfeeding duration, alcohol intake, isoflavone intake, education level	
			Low (0.7–4.5 ng/mL)	NR	1		
			Middle (4.5–6.7 ng/mL)	NR	0.78 (0.40–1.49)		
			High (6.73–62.98 ng/mL)	NR	0.62 (0.30–1.32)		
			Trend-test *P*-value, 0.23				

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Itoh et al. (2021) Japan Enrolment, May 2001 to September 2005 Case–control (cont.)		Breast (ER+ and PR–), incidence	Serum PFOA concentration (OR):			Age and residential area (urban or rural), BMI, height, menopausal status and age at menopause, age at first childbirth, family history of breast cancer, smoking status, physical activity, age at menarche, number of births, breastfeeding duration, alcohol intake, isoflavone intake, education level	
			Low (0.7–4.5 ng/mL)	NR	1		
			Middle (4.5–6.7 ng/mL)	NR	0.86 (0.44–1.68)		
			High (6.73–62.98 ng/mL)	NR	0.27 (0.11–0.69)		
			Trend-test *P*-value, 0.007				
		Breast (ER+ and PR+), incidence	Serum PFOA concentration (OR):				
			Low (0.7–4.5 ng/mL)	NR	1		
			Middle (4.5–6.7 ng/mL)	NR	0.63 (0.39–1.01)		
			High (6.73–62.98 ng/mL)	NR	0.57 (0.33–0.97)		
			Trend-test *P*-value, 0.035				
		Breast (ER – and PR–), incidence	Serum PFOS concentration (OR):				
			Low (1.10–11.5 ng/mL)	NR	1		
			Middle (11.5–17.0 ng/mL)	NR	0.61 (0.31–1.20)		
			High (17.1–377.33 ng/mL)	NR	0.44 (0.20–0.96)		
			Trend-test *P*-value, 0.037				
		Breast (ER+ and PR–), incidence	Serum PFOS concentration (OR):				
			Low (1.10–11.5 ng/mL)	NR	1		
			Middle (11.5–17.0 ng/mL)	NR	1.07 (0.52–2.20)		
			High (17.1–377.33 ng/mL)	NR	0.33 (0.13–0.83)		
			Trend-test *P*-value, 0.016				

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Itoh et al. (2021) Japan Enrolment, May 2001 to September 2005 Case–control (cont.)		Breast (ER+ and PR+), incidence	Serum PFOS concentration (OR): Low (1.10–11.5 ng/mL) Middle (11.5–17.0 ng/mL) High (17.1–377.33 ng/mL) Trend-test *P*-value, 0.0001	 NR NR NR	 1 0.56 (0.34–0.90) 0.33 (0.18–0.59)	Age and residential area (urban or rural), BMI, height, menopausal status and age at menopause, age at first childbirth, family history of breast cancer, smoking status, physical activity, age at menarche, number of births, breastfeeding duration, alcohol intake, isoflavone intake, education level	

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Liu et al. (2022) Jinan City, Shandong Province, east China 2016–2017 Case–control	Cases: 134 cases were diagnosed with thyroid cancer by pathological examination at the Shandong Provincial Qianfoshan Hospital; participants in the case group stopped taking thyroid medication for 2 weeks Controls: 185 controls were randomly selected from patients undergoing routine medical visits at the hospital with normal thyroid B-ultrasound examination and no history of thyroid disease or taking iodine or thyroid hormone drugs during the blood collection, and frequency-matched to the case group on age (± 5 yr) and sex	Thyroid, incidence	Serum PFOA (OR): 1st quartile (< 7.9 ng/mL) 2nd quartile (7.9 to < 10.9 ng/mL) 3rd quartile (10.9 to < 16.1 ng/mL) 4th quartile (≥ 16.1 ng/mL) Trend-test *P*-value, < 0.001	 69 23 21 21	 1 0.24 (0.12–0.50) 0.24 (0.11–0.49) 0.20 (0.09–0.44)	Age, sex, diabetes status	*Exposure assessment critique*: Key strengths were that serum levels represent the combined exposure through all exposure pathways; measurement error low. Key limitations were that if thyroid cancer alters ADME of PFAS there could be possible differential exposure misclassification as serum collected between treatment periods for cases; single samples at time of case hospitalization may not reflect exposure at crucial windows in cancer development.
		Thyroid, incidence	Serum PFOS (OR): 1st quartile (< 4.7 ng/mL) 2nd quartile (4.7 to < 7.5 ng/mL) 3rd quartile (7.5 to < 10.8 ng/mL) 4th quartile (≥ 10.8 ng/mL) Trend-test *P*-value, 0.001	 49 48 17 20	 1 0.81 (0.42–1.53) 0.26 (0.12–0.57) 0.28 (0.12–0.66)	Age, sex, diabetes status	

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Liu et al. (2022) Jinan City, Shandong Province, east China 2016–2017 Case–control (cont.)	Exposure assessment method: quantitative serum measurements; analytical method was state-of-the-art; a single blood sample was collected during the same time period for cases and matched controls; blood was collected between treatment periods; control samples collected during routine visits to the hospital						*Other strengths*: use of novel statistical methods to evaluate the impact of PFAS on thyroid function and thyroid hormones using a WQS model. *Other limitations*: limited exposure contrast; small sample size; limited confounding adjustment; potential for reverse causation.
Velarde et al. (2022) Philippines 2018 Case–control	Cases: 75 cases recruited through the Philippine General Hospital Breast Cancer Center, including Filipino women aged 18–60 yr, with no comorbidity Controls: 75 women aged 18–59 yr, without prior diagnosis of cancer and without family history of breast, ovarian, and endometrial cancer in first-degree relatives; controls were recruited through posters, social media advertisements, and by word of mouth	Breast, incidence	Serum PFOA concentration (OR): 1st quartile (0.56–1.47 ng/mL) 2nd quartile (1.50–1.77 ng/mL) 3rd quartile (1.77–2.30 ng/mL) 4th quartile (2.31–8.46 ng/mL) Trend-test *P*-value, 0.380	 18 14 21 13	 1 0.64 (0.21–1.90) 1.05 (0.38–2.93) 0.44 (0.14–1.36)	Age, region of residence	*Exposure assessment critique*: Key strengths were that serum levels represent the combined exposure through all exposure pathways; measurement error low. Key limitations were that if breast cancer alters ADME of PFAS there could be possible differential exposure misclassification as serum collected at case identification

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Velarde et al. (2022) Philippines 2018 Case–control (cont.)	Exposure assessment method: quantitative serum measurements; analytical method was state-of-the-art; a single serum sample was collected from cases and non-cancer community controls; measured 12 PFAS but did not measure isomers of PFOA or PFOS	Breast, incidence	Serum PFOS concentration (OR): 1st quartile (0.17–2.15 ng/mL) 2nd quartile (2.20–3.02 ng/mL) 3rd quartile (3.05–3.82 ng/mL) 4th quartile (3.90–23.03 ng/mL) Trend-test *P*-value, 0.400	 9 11 11 35	 1 1.36 (0.42–4.52) 1.25 (0.38–4.17) 2.38 (0.81–7.31)	Age, region of residence	(however, cases had not received neoadjuvant chemotherapy before blood sample used for PFAS measurements); single samples at time of case and control identification may not reflect exposure at crucial windows in cancer development; no info on other carcinogens (e.g. alcohol and smoking). *Other strengths*: histologically confirmed malignant breast cancer. *Other limitations*: lack of adjustment for important confounders; small sample size and limited statistical power; no information concerning hormone-receptor status; cross sectional design; strategy for recruiting controls could have induced a control selection bias if people positively

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Velarde et al. (2022) Philippines 2018 Case–control (cont.)							responding to advertisement had healthier lifestyle and a higher medical awareness compared with the source population for cases; analysis by each PFAS separately did not account for isomers of PFOA or PFOS; measured a variety of other exposures but analysed separately from PFAS relative to outcome. *Other comments*: All participants had no prior use of hormonal contraceptives or HRT within 1 mo from the last day of use of an oral agent, or within 6 mo from the last day of use of an intramuscular agent.

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Li et al. (2022b) China 2012–2016 Case–control	Cases: 373 cases recruited at diagnosis from the Tianjin Medical University Cancer Institute and Hospital Controls: 657 controls were randomly selected from the participants in the Chinese National Breast Cancer Screening Program; cohort from a time period similar to that of the cases Exposure assessment method: quantitative plasma measurements; analytical method was state-of-the-art; a single blood sample was collected; blood was collected at the hospital before treatment	Breast, incidence	Plasma PFOA concentration (OR):			Age, BMI, smoking history, age at menarche, age of menopause, parity, breastfeeding duration, use of estrogen or estrogen replacement therapy, family history of breast cancer, education, monthly household income per capita, red meat consumption, pickled, fried, smoked, and barbecued food consumption.	*Exposure assessment critique*: Key strengths were that plasma levels represent the combined exposure through all exposure pathways; blood samples of cases were collected within a week after breast cancer diagnosis and before treatment; measurement error low. Key limitations were that if breast cancer alters ADME of PFAS there could be possible differential exposure misclassification, as plasma was collected after diagnosis in cases; single samples at time of case hospitalization may not reflect exposure at crucial windows in cancer development.
			1st quartile (< 2.4 ng/mL)	96	1		
			2nd quartile (2.24–3.35 ng/mL)	67	0.66 (0.41–1.08)		
			3rd quartile (3.35–5.11 ng/mL)	83	1.19 (0.75–1.90)		
			4th quartile (≥ 5.11 ng/mL)	127	2.83 (1.79–4.49)		
			Continuous (per standard deviation on natural log scale)	373	1.57 (1.31–1.89)		
			Trend-test *P*-value, 0.000				
		Breast, incidence	Plasma PFOS concentration (OR):				
			1st quartile (< 7.45 ng/mL)	119	1		
			2nd quartile (7.45–12.18 ng/mL)	85	0.61 (0.40–0.95)		
			3rd quartile (12.18–17.72 ng/mL)	83	0.58 (0.37–0.91)		
			4th quartile (≥ 17.72 ng/mL)	86	0.64 (0.41–1.00)		
			Continuous (per standard deviation on natural log scale)	373	0.81 (0.68–0.96)		
			Trend-test *P*-value, 0.002				

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Li et al. (2022b) China 2012–2016 Case–control (cont.)		Breast, incidence	Plasma PFOA concentration (OR for one standard deviation increase on natural log scale): ER– ER+ PR– PR+	 96 218 131 183	 1.08 (0.82–1.41) 1.47 (1.19–1.80) 1.03 (0.81–1.30) 1.36 (1.09–1.69)	Age, BMI, smoking history, age at menarche, age of menopause, parity, breastfeeding duration, use of estrogen or estrogen replacement therapy, family history of breast cancer, education, monthly household income per capita, red meat consumption, pickled, fried, smoked, and barbecued food consumption.	*Other strengths*: histologically confirmed malignant breast cancer; adjustment for important confounding variables; detailed information on diet; available information on the ER/PR status of breast cancer; large number of cases and controls allowed for stratified analyses with good statistical power. *Other limitations*: cross-sectional design.

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Li et al. (2023) Shijiazhuang, Hebei Province, China January to May 2022 Case–control	Cases: 150 recent hospital-based diagnoses of thyroid cancer, histologically confirmed by the hospital pathology unit, among adults aged 20–78 yr residing in Shijiazhuang for 10 yr or longer Controls: 150 healthy individuals, aged 26–83 yr, receiving routine physical examinations and residing in Shijiazhuang for 10 yr or longer and without thyroid nodules or thyroid disease; controls were individually matched to cases on sex and age (± 5 yr) Exposure assessment method: plasma measurements of all participants	Thyroid, incidence	Plasma PFOA concentration (OR): 1st tertile 2nd tertile 3rd tertile Continuous (per unit on natural log scale) Trend-test *P*-value, 0.006	 NR NR NR 150	 1 0.14 (0.05–0.39) 0.32 (0.15–0.69) 0.78 (0.52–1.17)	Age, sex, BMI, smoking status, drinking status, education, household income	*Exposure assessment critique*: Key strengths were that plasma levels represent the combined exposure through all exposure pathways; measurement error low. Key limitations were that if thyroid cancer alters ADME of PFAS there could be possible differential exposure misclassification; single samples at time of case hospitalization may not reflect exposure at crucial windows in cancer development. *Other limitations*: Selection bias due to selection of controls among participants who were undergoing routine physical examination; potential for reverse causation.

Table 2.4 (continued)

Reference, location, enrolment/ follow-up period, study design	Population size, description, exposure assessment method	Cancer type (histopathology), incidence or mortality	Exposure category or level	Exposed cases or deaths	Risk estimate (95% CI)	Covariates controlled	Comments
Li et al. (2023) Shijiazhuang, Hebei Province, China January to May 2022 Case–control (cont.)		Thyroid, incidence	Plasma PFOS concentration (OR):			Age, sex, BMI, smoking status, drinking status, education, household income	
			1st tertile	NR	1		
			2nd tertile	NR	0.68 (0.33–1.41)		
			3rd tertile	NR	1.21 (0.60–2.45)		
			Continuous (per unit on natural log scale)	150	1.02 (0.77–1.36)		
			Trend-test *P*-value, 0.655				

ADME, absorption, distribution, metabolism, and excretion; AL, Alabama; APFO, ammonium perfluorooctanoate; approx., approximately; BMI, body mass index; CA, California; CI, confidence interval; CPS-II, Cancer Prevention Study II; CYP, cytochrome P450; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; E3N, Etude épidémiologique auprès de femmes de la Mutuelle générale de l'Education nationale; ER, estrogen receptor; *N*-EtFOSAA, 2-(*N*-ethyl-perfluorooctane sulfonamido) acetic acid; β-HCH, β-hexachlorocyclohexane; HR, hazard ratio; HRT, hormone replacement therapy; ICD, International Classification of Diseases; IQR, interquartile range; MET-h, metabolic equivalent of task per hour; MHT, menopausal hormone therapy; MN, Minnesota; mo, month(s); NC, not calculated; NHL, non-Hodgkin lymphoma; NR, not reported; NTUH, National Taiwan University Hospital; OH, Ohio; OR, odds ratio; PCB, polychlorinated biphenyl; PFAS, per- and polyfluoroalkyl substances; PFCA, perfluoroalkyl carboxylic acid; PFHpS, perfluoroheptanesulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; POP, persistent organic pollutant; POSF, perfluorooctanesulfonyl fluoride; ppm, parts per million; PR, progesterone receptor; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TFE, tetrafluoroethylene; US, United States; USA, United States of America; vs, versus; WQS, weighted quantile sum; WV, West Virginia; yr, year(s).

few women were included in this occupationally exposed cohort and there were few cases of breast cancer, limiting the ability to draw conclusions. The low number of cases may have been further affected by residential migration out of Minnesota and Wisconsin. Linkage to a cancer registry was a strength here when considering breast cancer, since it is not a cancer with a high rate of fatality and relying on NDI linkage alone would underestimate cases.]

Alexander et al. (2003) investigated a cohort of 2083 (353 women) PFOS-exposed production workers (Section 2.1.2). Mortality follow-up was conducted using linkage to the NDI until 1998. PFOS exposure was estimated based on a JEM that was validated from a subset of workers from whom blood samples had been collected. Only 17% of the cohort were women. There were two breast cancer-specific deaths identified (both among workers who only held non-exposed jobs); the resulting SMR was very imprecise. [The Working Group noted that there were very few women included in this occupationally exposed cohort and only 2 cases of breast cancer, both among workers holding non-exposed jobs, limiting the ability to draw conclusions. Further, there was little information available for confounding adjustment. The study relied on NDI linkage to identify cases, which would have underestimated the number of breast cancer cases, given the favourable survival after diagnosis, resulting in non-differential outcome misclassification that probably caused bias towards the null.]

Steenland and Woskie (2012) conducted a study of PFOA-exposed workers at the polymer-production plant in Parkersburg, West Virginia, USA (see Section 2.1.3). There were 5791 workers (19% women) who were employed for ≥ 1 day between 1948 and 2002 and for whom there were sufficient work history details to estimate PFOA exposure using a JEM informed by a subset with measured PFAS levels. A total of 4 deaths related to breast cancer were observed during follow-up from 1952 to 2008; mortality was not elevated overall, nor did it increase with quartile of estimated PFOA exposure. [The Working Group noted that although this study was in a highly exposed cohort, it was not well powered for breast cancer evaluation because of the small proportion of women, the few breast cancer-related deaths identified, and the lack of incidence data.]

Barry et al. (2013) conducted an investigation of community residents and workers who were exposed to PFOA from a polymer-production plant in the West Virginia and Ohio region, USA (Section 2.1.5). The study included 32 254 community residents and workers (17 360 women) who had a measurement of serum PFOA between 2005–2006, had participated in at least one survey between 2008 and 2011, and for whom either environmental or occupational modelled cumulative PFOA estimates were available. There was a modest inverse association between estimated cumulative PFOA exposure levels (natural log-transformed) and validated breast cancer (559 cases) with a hazard ratio of 0.94 (95% CI, 0.89–1.00), and results remained similar with a 10-year lag. [The Working Group noted that this study was informative because of its large size and consideration of cancer risk in highly exposed community members and in people exposed occupationally. It also considered confounders including education and alcohol intake, although it did not report information on other established breast cancer risk factors such as reproductive history. However, these results were based on estimated PFOA serum levels using data from 2005–2006, which may not include the most etiologically relevant time window. Finally, this study did not include information on breast cancer characteristics, including hormone receptor-related tumour subtypes, and presented results for breast cancer overall, which could mask any subtype-specific associations.]

Ghisari et al. (2017) evaluated the association between serum PFAS concentrations and breast cancer risk in a nested case–control study of pregnant nulliparous women in Denmark (see Section 2.1.7). PFAS, including PFOA and PFOS, were measured in blood samples collected during the first trimester of pregnancy (1996–2002), and breast cancer cases in the mothers were ascertained using linkage to a nationwide cancer registry, with follow-up until 2010. The study included 158 cases of breast cancer and 215 randomly selected controls. After adjusting for confounders, no association was observed between serum PFOA or PFOS concentrations and breast cancer incidence. However, when considering interactions with cytochrome P450 (CYP) family member 19 (CYP19, aromatase), which acts on the aromatization of androgens to estrogens, increases in levels of both PFOA and PFOS were associated with a notably higher incidence of breast cancer among women who had the CC genotype (relative risk for a 1-unit increase in natural log-transformed PFOA, 7.24; 95% CI, 1.00–52; and relative risk for a 1-unit increase in natural log-transformed PFOS, 6.42; 95% CI, 1.08–38.3), with significant *P* values for interaction (for PFOA, $P = 0.047$; for PFOS, $P = 0.055$). [The Working Group noted that this study had a number of important strengths, including serum PFAS levels that were measured at baseline and adjustment for several relevant breast cancer risk factors. Pregnancy may be an important window of susceptibility during which exposures may be particularly relevant for subsequent risk of breast (Terry et al., 2019). The study was also somewhat underpowered to investigate interactions with genotype and had very few years of follow-up after pregnancy, therefore focusing on premenopausal breast cancer. This study did not include information on diagnoses of postmenopausal breast cancer or other characteristics, including hormone-receptor tumour subtypes, and presented results for breast cancer overall, which could mask any subtype-specific associations.]

Hurley et al. (2018) analysed serum PFAS levels in relation to breast cancer risk in a nested case–control study within the prospective CTS cohort in the USA (see Section 2.1.8). Breast cancer cases were identified by linkage to cancer registries and were analysed in relation to blood samples collected on average 35 months after a cancer diagnosis and any treatment (range, 9 months to 8.5 years). Average serum PFOA and PFOS levels in this cohort (median in controls, PFOA, 2.48 ng/mL, and PFOS, 6.95 ng/mL) were generally lower than those measured in previous studies (e.g. Ghisari et al., 2017), with the exception of PFOA in the study by Wielsøe et al. (2017). Among the 902 cases and 858 controls with serum PFAS concentrations, there was little evidence for an association between breast cancer and either PFOA or PFOS. There was also no association observed when the analyses were limited to either premenopausal or postmenopausal breast cancers or when considering the combined ER/PR status of the tumour. [The Working Group noted that this study included several established breast cancer risk factors and was able to consider stratification by menopausal status and hormone-receptor status, which are important factors to consider. However, the collection of blood samples on average 35 months after a case diagnosis was a major limitation as it was unclear whether these measurements reflect the relevant etiological window for breast cancer or whether they may have been influenced by breast cancer or any treatment.]

Mancini et al. (2020a) investigated the association between serum PFAS measures and breast cancer risk in a nested case–control study in the E3N cohort of women in France (Section 2.1.10). Blood samples were collected in the period 1994–1999, and women were followed for breast cancer until 2013. There were 194 cases of postmenopausal breast cancer and 194 matched controls. For PFOA, the association for all breast

cancers was elevated in the second quartile but not in the third and fourth quartiles. When stratifying by ER and PR status, this increase in risk for the second quartile was driven by ER– or PR– tumours (e.g. quartile 2 versus quartile 1 for ER–, OR, 7.73; 95% CI, 1.46–41.08), although estimates were imprecise. A non-monotonic association was also observed for increasing serum levels of PFOS, with higher ORs in the second and third quartile, and associations that were elevated but with wide confidence intervals for the fourth quartile. However, a monotonic trend with increasing PFOS levels was observed for ER+ and, separately, PR+ tumours (e.g. quartile 4 versus quartile 1 for ER+, OR, 2.33; 95% CI, 1.11–4.90). [The Working Group noted that this study was particularly informative since serum samples were collected prospectively, there was a long follow-up period, and the authors were able to evaluate how associations varied by ER or PR status of the tumour, although the confidence intervals were wide.]

Chang et al. (2023) conducted a nested case–control study within the PLCO Cancer Screening Trial (Section 2.1.11). This study included 621 cases of invasive postmenopausal breast cancer diagnosed until November 2013 and 621 controls in postmenopausal women who were selected with matching on age at baseline, date of blood draw, and baseline use of hormone replacement therapy. There was no association between PFOA, by quartiles of exposure, and overall breast cancer risk. The ORs for serum PFOS, categorized in quartiles, were elevated but mainly with wide confidence intervals in relation to overall breast cancer risk. However, for PFOS, associations were evident for hormone receptor-positive breast cancer (ER+/PR+ quartile 3 versus quartile 1, OR, 2.19; 95% CI, 1.21–3.98 and quartile 4 versus quartile 1, OR, 1.89; 95% CI, 0.97–3.69). For PFOA, there was a non-monotonic positive exposure–response relation observed for ER–/PR– tumours, with wide confidence intervals (ER–/PR–: quartile 3 versus quartile 1, OR, 2.23; 95% CI, 0.90–5.54; and quartile 4 versus quartile 1, OR, 1.62; 95% CI, 0.62–4.23). [The Working Group noted that this study was very informative because it was the largest prospective study evaluating prediagnostic serum PFAS levels in relation to breast cancer risk. The findings from this report were strengthened by the evaluation of differences in joint ER/PR status of the tumour. However, the assessment of PFAS levels using untargeted measurement methods limited direct comparisons with other studies. Finally, these results were generalizable only to postmenopausal women, because premenopausal breast cancer cases were not included.]

In a case–control study nested in the CHDS cohort in California, USA (see Section 2.1.12), Cohn et al. (2020) estimated the relation between maternal serum PFAS levels during pregnancy and the daughter's risk of breast cancer by age 52 years. There were 102 cases identified using validated self-report and registry linkage and they were matched to 310 controls. No association was observed for maternal PFOA exposure in utero in relation to breast cancer risk in the daughters, although the specific results were not reported. Maternal PFOS exposure in utero was inversely associated with breast cancer risk in daughters in a model that included terms for $\log_2$-transformed *N*-ethyl-perfluorooctane sulfonamido acetic acid (*N*-EtFOSAA), which is a precursor of PFOS, $\log_2$-transformed total cholesterol, and their interaction. The OR for the fourth quartile median versus the first quartile median (an increase of 3.15 ng/mL) in $\log_2$-transformed maternal PFOS was 0.3 (95% CI, 0.1–0.9). [The Working Group noted that although this study was unique in its focus on maternal serum PFAS levels in relation to daughter's breast cancer risk, it did not incorporate other measures of PFAS during childhood, adolescence, or adulthood, which may also be relevant. Additionally, the case counts were small, especially with stratification, which meant that interpretation of these findings was challenging and that the findings were not

easily comparable to those of other studies. This study mainly focused on premenopausal breast cancer diagnoses or did not include other breast cancer characteristics, including hormone-receptor tumour subtypes, and presented results for breast cancer overall, which could mask any subtype-specific associations.]

Li et al. (2022a) followed more than 60 000 individuals (more than 28 000 of whom were women) who lived in Ronneby municipality in Sweden between 1985 and 2013; approximately one third of the participants were exposed to water contaminated with PFAS, primarily with PFOS and PFHxS and, to a lesser extent, PFOA (Section 2.1.13). Exposure assessment was based on annual residential addresses and information on drinking-water supply, and cases were identified on the basis of linkage to the cancer registry until 2016. With 681 cases of female breast cancer identified, there was no evidence of an excess risk of breast cancer; SIRs were below the null and were similar for women both with "never-high" or "ever-high" exposure living at an address supplied with PFAS-contaminated water compared with an external reference group. In the internal cohort comparison analysis, there was no difference in the hazard ratios for breast cancer across categories based on estimated duration or timing of exposure. [The Working Group noted that although this study included a large general population sample with a strong exposure contrast and a near-complete registry-based case identification, there was limited control for confounding, particularly for established breast cancer risk factors such as education and reproductive history, and the mixed exposure to multiple PFAS did not allow for the identification of associations with individual compounds. This study did not incorporate information on other breast cancer characteristics, including hormone-receptor status, and it presented results for breast cancer overall, which could mask any subtype-specific associations.]

Feng et al. (2022) evaluated the association between plasma PFAS and breast cancer risk in an ongoing prospective study in Shiyan, China, of retired workers from an automotive company (Section 2.1.14). Incident breast cancer cases were identified by medical record review or death certificates. The nested case–cohort sample included a random subcohort of 990 participants and all non-subcohort participants identified with incident breast cancer (n = 213). The random subcohort included 13 cases of breast cancer, thus there was a total of 226 incident breast cancer cases. Plasma PFAS levels were quantified for the entire case–cohort sample. Increasing levels of serum PFOA were associated with a higher risk of breast cancer (natural log-transformed PFOA levels, HR, 1.35; 95% CI, 1.03–1.78; quartile 4 versus quartile 1, HR, 1.69; 95% CI, 1.05–2.70), but no increase in risk was observed for PFOS. The association for PFOA was similar when the analysis was restricted to postmenopausal women. [The Working Group noted that this study provided compelling evidence, using prospective sample collection and a case–cohort design with adjustment for many potential confounders. However, it was unable to explore how this association may vary by hormone-receptor tumour subtype and, by presenting results for breast cancer overall, could mask any subtype-specific associations.]

Winquist et al. (2023) evaluated the concentrations of several PFAS compounds in serum samples in relation to breast cancer incidence as part of a nested case–cohort study in the ACS prospective CPS-II LifeLink Cohort. Between 1998 and 2001, participants were selected if they had no previous cancer diagnosis and donated blood samples at a median age of 70 years (69 years for women) (Section 2.1.21). Cancer cases were identified by self-report and using NDI linkage. There were 786 cases of postmenopausal breast cancer and 499 women in the subcohort, and the median follow-up time was 14 years. Higher serum PFOA and PFOS concentrations were

not related to higher incidence of breast cancer (PFOA, quartile 4 versus quartile 1, HR, 0.82; 95% CI, 0.57–1.17; PFOS, quartile 4 versus quartile 1, HR, 0.70; 95% CI, 0.48–1.01). [The Working Group noted that this study included prospective sample collection and a case–cohort design with adjustment for many potential confounders. However, the blood sample used to measure PFAS was collected at a median age of 69 years, which is after the peak age at diagnosis for breast cancer. Further, it did not consider variability in the associations by hormone-receptor tumour subtype and by presenting results for breast cancer overall could mask any subtype-specific associations.]

(b) Case–control studies and meta-analyses

The eight case–control studies contributing evidence on PFOA and PFOS exposure and risk of breast cancer in women are described below. [The Working Group noted that nearly all the case–control studies listed below had a design in which exposure was measured after disease diagnosis, thus reverse causation bias cannot be excluded. Indeed, the disease could potentially affect PFOA and PFOS internal levels as a consequence of physiological changes associated with tumour development, such as altered albumin levels or altered glomerular filtration rate. Despite this concern, the Working Group considered it unlikely that such alterations would be observed in patients with breast cancer at diagnosis and that there was too little information available concerning the toxicokinetics of PFOA and PFOS in patients with cancer to reach conclusions on the presence of reverse causation bias in case–control studies. In all the case–control studies, except for that by Vieira et al. (2013) in which PFOA serum levels were inferred from geocoded addresses, environmental exposure, and toxicokinetic models, exposure classification was based on PFOA and PFOS measurements in blood samples collected only once when entering the study. The Working Group also questioned whether blood PFOA and PFOS levels measured at the time of diagnosis reflect exposure during the most relevant windows of exposure with regard to breast cancer risk. Indeed, for cancer (and in particular for breast cancer) the relevant time windows of exposure are several years before diagnosis, so that the levels of exposure at the time of diagnosis may not be pertinent to the disease. Nevertheless, since there is some evidence that single samples may represent long-term average levels of exposure to PFOA over a 5–8-year period (Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636), and since there was limited information concerning the most relevant window of exposure to PFOA and PFOS with regard to breast cancer, the Working Group could not come to a conclusion on the informativeness of these studies.]

Vieira et al. (2013) investigated the relation between exposure to PFOA and breast cancer risk among residents living near the polymer-production plant in Parkersburg, West Virginia, USA, in two case–control studies (Vieira et al., 2013) (Section 2.1.22). In the case–control study in West Virginia and Ohio, 4057 cases of female breast cancer diagnosed from 1996 through 2005 in five Ohio counties and eight West Virginia counties were included in the study, whereas controls comprised all other cancers registered during the same study period (excluding kidney, pancreatic, testicular, and liver cancers). Of the 13 counties included in this study, 6 areas were classified as contaminated public water districts, and living within a contaminated water district was the exposure of interest for the main analyses. In the other case–control study, additional analyses were conducted only for Ohio counties for which it was possible to geolocalize the street addresses for all cancer cases and then to estimate serum PFOA concentration as an exposure metric assuming 10 years residence and latency. All analyses were restricted to women and

adjusted for age, race (White or non-White, only for Ohio), smoking status, and health insurance provider. No evidence of associations with breast cancer risk was observed in the two studies. [The Working Group noted that other types of cancer were used as controls and that the presence of exposure misclassification bias cannot be excluded because the exposure was estimated on the basis of the address of residence at diagnosis, although participants could have moved between water districts. Potential exposure misclassification was probably non-differential, so the bias would be expected to be towards the null. Finally, the Working Group noted that several important confounding variables, mainly related to reproductive history (e.g. age at menarche, number of pregnancies, age at menopause) and exogenous hormone exposure (e.g. use of contraceptive pill, use of hormone replacement therapy), were not included in the analyses.]

Bonefeld-Jørgensen et al. (2011) conducted a case–control study among women of Inuit descent in Greenland. Between 2000 and 2003, 31 women with breast cancer were recruited at the Dronning Ingrids Hospital in Nuuk, where all breast cancer cases of Greenland are registered. Women acting as controls (n = 115) were selected by frequency-matching on age and district of residence from a cross-sectional study conducted in 2000 (Côté et al., 2006) and from the Arctic Monitoring and Assessment Programme study conducted between 1999 and 2005 (Deutch et al., 2007). This study was extended by Wielsøe et al. (2017), who enrolled 66 cases and 62 controls during 2011–2014. Although cases were always recruited at the Dronning Ingrids Hospital in Nuuk, controls enrolled during 2011–2014 were selected by frequency-matching on age and district of residence among patients admitted to the hospital in the department of orthopaedic surgery, or to the department of gynaecology and obstetrics because of the diagnosis of non-malignant abnormities in the uterus, ovaries, or breast. Controls recruited from 2000 to 2003 were then reduced to 1 control per case, so that the final study population included 77 cases of breast cancer and 81 controls. [The Working Group noted that it was unclear how the controls for the period 2000–2003 were selected from the two surveys. Moreover, the authors did not explain on which criteria the final study population was selected, so that selection bias could not be excluded. The Working Group also noted that controls enrolled between 2011 and 2014 were hospital patients attending the orthopaedic surgery department or with non-malignant abnormalities in the uterus, ovary, or breast. If there were an association between PFOA or PFOS exposure and the health conditions affecting the patients recruited as controls, selecting controls from among women admitted at the hospital could have introduced a bias.] Blood samples were collected at diagnosis for the cases and when enrolled in the study for the controls, and PFOA and PFOS serum levels were measured for both cases and controls. After adjusting for age, BMI, serum cotinine levels, number of pregnancies, and breastfeeding, the authors reported a positive association between serum levels of PFOA (OR per unit increase of PFOA, 1.26; 95% CI, 1.01–1.58) and of PFOS (OR per unit increase of PFOS, 1.02; 95% CI, 1.01–1.03) and breast cancer risk. [The Working Group noted that no information was available concerning the delay between diagnosis and the collection of blood samples used for PFAS measurements, thus it could not be excluded that patients with breast cancer changed their behaviours after diagnosis and that this change could have an impact on circulating levels of PFAS. Moreover, the authors did not specify whether the women enrolled as cases had received cancer treatment before blood samples were collected. This could potentially affect PFOA and PFOS internal levels because of physiological changes associated with the treatment. The lack of evidence on the impact of cancer treatment on PFOA and PFOS internal levels did not permit the Working Group to

reach a conclusion on the possible presence of bias. Finally, the Working Group noted that the median serum level of PFOS (45.60 ng/mL) for breast cancer cases among women recruited between 2000 and 2003 was more than double that measured in controls (18.06 ng/mL) selected in the same time period but also those measured in cases (19.35 ng/mL) and controls (18.20 ng/mL) recruited between 2011 and 2014. The authors did not provide an explanation or interpretation of this important variation in PFOS levels that would be expected to have had an impact on the results.] Additional analyses to explore interactions between gene polymorphisms and PFOA and PFOS serum levels with regard to breast cancer risk were conducted using the same study population as Bonefeld-Jorgensen et al. (2011), including 31 cases and 115 controls (Ghisari et al., 2014). [The Working Group noted that the interaction between genotype and exposure was not formally tested by Ghisari et al. (2014), so that the results were considered to be not informative. Moreover, the limited number of cases included had a strong impact on the statistical power of the analyses, preventing correct interpretation of the results.]

Between 2014 and 2015, 120 cases of histologically confirmed breast cancer were consecutively recruited from women attending the National Taiwan University Hospital, China (Tsai et al., 2020). A total of 119 women without any history of malignancy were recruited as controls between 2014 and 2016 through advertisements of posters and flyers at the hospital and in the community. All participants answered a questionnaire and donated a blood sample at enrolment. For the cases, blood samples were collected before receiving any treatment for breast cancer. Plasma PFOA and PFOS levels were measured for both cases and controls. Adjusted ORs of 0.89 (95% CI, 0.59–1.34) and 1.07 (95% CI, 0.64–1.79) were calculated for a natural log 1-unit increase in PFOA and PFOS, respectively. When the analyses were stratified on the basis of age of participants (> 50 years versus ≤ 50 years), an adjusted OR of 2.34 (95% CI, 1.02–5.38) for PFOS exposure was observed for women aged ≤ 50 years, whereas an adjusted OR of 0.62 (95% CI, 0.29–1.29) was observed for women aged > 50 years. When also considering the tumour ER status, PFOS exposure was significantly associated only with risk of ER+ breast cancer in women aged ≤ 50 years (OR per unit increase in natural log-transformed PFOS levels, 3.25 (95% CI, 1.29–8.23). The other results were generally not positive. [The Working Group noted that the small number of cases and controls included in the study could have limited the statistical power of the analyses, especially when stratifying on the basis of age and tumour hormone-receptor status. Moreover, the Working Group noticed that the recruitment strategy for the controls could have induced a selection bias, because people positively responding to advertisement through posters and flyers could have had healthier lifestyles and a higher medical awareness compared with the source population for cases.]

A multicentric hospital-based case–control study conducted in Japan between 2001 and 2005 included 401 cases of histologically confirmed invasive breast cancer (Itoh et al., 2021). Controls were selected from among individuals attending hospital medical check-ups during the study period who had not been diagnosed with cancer. The controls were matched individually to cases on age and residential area (urban or rural). At recruitment, all participants completed a self-administered questionnaire, and a blood sample was collected. Among participants serving as cases, blood samples were collected before any cancer treatment. Multivariable analysis showed a precise inverse association between risk of breast cancer and serum concentrations of PFOA (OR for fourth quartile versus first quartile, 0.21 (95% CI, 0.10–0.45) and PFOS (OR for fourth quartile versus first quartile, 0.14; 95% CI, 0.07–0.31). Results from models that additionally adjusted for vegetable intake, fish and shellfish

intake, calendar year of blood sampling, and quartiles of serum lipid-adjusted total concentration of PCBs remained virtually unchanged. The association between PFOA or PFOS and risk of breast cancer did not differ accordingly to menopausal status or hormone-receptor status. [The Working Group noted that the use of medical check-up examinees as controls may have caused selection bias because of their higher medical awareness and possibly different socioeconomic status compared with the source population for cases. Moreover, educational and socioeconomic status were not included as adjustment variables in the main analyses.]

Velarde et al. (2022) recruited 75 cases of histologically confirmed breast cancer in women aged 18–60 years in the Philippines, with no comorbidity, who visited the Philippine General Hospital between January and December 2018. Patients who underwent neoadjuvant chemotherapy were excluded from the study. Controls were randomly recruited through posters, social media advertisements, and by word of mouth. The control group included 75 women within the age range of 18–59 years, without a previous diagnosis of cancer and without a family history of breast, ovarian, or endometrial cancer in first-degree relatives. This study did not observe any associations between serum PFOA and PFOS levels and breast cancer risk. [The Working Group noted that the study did not adjust for important confounding variables, such as anthropometric characteristics, reproductive history, and hormone exposure. Indeed, the final model included only age and region of residence as covariables. Moreover, the small number of included cases and controls limited the statistical power of the analyses and thus the informativeness of the results. Finally, the Working Group noted that the recruitment strategy for the controls may have caused selection bias, because people positively responding to advertisements through posters and social media could have a higher medical awareness or possibly a different socioeconomic status compared with the source population for cases.]

Li et al. (2022b) conducted a case–control study that included 373 cases of breast cancer and 657 controls, all participants having available blood samples. Cases were recruited at the Tianjin Medical University Cancer Institute and Hospital, China, between January 2012 and December 2016. Diagnosis of malignant breast cancer was confirmed histologically, and a blood sample was collected within 1 week after diagnosis and before receiving any treatment. Controls were randomly selected among women participating in the Chinese National Breast Cancer Screening Program (CNBCSP) cohort. The CNBCSP was launched in 2012 and included women without a history of cancer who lived in four cities (Shijiazhuang, Tangshan, Xingtai, and Handan) in Hebei Province for ≥ 3 years, and were aged 40–74 years (Wu et al., 2023). Both case and control participants answered a questionnaire (including dietary information) at recruitment. Li et al. (2022b) found that plasma concentrations of PFOA were positively associated with breast cancer risk. The authors estimated an adjusted OR for an increase of 1 standard deviation (SD) in natural log-transformed PFOA plasma levels of 1.57 (95% CI, 1.31–1.89). PFOA was more strongly associated with the ER+ (OR, 1.47; 95% CI, 1.19–1.80) and PR+ (OR, 1.36; 95% CI, 1.09–1.69) breast cancer than with receptor-negative tumours. An inverse association was observed between PFOS plasma levels and breast cancer risk, with an OR for one SD increase in natural log-transformed PFOS plasma levels of 0.81 (95% CI, 0.68–0.96). [The Working Group considered as strengths of this study that all cases were histologically confirmed malignant breast cancer, and blood samples were collected within 1 week after diagnosis and before any cancer treatment. Moreover, the Working Group noted that the large number of cases and controls permitted stratified analyses while still ensuring a good statistical power.

The Working Group noted as a limitation the fact that the controls were selected from women participating in the breast cancer screening programme, who may have had a higher medical awareness and possibly different socioeconomic status compared with the source population for cases.]

Three meta-analyses have been conducted on the association between exposure to PFOA and PFOS and breast cancer risk. The first meta-analysis (Jiang et al., 2022) included eight studies: seven case–control studies, among which three were case–control studies nested in prospective cohort studies, and one cross-sectional study. The exposure assessment for all included studies was based on PFOA and PFOS blood measurements. The overall results showed that PFOA was positively associated with breast cancer risk, and the pooled OR was 1.32 (95% CI, 1.19–1.46), whereas PFOS was not associated with breast cancer risk (pooled OR, 1.01; 95% CI, 0.87–1.17). [The Working Group noted that the present meta-analyses included studies with different designs (case–control studies, nested case–control studies, cross-sectional study) which could have caused heterogeneity and instability of the pooled OR. Moreover, the Working Group noted that the results were mainly driven by the only cross-sectional study included in the meta-analyses (Omoike et al., 2021) and that this study was identified as the main source of heterogeneity by the authors. Finally, the Working Group noted that the authors counted studies multiple times when performing comparisons between exposure categories.]

In the second meta-analysis, Cong et al. (2023) included eleven studies: nine case–control studies, of which three were nested in prospective cohort studies, one cohort study, and one case–cohort study. PFOA and PFOS blood levels were used as the main exposure variable in all studies except for one study in which individual cumulative PFOA serum concentration estimates were calculated retrospectively from 1952 through 2011. The results of the meta-analyses found little evidence of a positive association between PFOA and PFOS and breast cancer risk (pooled OR, 1.07; 95% CI, 0.84–1.38; and pooled OR, 1.01; 95% CI, 0.95–1.08, respectively). The authors observed significant heterogeneity among the included studies for both PFOA (I^2 = 85.9%; P < 0.001) and PFOS (I^2 = 65.7%; P = 0.003). When omitting one study at a time from the pooled analyses, a weakly positive OR was observed for PFOS in relation to breast cancer when excluding Itoh et al. (2021) (pooled OR, 1.02; 95% CI, 1.01–1.03, I^2 = 2.6%; P = 0.41). Results remained unchanged for PFOA. [The Working Group noted that studies having different designs (case–control studies, nested case–control studies, case–cohort study and cohort study) and applying different methods to estimate the exposure were included in this meta-analysis and that this could explain the high observed heterogeneity. Moreover, the results of the meta-analyses seemed to be strongly influenced by the only study that highlighted an inverse association between PFOA and PFOS and breast cancer risk.]

The third meta-analysis on the association between exposure to PFOA and PFOS and breast cancer risk was conducted by Chang et al. and included 11 case–control studies, 5 of which were nested in prospective cohort studies (Chang et al., 2024). For all studies included in the meta-analyses PFOA and PFOS levels were measured in blood samples (serum or plasma). The results of the meta-analyses were not consistent with an association between PFOA and PFOS blood levels and the risk of breast cancer overall, but they noted substantial heterogeneity across studies. Indeed, the authors estimated a rate ratio for a natural log-unit increase of PFOA of 0.95 (95% CI, 0.77–1.18; I^2 = 67%; P for heterogeneity, < 0.01) and for a natural log-unit increase of PFOS of 0.98 (95% CI, 0.87–1.11; I^2 = 54%; P for heterogeneity, 0.02). In subanalyses, when limiting to studies with prospectively collected blood samples, there was a positive association

with PFOA (RR, 1.16; 95% CI, 0.96–1.40). [The Working Group noted that this meta-analysis incorporated important subgroup analyses, including by timing of sample collection and tumour subtype. However, there was substantial heterogeneity across the published studies, limiting the informativeness of the results.]

2.4.2 Cancer of the thyroid gland

See Table 2.4.

The Working Group identified six cohort studies and three case–control studies investigating the risk of thyroid cancer associated with PFOA or PFOS exposure. Among the cohort studies, two were occupational cohorts (Leonard et al., 2008; Lundin et al., 2009), one was a combination of general population members and workers (Barry et al., 2013), one was composed of residents in area with highly contaminated drinking-water (Ronneby Register cohort; Li et al., 2022a), one nested case–control study was within the FMC (Madrigal et al., 2024), and one nested case–control study was within the Bio*Me* biobank (van Gerwen et al., 2023). One of the case–control studies was population-based (Vieira et al., 2013) and two were hospital-based (Liu et al., 2022; Li et al., 2023).

(a) Cohort studies

Lundin et al. (2009) conducted a mortality study in a cohort of 3993 employees of an APFO-manufacturing facility in Cottage Grove, Minnesota, USA (see Section 2.1.1). The cohort was followed until 31 December 2002, and 807 decedents were identified. Using rates for the state of Minnesota as the referent, SMRs were calculated for different jobs classified by exposure to APFO (the ammonium salt of PFOA). There was only 1 observed death from thyroid cancer, which was assigned to the "never" exposure group. The SMR for the "never" exposure group was 2.16 (95% CI, 0.05–12.00). [The Working Group noted that the important limitations of the study included the small occupational cohort with only 1 death from thyroid cancer and crude exposure assessment by job classification, which made this study uninformative for the evaluation of an association with thyroid cancer.]

Leonard et al. (2008) conducted a retrospective cohort mortality study for the PFOA cohort in a polymer-production plant in Parkersburg, West Virginia, USA, which included 6027 participants who had worked at the facility between 1948 and 2002 (Section 2.1.3). SMRs were calculated by comparing the observed number of deaths to expected numbers derived from mortality rates for three reference populations (the US population, the West Virginia state population, and an eight-state regional employee population from the same company). There were only 3 observed deaths for thyroid cancer. The SMRs for the cohort from the Parkersburg plant were [3.120] (95% CI, [0.644–9.119]), [2.856] (95% CI, [0.589–8.347]), and [6.286] (95% CI, [1.297–18.369]), respectively, for the three reference populations (the US population, the West Virginia population, and the workers in the same company and region). [The Working Group noted that the major limitation of the study was the limited statistical power to evaluate mortality rates for thyroid cancer because of the small numbers of observed deaths, which made this study uninformative for the evaluation of an association with thyroid cancer.]

Barry et al. (2013) examined PFOA exposures and incident cancers among community residents and workers who were exposed to PFOA from a chemical plant, using the C8 Health Project cohort combined with the worker cohort from the polymer-production plant in Parkersburg, West Virginia, USA (Section 2.1.5). There were 32 254 participants in the entire cohort, with 28 541 participants classified as the community group and 3713 as the occupational group. There were 98 cases of primary thyroid cancer reported. The analysis included 86 cases of validated primary thyroid cancer with complete

covariate information. In the total cohort, the hazard ratios for a 1-unit increase in natural log-transformed estimated cumulative PFOA exposure in relation to thyroid cancer were 1.10 (95% CI, 0.95–1.26) for unlagged exposures and 1.04 (95% CI, 0.89–1.20) for exposures lagged by 10 years. When stratified by community residents and workers, the hazard ratios for cumulative PFOA exposure in relation to thyroid cancer were 1.04 (95% CI, 0.89–1.23) and 1.93 (95% CI, 1.00–3.71), respectively, for unlagged exposures, and 1.00 (95% CI, 0.84–1.20) and 1.12 (95% CI, 0.61–2.05), respectively, for exposures lagged by 10 years. In sensitivity analyses, when excluding years before each participant began living or working in the contaminated water districts in the survival models, results were similar to the reported results above. When calculating hazard ratios by PFOA quartile in the total cohort, there was no indication of an exposure–response relation between PFOA exposure and thyroid cancer. However, an exposure–response relation was indicated when calculating hazard ratios by PFOA quartile among the occupational group (8 cases) but not the community group (78 cases). [The Working Group noted as strengths the large cohort, strong exposure contrast, assessment of individual cumulative PFOA exposure, and lagged analyses. Limitations included self-reported cancer cases, the low sample size for thyroid cancer, and lack of evaluation of residents' co-exposure to other PFAS.]

Li et al. (2022a) studied cancer incidence in the Ronneby Register cohort, which included a community of residents in Sweden with high-level environmental exposure to PFAS, dominated by PFOS and PFHxS, in drinking-water (Section 2.1.13). SIRs were calculated by comparing with a regional external reference population (the population of Blekinge County excluding Ronneby municipality) and the national reference population (the whole population of Sweden). By the end of the follow-up on 31 December 2016, there were 17 cases of incident thyroid cancer in men and 48 cases in women. External comparisons and internal comparisons were both performed within the Ronneby Register cohort. To facilitate comparison, Ronneby residents were assigned to mutually exclusive groups: "never-high" and "ever-high" based on the source of drinking-water at their residence. When compared with the regional external reference population, women in the ever-high group had nominally higher estimates (defined as > 25% difference) for cancers of the thyroid than did women in the never-high group, with an SIR of 2.08 (95% CI, 1.19–3.38) in the ever-high group, and 1.38 (95% CI, 0.94–1.95) in the never-high group. However, that relation was not observed among men. In internal comparisons, the never-high group was used as the referent, and the thyroid cancer hazard ratio for different groups was calculated. The authors observed modestly increased point estimates but with wide confidence intervals, which showed limited indications of an exposure–response relation between PFAS exposure and the incidence of thyroid cancer for time period of high exposure ("early-high" in 2004 or earlier versus "late-high" in 2005 or later) or for duration of time in a high-exposure area ("short-high" for ≤ 10 years versus "long-high" for ≥ 11 years) compared with "never-high" group. [The Working Group noted as strengths the large study population, strong exposure contrast, and unbiased inclusion. The group-based exposure assessment can be assumed to provide unbiased risk estimates but less exposure contrast and broader confidence intervals than would be expected with individual-level estimates. However, even at the group level, there was a large exposure contrast, which was one of the strengths of this study. The main limitations were the crude exposure assessment, not including individual water intake or sources of exposure other than drinking-water, the mixed exposure profile, and the limited information on potential confounders.]

Madrigal et al. (2024) conducted a nested case–control study of papillary thyroid cancer in the FMC, restricting eligibility to women for whom serum samples were collected in their first pregnancy and whose pregnancy resulted in a full-term live birth, with delivery dates from 1987 to 2010 (see Section 2.1.18). Thyroid cancer cases and controls were identified by the nationwide Finnish Cancer Registry and the population registry until 2016. All cases were randomly selected women with primary papillary thyroid cancer diagnosed ≥ 3 years after the delivery date, without a history of other cancers. Controls were individually matched to cases on year of delivery (increments of 4–5 years) and age at first birth (increments of 3 years). A total of 800 participants (400 cases of thyroid cancer and 400 controls) were included in the nested case–control analysis. No clear pattern was observed in the association between papillary thyroid cancer risk and serum concentrations of PFOA (OR per $\log_2$, 0.90; 95% CI, 0.68–1.19) or PFOS (OR per $\log_2$, 1.14; 95% CI, 0.81–1.95). When stratified by age at diagnosis (< 40 years, ≥ 40 years), the associations per each doubling in concentrations of PFOA and PFOS were elevated but imprecise (OR per $\log_2$, 1.20; 95% CI, 0.71–2.01; and OR per $\log_2$, 1.14; 95% CI, 0.68–1.93; respectively) among women diagnosed before age 40 years. However, among women diagnosed at age ≥ 40 years, the associations were inverse or were close to 1.0 (OR per $\log_2$, 0.70; 95% CI, 0.45–1.08; and OR per $\log_2$, 1.01; 95% CI, 0.60–1.71; for PFOA and PFOS, respectively). [The Working Group noted that use of a single prediagnostic sample would result in only minor misclassification of long-term exposure over a period of 5–8 years, on the basis of a simulation study (Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636). The lack of information on pre-pregnancy BMI (a risk factor for thyroid cancer) and the population's low-level exposure with small exposure contrast were noted as limitations.]

van Gerwen et al. (2023) conducted a case–control study nested within the Bio*Me* biobank of Mount Sinai hospital in New York (see Section 2.1.20). Among 88 cases (57 with < 1 year between sample collection and thyroid cancer diagnosis) and 88 controls, plasma PFOA concentration was not associated with thyroid cancer risk, whereas plasma concentrations of branched PFOS and linear-PFOS were associated with increased thyroid cancer risk (ORs for increment of $\log_2$-plasma concentration of branched PFOS and linear-PFOS were 1.32; 95% CI, 0.99–1.81; and 1.56; 95% CI, 0.99–1.81; respectively). In the sensitivity analysis restricted to 31 cases with > 1 year between sample collection and incident thyroid cancer diagnosis (median time, 3.7 years), $\log_2$-plasma concentrations of branched PFOS and linear-PFOS were also associated with increased risk of thyroid cancer (OR, 3.09; 95% CI, 1.73–6.13; and OR, 2.67; 95% CI, 1.59–4.88; respectively). [The Working Group noted the limited follow-up time in this study and that use of a single prediagnostic sample would result in only minor misclassification of long-term exposure over a period of 5–8 years, on the basis of a simulation study carried out by the Working Group (Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636).]

(b) Case–control studies

One population-based case–control study was conducted by Vieira et al. (2013) among residents of 13 counties in Ohio and West Virginia surrounding the Parkersburg polymer-production facility (see Section 2.1.22). The final data set included 343 cases of thyroid cancer. Controls were defined as all other cancers in the study data set, except for cancers of the kidney, pancreas, testis, liver, and thyroid. All cancer diagnoses were classified as exposed (living within a

contaminated water district) or unexposed (not living in a contaminated water district) using geocoding. The AORs varied among the water districts exposed to contaminated water, with the AOR of the overall exposure risk being 1.1 (95% CI, 0.7–1.5). Furthermore, for each case in Ohio, annual PFOA serum levels were calculated by linking environmental, exposure, and toxicokinetics models. The AORs were calculated using individual-level exposure categorized on the basis of the distribution of annual PFOA serum concentrations among the exposed study population. Using the unexposed group as the reference category, the AORs for very high, high, medium, and low individual-level exposures were 0.8 (95% CI, 0.2–3.5), 0.7 (95% CI, 0.2–2.1), 0.9 (95% CI, 0.4–2.3), and 0.9 (95% CI, 0.4–2.3), respectively. [The Working Group noted that the strengths of the study included its focus on a population with high PFOA exposure, the strong contrast in exposure levels, and the estimation of individual-level exposure for a subset of the people. Limitations included the use of other cancers as the referent, the lack of geocoded residence information among participants from West Virginia, and the risk of exposure misclassification (reliance on the address at the time of diagnosis rather than a complete residential history in analyses among Ohio participants).]

Liu et al. (2022) conducted a hospital-based case–control study in the Shandong Provincial Qianfoshan Hospital in Jinan City, Shandong Province, China, from 2016 to 2017. A total of 319 participants (134 cases of thyroid cancer and 185 controls) were included in the case–control analysis. The control group was randomly selected from patients undergoing routine medical visits at the hospital, with normal thyroid B-ultrasound examination, without a history of thyroid disease, and without taking iodine or thyroid hormone drugs during the blood collection. Serum samples of the participants were used to assess exposure to individual PFAS compounds. Serum samples for the case group were collected after the patients had stopped taking thyroid medication for 2 weeks under the guidance of their doctors. Serum samples for the control group were collected when they underwent routine medical visits at the hospital. The associations between serum levels of PFAS (including PFOA and PFOS) and thyroid cancer were examined using logistic regression models. Concentrations of PFAS compounds were categorized into quartiles according to the distribution in the control group. Compared with the first quartile of PFOA concentration, the ORs for the second, third, and last quartiles were 0.24 (95% CI, 0.12–0.50), 0.24 (95% CI, 0.11–0.49), and 0.20 (95% CI, 0.09–0.44), respectively, with a P for trend of < 0.001. Compared with the first quartile of PFOS concentration, the ORs for the second, third, and last quartiles of PFOS concentration were 0.81 (95% CI, 0.42–1.53), 0.26 (95% CI, 0.12–0.57), and 0.28 (95% CI, 0.12–0.66), respectively, with a P for trend of 0.001. [The Working Group noted that the limitations of the study included the sampling of serum after diagnosis and treatment, limited exposure contrast, small sample size, and the likelihood of potential reverse causation.]

Li et al. (2023) conducted a hospital-based case–control study in the Fourth Hospital of Hebei Medical University in Shijiazhuang, Hebei Province, from January to May 2022. All cases were newly arising thyroid cancer cases in the hospital, confirmed histologically by the hospital pathology unit, among patients who had resided in Shijiazhuang for ≥ 10 years. Controls were healthy individuals attending routine physical examinations in the health examination centre who had resided in Shijiazhuang for ≥ 10 years without thyroid cancer or other malignancies and were individually matched to cases on age (± 5 years) and sex. A total of 300 participants (150 cases of thyroid cancer and 150 healthy controls) were included in the case–control analysis. Plasma samples were collected before the start of thyroid cancer therapy for the cases

and during the physical examination for the controls. The associations between plasma levels of PFAS compounds (including PFOA and PFOS) and thyroid cancer were examined using conditional logistic regression and restricted cubic spline models. Plasma PFAS concentrations were analysed as continuous variables and categorized variables (classified into tertiles according to the distribution among controls). The results showed no consistent indication of a positive exposure–response relation between plasma PFOA or PFOS and thyroid cancer, with the ORs associated with a 1-unit increase in natural log-transformed levels being 0.78 (95% CI, 0.52–1.17) and 1.02 (95% CI, 0.77–1.36), respectively. Further, compared with the first tertile of PFOA concentration, the OR for the highest tertile of PFOA concentration was 0.32 (95% CI, 0.15–0.69), indicating an inverse association between PFOA and thyroid cancer risk (*P* for trend, 0.006). However, the restricted cubic spline model did not show this inverse dose–response relation. [The Working Group noted that the study relied on postdiagnostic serum samples, which might have been affected by reverse causation. The Working Group noted that only minor misclassification of long-term exposure because of reliance on a single prediagnostic sample would be expected, according to a simulation study (Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636).]

2.5 Cancers of the digestive tract

2.5.1 Liver cancer

See Table S2.5 (Annex 4, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.who.int/636).

There were 11 epidemiological studies with information on liver cancer. Most were cohort studies, but three were case–control studies (one nested within a cohort), and one was a case–cohort study. Six studies were conducted in the USA (Alexander et al., 2003; Steenland and Woskie, 2012; Barry et al., 2013; Vieira et al., 2013; Raleigh et al., 2014; Goodrich et al., 2022), and one each in Denmark (Eriksen et al., 2009), China (Cao et al., 2022), Italy (Girardi and Merler, 2019), and Sweden (Li et al., 2022a). One included cohorts from multiple countries (Consonni et al., 2013). Five were occupational cohort mortality studies (Alexander et al., 2003; Steenland and Woskie, 2012; Consonni et al., 2013; Raleigh et al., 2014; Girardi and Merler, 2019); for four of these PFOA was the exposure of interest, whereas for one (Alexander et al., 2003) the exposure of interest was PFOS. The three community cohort studies (Eriksen et al., 2009; Barry et al., 2014; Li et al., 2022a) had incident cancer data, as did all three of the case–control studies (Vieira et al., 2013; Cao et al., 2022; Goodrich et al., 2022). Eriksen et al. (2009) reported results for PFOA and PFOS, Barry et al. (2014) reported on PFOA, and Li et al. (2022a) was not able to identify a specific PFAS of interest, but levels of PFOS were the highest in the studied population. Among the case–control studies, Vieira et al. (2013) focused on PFOA, whereas Cao et al. (2022) and Goodrich et al. (2022) reported results for both PFOA and PFOS. One additional study (Olsen et al., 2004) had some cross-sectional data on liver cancer among active and some inactive employees, but it was not considered informative regarding liver cancer incidence or mortality and therefore is not discussed further.

(a) Cohort, case–cohort, and nested case–control studies

Raleigh et al. (2014) studied liver cancer mortality among 4668 PFOA-exposed workers and 4359 unexposed workers at a different plant, all working for ≥ 1 year (Section 2.1.1 for more details). Using Minnesota rates as the referent, the SMR for exposed workers was 0.81 (95% CI, 0.35–1.59; 8 deaths from liver cancer). When

estimated PFOA air exposure was divided into four quartiles, the SMRs for exposed workers versus the Minnesota population were 1.40, 0.86, 0.75, and 0.00, based on only 4, 2, 2, and 0 deaths from liver cancer, respectively. When exposed workers were compared with non-exposed workers, combined quartiles 1 and 2 of cumulative PFOA exposure showed a hazard ratio of 2.09 (95% CI, 0.69–6.31), whereas combined quartiles 3 and 4 had a hazard ratio of 0.67 (95% CI, 0.14–3.27).

Alexander et al. (2003) studied mortality in a cohort of 2083 production workers (145 deaths) who were exposed to PFOS at a plant in Decatur, Alabama, USA, that produced speciality films and fluorochemicals, and who had worked ≥ 1 year at the plant between 1961 and 1997 (Section 2.1.2). On the basis of only 2 deaths from biliary and liver cancer, these authors estimated an SMR for the entire cohort (using an Alabama referent) of 1.61 (95% CI, 0.20–5.82).

Steenland and Woskie (2012) studied mortality from liver and gall bladder cancer among 5791 workers exposed to PFOA at a polymer-production plant in Parkersburg, West Virginia, USA (Section 2.1.3). Compared with non-exposed workers at other plants within the same company, the authors found an SMR of 1.07 (95% CI, 0.51–1.96) based on 10 deaths from liver and gall bladder cancer. By quartile of estimated cumulative exposure, SMRs were 2.39 (95% CI, 0.65–6.13; 4 deaths), 0 (95% CI, 0–1.81; 0 deaths;), 2.01 (95% CI, 0.65–4.68; 5 deaths), and 0.32 (95% CI, 0.01–1.76; 1 death).

[The Working Group noted that, for all these occupational cohort mortality studies (Alexander et al., 2003; Steenland and Woskie, 2012; Raleigh et al., 2014), the numbers of deaths from liver cancer were too small to be informative.]

Eriksen et al. (2009) conducted a case–cohort study (67 patients with liver cancer and 782 cancer-free participants selected randomly from the full cohort) in a general population national cohort of 57 053 people in Denmark. Analyses of liver cancer incidence were done using baseline-measured plasma levels of both PFOA and PFOS (Section 2.1.4). All participants had no previous diagnoses of cancer at the beginning of follow-up. Follow-up for cancer patients ranged from 0 to 12 years (median, 7 years). Analyses of IRRs for liver cancer by quartile of PFOA, using quartile 1 as referent, were 1.00 (95% CI, 0.44–2.23), 0.49 (95% CI, 0.22–1.09), and 0.60 (95% CI, 0.26–1.37), respectively, based on 17, 17, and 16 cases, respectively. Corresponding IRRs for PFOS were 0.62 (95% CI, 0.29–1.33), 0.72 (95% CI, 0.33–1.56), and 0.59 (95% CI, 0.27–1.27). [The Working Group noted that the number of cases was larger in the case–cohort study by Eriksen et al. (2009) (67 cases) compared with other studies reporting on liver cancer after PFOA or PFOS exposure; however, this study was limited to some degree by low exposure contrasts for both PFOA and PFOS.]

Barry et al. (2013) analysed liver cancer incidence in a cohort of 32 254 participants with both low and high exposure to PFOA from drinking-water (with high exposure being similar to the high levels in occupational cohorts), who were living near the Parkersburg polymer-production plant in West Virginia, USA (Section 2.1.5). The median PFOA level measured in all cohort members in 2005–2006 was 26 µg/L [ng/mL], and the mean was 87 µg/L [ng/mL] (whereas in the USA the general population levels were about 4 µg/L [ng/mL] at the time). Approximately 12% of participants in this study had worked in the Parkersburg plant that was the source of the PFOA contamination. Cancer incidence was determined via interview with confirmation from medical records, or by matching to Ohio and West Virginia cancer registries. Liver cancer hazard ratios per unit natural log-transformed cumulative serum level were 0.73 (95% CI, 0.43–1.23) and 0.74 (95% CI, 0.43–1.26), based on 9 cases, for unlagged and 10-year lagged estimates, respectively. [The Working Group noted

that the exposure–response analysis was based on a continuous variable, with serum levels over time estimated by a model with good correlation (ρ = 0.71) to observed serum levels, which were available in 2005 or 2006 for all cohort members. However, the number of deaths from or number of cases of incident liver cancer in Barry et al. (2014) (8 cases) was too small to draw conclusions.]

Consonni et al. (2013) conducted an international cohort mortality study of male workers at six TFE-production sites, who were concomitantly exposed to APFO (or equivalently PFOA) (Spearman correlation, 0.72). [The Working Group noted that the high correlation between TFE and PFOA exposure precluded evaluation of the effects of the individual compounds (Section 2.1.6). At two plants there was also possible exposure to vinyl chloride, a liver carcinogen, but no details were given.] Restricting the cohort to workers who ever had exposure to APFO, the authors reported an SMR for liver and bile duct cancer (versus national rates) of 1.43 (95% CI, 0.57–2.94), based on 7 deaths from liver cancer. The authors reported a trend with increasing cumulative APFO exposure that was estimated on the basis of a JEM, with liver cancer SMRs for low-, medium-, and high-exposure groups of 0.70 (95% CI, 0.02–3.87; 1 death), 1.25 (95% CI, 0.15–4.52; 2 deaths), and 2.14 (95% CI, 0.58–5.49; 4 deaths) (*P* for trend, 0.24).

Girardi and Merler (2019) studied mortality among industrial workers who were exposed to very high levels of PFOA and, to a somewhat lesser extent, PFOS (Section 2.1.9). In a subsample of 120 workers for whom 696 serum samples were available, the geometric mean concentration of PFOA was 4048 ng/mL (a geometric mean of 8862 ng/mL was found in the subgroup of PFOA operators), whereas for PFOS it was 148.8 ng/mL. SMRs and risk ratios for liver cancer mortality in exposed workers (7 deaths) versus the general population (SMR, 2.32; 95% CI, 1.11–4.87) and versus non-exposed workers at another plant (risk ratio, 6.69; 95% CI, 1.71–26.2) were elevated. Relative to non-exposed workers (3 deaths), liver cancer mortality increased by estimated cumulative serum levels of PFOA by tertile, with risk ratios of 3.07 (95% CI, 0.31–30.0; 1 death), 8.39 (95% CI, 1.40–50.3; 2 deaths), and 9.28 (95% CI, 2.07–41.5; 4 deaths), by tertile of increasing serum level. Death from liver cirrhosis was also markedly elevated, based on 6 deaths (SMR, 1.71; 95% CI, 0.77–3.81; and risk ratio, 3.87; 95% CI, 1.18–12.7), compared with the unexposed workers cohort. [The Working Group noted that the authors suggested that the excess of cirrhosis could be due to high exposure to PFOA, as PFOA is a liver toxin. The Working Group noted the excess of cirrhosis could be a sign of confounding by alcohol, which is also associated with liver cancer.]

[The Working Group also noted that the number of liver cancer deaths in the occupational cohort mortality study by Consonni et al. (2013) was too small to be informative. The study by Girardi and Merler (2019) also had only a small number of cases, making it less informative, but was notable for the strong exposure–response relation, with very high PFOA exposure, and good exposure estimation.]

Li et al. (2022a) studied liver cancer incidence in Ronneby, Sweden, in 60 507 residents. One third of households were exposed to relatively high levels of both PFOS and, to a lesser extent, PFOA from drinking-water contaminated by nearby military firefighting operations (based on a subset with serum levels, PFOS being the most elevated). The authors were unable to separate exposures to different PFAS, particularly PFOS and PFHxS (Section 2.1.13). In a sample of 3084 Ronneby residents and 226 non-Ronneby residents, the geometric means for the high-exposure group in Ronneby (n = 2052) were 199, 176, and 11 ng/mL for PFOS, PFHxS, and PFOA, respectively. For men who never resided in a high-exposure area, the SIR for liver cancer (area surrounding Ronneby used as a reference) was 1.12 (95% CI, 0.72–1.66; 24 cases), and for women

it was 0.98 (95% CI, 0.45–1.86; 9 cases). For men ever living in a high-exposure area, the SIR was 1.52 (95% CI, 0.70–2.89; 9 cases) and for women the corresponding estimate was 1.52 (95% CI, 0.41–3.88; 4 cases).

[The cohort study in Ronneby, Sweden, by Li et al. (2022a) had a larger number of cases (n = 25) compared with other studies reporting on liver cancer after PFOA or PFOS exposure, but a limitation was the ecological assignment of exposure on the basis of residence, and some uncertainty regarding the role of PFOS versus that of PFHxS, another PFAS that was present at high levels in the drinking-water.]

Goodrich et al. (2022) conducted a nested case–control study of PFOA and PFOS (baseline measurements), and HCC not of viral origin, in a large multiethnic cohort, with 50 cases and 50 controls (Section 2.1.16). Geometric mean concentrations of plasma PFOA and PFOS did not differ between cases and controls, and the use of continuous measures of PFOA and PFOS did not show any statistically significant positive associations with liver cancer. When restricting the definition of exposure to above the 85th percentile for PFOS (54.9 ng/mL, which corresponded to the 90th percentile in NHANES) and PFOA (8.6 ng/mL), exposure was associated markedly with liver cancer for PFOS (OR for PFOS, 4.50; 95% CI, 1.20–16.00), but not for PFOA (OR for PFOA, 1.20; 95% CI, 0.52–2.80), after adjusting for the matching variables of age, sex, race or ethnicity, and study site. However further adjustment for BMI lowered the OR for high PFOS (> 54.9 ng/mL) relative to low PFOS to 2.90 (95% CI, 0.78–10.00).

(b) Case–control studies

Vieira et al. (2013) conducted two case–control studies of incident liver cancer among residents of 13 counties in Ohio and West Virginia, USA, which included both contaminated and non-contaminated water districts near the same Parkersburg polymer-production plant in West Virginia that was the source of contamination in the population studied by Barry et al. (2013) (see Section 2.1.22). In the first case–control study, cases and controls (all other cancer cases excluding kidney, pancreatic, testicular, and liver cancers) obtained from both Ohio and West Virginia cancer registries were compared with regard to residence in a contaminated or non-contaminated water district. The liver cancer OR for exposed water district residents was 1.1 (95% CI, 0.7–1.6; 23 exposed cases) versus residents in non-contaminated water districts. These authors also conducted a separate case–control study among Ohio residents; cases were participants with liver cancer and controls were participants with other cancers in the Ohio counties, again excluding kidney, pancreatic, testicular, and liver cancers. Exposure in the second study was based on estimated individual serum levels of PFOA at specific addresses at specific points in time. The methods for estimating individual serum PFOA levels from linked environmental, exposure, and toxicokinetics models are described in detail elsewhere (Shin et al., 2011a). The environmental models integrated facility emissions data; fate, and transport characteristics of PFOA; addresses of cases and controls; and hydrogeological properties of the study area to estimate PFOA air and water concentrations from 1951 through 2008. Exposure was the estimated individual serum level 10 years before the diagnosis dates for cases and controls. Relative to non-contaminated water districts (50 cases), the ORs for those with low, medium, and high exposure 10 years before diagnosis were 1.1 (95% CI, 0.4–3.1; 4 cases), 0.9 (95% CI, 0.3–2.5; 4 cases), and 1.0 (95% CI, 0.3–3.1; 3 cases), respectively (there were no cases among those with very high exposure).

Cao et al. (2022) studied 203 cases of incident liver cancer compared with 203 hospital-based controls in a hospital in China during 2019–2021. [The Working Group noted that the study did not mention how controls were matched.] Serum PFOA and PFOS were measured in study

participants. [The Working Group noted that the timing of collection with respect to cancer diagnosis was not reported.] In cases and controls combined, the mean serum PFOS and PFOA concentrations were 9.8 ng/mL and 8.3 ng/mL, respectively. Log-transformed PFOS (a continuous variable) was associated with liver cancer (OR, 2.609; 95% CI, 1.179–4.029), after adjustment for covariates, but log-transformed PFOA was not (OR, 1.036; 95% CI, 1.002–1.070). [The Working Group considered that the base of log transformation of PFOS was 10; however, it was not specified in the manuscript.]

[The Working Group noted that the three case–control studies had large numbers of cases but suffered from other limitations. The study by Vieira et al. (2013), which included two different case–control studies, had a fairly large number of cases in the first study (179 cases, 23 exposed) but was limited by an ecological assignment of exposure. The second case–control study in Vieira et al. (2013) had fewer cases (61 cases, 11 exposed), with better assessment of estimated individual exposure levels, but was again limited by small numbers of exposed cases. The two other case–control studies by Goodrich et al. (2022) and Cao et al. (2022) showed some positive associations but had their own limitations. In the nested case–control study by Goodrich et al. (2022), positive findings for PFOS were observed only when baseline plasma concentrations were dichotomized between the top 15% and the bottom 85% and were diminished after control for BMI. In the other case–control study by Cao et al. (2022), serum levels were available only at time of diagnosis, making etiological inference difficult.]

(c) Meta-analysis

Seyyedsalehi and Boffetta (2023) published a meta-analysis of liver cancer in relation to PFAS that included all the studies cited in the present monograph as well as two ecological studies judged to be not informative, and one other that was a predecessor of the study by Steenland and Woskie (2012) cited here [for those reasons, the Working Group did not considered this meta-analysis to be informative].

2.5.2 Pancreatic cancer

See Table S2.5 (Annex 4, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.who.int/636).

A total of nine studies investigating the association between PFAS (mainly PFOA) and cancer of the pancreas are presented below according to three different types of population: three studies among workers in chemical plants producing or using PFOA (Steenland and Woskie, 2012; Consonni et al., 2013; Raleigh et al., 2014), three from communities surrounding a plant from which there had been environmental release of PFOA and contamination of public and private water supplies (Barry et al., 2013; Vieira et al., 2013; Li et al., 2022a), and three from studies in the general population with background exposures (Eriksen et al., 2009; Winquist et al., 2023; Zhang et al., 2023).

Raleigh et al. (2014) investigated mortality and cancer incidence among APFO-production workers ($n = 4668$) compared with tape and abrasives production workers ($n = 4359$) in two manufacturing facilities owned by the same company in Minnesota, USA, between 1947 and 2002 (see Section 2.1.1). Hazard ratios for mortality using the unexposed workers as the referent were calculated for quartile-based categories of PFOA exposure created using a task-based JEM; the hazard ratios were 0.32 (95% CI, 0.08–1.35), 0.89 (95% CI, 0.34–2.31), 0.82 (95% CI, 0.32–2.12), and 1.23 (95% CI, 0.50–3.00) on the basis of 18 deaths from pancreatic cancer observed in all the exposed categories. Hazard ratios for incidence in exposed workers compared with unexposed workers were 0.13 (95% CI, 0.02–1.03; 1 case) for quartiles 1 and 2 combined and 1.36 (95% CI,

0.59–3.11; 9 cases) for the upper two quartiles combined (Raleigh et al., 2014).

Steenland and Woskie (2012) studied mortality among 5791 workers employed for ≥ 1 day at a polymer-production plant in Parkersburg, West Virginia, USA, between 1948 and 2002 (see Section 2.1.3). For exposed workers compared with other non-exposed workers at other plants within the same company and region, SMRs calculated for pancreatic cancer by quartile of cumulative serum PFOA level (estimated using a JEM) were 1.18 (95% CI, 0.32–3.03; 4 cases), 1.02 (95% CI, 0.28–2.61; 4 cases), 1.09 (95% CI, 0.35–2.54; 5 cases), and 0.92 (95% CI, 0.30–2.16; 5 cases) from the lowest to the highest quartile categories, respectively.

[Both of these occupational cohort studies (Steenland and Woskie, 2012; Raleigh et al., 2014) had the advantage of the ability to evaluate associations with PFOA in a population exposed to levels much higher than those in the general population; however, a major limitation for both was the small number of observed cases.]

Eriksen et al. (2009) conducted a case–cohort study within a prospective cohort of men and women from the general population in Denmark. Eligible participants were aged 50–65 years at enrolment. The investigators measured PFOA and PFOS concentrations in plasma samples collected before cancer diagnosis (Section 2.1.4). IRRs were calculated on the basis of 128 cases of pancreatic cancer and 772 subcohort participants and were adjusted for age, sex, smoking status, smoking intensity, smoking duration, dietary fat intake, and fruit and vegetable intake. IRRs for pancreatic cancer were 1.55 (95% CI, 0.85–2.80) and 0.91 (95% CI, 0.51–1.65) in the highest quartiles of plasma PFOA and PFOS concentration, respectively, compared with the lowest quartile. The IRR per increase in PFOA of 1 ng/mL was 1.03 (95% CI, 0.98–1.10) and that per increase in PFOS of 10 ng/mL was 0.99 (95% CI, 0.86–1.14). [The strengths of this study included a relatively large number of cases and adjustment for potential confounders such as smoking. Because the PFOA and PFOS measurements were from samples collected before diagnosis, concentrations were less likely to be influenced by the presence of cancer. However, a single measurement at enrolment may not reflect exposure at crucial windows in cancer development. Since the study was carried out among the general population with background exposure levels, exposure contrasts might be too small to detect an association.]

Within communities surrounding a plant from which there had been environmental release of PFOA and contamination of public and private water supplies, the C8 Science Panel (Section 2.1.5) conducted a cohort study of a total of 32 254 community residents and workers exposed to PFOA from a fluoropolymer-production plant in the Mid-Ohio Valley on the border of West Virginia and Ohio, USA (Barry et al., 2013). For community participants, annual estimates of cumulative serum PFOA concentrations were estimated from 1952 to 2011 using a model by Shin et al. (2011a, b). For the workers, estimates of occupational PFOA exposure were calculated as described in Woskie et al. (2012) and were combined with estimates of environmental exposure. Self-reported cancer according to the surveys administered in 2008–2011 was verified through medical records and cancer registry review. The hazard ratio per unit of natural log-transformed estimated cumulative PFOA serum concentration was 1.00 (95% CI, 0.78–1.29; 24 cases) after adjustment for time-varying smoking, time-varying alcohol consumption, sex, education, birth year (5-year calendar intervals), and age. [The strengths of this study included its use of individual-level exposure modelling using lifetime residential history, the validation of the exposure modelling, the wide range of PFOA exposure levels, and control for potential confounders such as smoking. The main limitation was the small number of cases of incident pancreatic cancer.

In addition, community members and workers who died before enrolment would not have been included, owing to the design of the study as a survivor cohort. This might lead to the potential underascertainment of cancers with a high fatality rate in this population. However, given that PFOA exposure was considered unlikely to be related to survival time, the impact of this aspect of the study design on the resulting risk estimates was likely to be minimal (Barry et al., 2015).]

Consonni et al. (2013) conducted a mortality study in the pooled international TFE cohort that included 5879 male workers who were ever employed or employed for a minimum of 6 or 12 months at one or more of six TFE-production sites in North America and Europe between 1950 and 2002 (see Section 2.1.6). Causes of death were ascertained from 1950 through 2008. Semiquantitative levels of work-related exposure to TFE and APFO were assessed by a plant- and job-specific exposure matrix with yearly estimates (in arbitrary units) of exposure from the start of TFE production until the end of 2002. Among the subset of workers who had ever been exposed to APFO (n = 4205), the SMR using national rates as a referent was 1.05 (95% CI, 0.51–1.94; 10 deaths). In addition, the SMRs for groups with low, medium, and high cumulative APFO exposure were 0 (0 deaths), 1.30 (95% CI, 0.35–3.33, 4 deaths), and 1.84 (95% CI, 0.67–4.00, 6 deaths), respectively (P for trend, 0.34). [Consonni et al. (2013) studied work-related exposure to TFE and/or APFO, and high correlations were observed between exposure to TFE monomer (IARC Group 2A; IARC, 2016) and PFOA, which precludes evaluation of effects of the individual compounds. This study observed fewer than 20 cases, and the small number was a major limitation.]

The Ronneby Register cohort (see Section 2.1.13 for details) comprised 60 507 individuals who had ever lived in the Ronneby municipality during the period when drinking-water was contaminated with a mixture of PFAS, mainly PFOS, PFHxS, and PFOA (1985–2013) (Li et al., 2022a). Cancer incidence data were obtained through linkage to the Swedish Cancer Register (1985–2016). SIRs for incident pancreatic cancer among residents who had ever lived in a highly exposed area were 0.46 (95% CI, 0.17–1.01; 6 cases) for men and 0.81 (95% CI, 0.39–1.50; 10 cases) for women, using the regional external population as the referent. Groups of residents who had ever lived in the contaminated area were subdivided by the number of years living at an ever-high area, and calendar year-, age-, and sex-adjusted hazard ratios compared the ever-high group to the never-high group comprising residents who had never lived in the contaminated area. Hazard ratios for this internal comparison were below unity. [The strengths of this study included the large general population sample with complete ascertainment and follow-up, owing to high-quality Swedish population registers with complete population coverage, and a strong documented exposure contrast. The limitations of this study were the mixed exposure profile without the possibility to single out effects caused by specific compounds, the small number of cases, and the lack of information on important confounders such as smoking. Additionally, SIRs from the external comparisons might be viewed as ecological comparisons.]

Zhang et al. (2023) conducted two independent nested case–control studies within the ATBC Cancer Prevention Study and the PLCO Cancer Screening Trial (Sections 2.1.11 and 2.1.19). Prediagnostic serum samples were measured for relative levels of PFOA and PFOS among 251 matched pairs from ATBC comprising male smokers aged 50–69 years at baseline (1985–1988) in Finland who were followed until December 2011, and 360 matched pairs from PLCO comprising men and women, mostly non-smokers, aged 55–74 years at baseline (1993–2001) in the USA who were followed until 15 May 2010. ORs for pancreatic ductal

adenocarcinoma were adjusted for age and date at blood draw, smoking, diabetes, and BMI. ORs were 2.37 (95% CI, 1.24–4.51) and 1.82 (95% CI, 0.82–4.03) in the highest quintiles of serum PFOA and PFOS concentrations, respectively, compared with the lowest quintile in ATBC. The ORs per SD increase were 1.27 (95% CI, 1.04–1.56) and 1.13 (95% CI, 0.88–1.45) for PFOA and PFOS, respectively. For PLCO, the ORs per SD increase were below unity for both PFOA and PFOS. ORs for only men who had ever smoked or were still in the habit of smoking were lower than those for all participants. [The strengths of this study included prediagnostic serum samples, the relatively large number of cases, and adjustment for potential confounders such as smoking. The limitations of this study included low-level exposure with a small exposure contrast. The Working Group noted that there was unexplained inconsistency between the results for the ATBC and the PLCO for male smokers only.]

Winquist et al. (2023) conducted a case–cohort study within the ACS CPS-II LifeLink Cohort (Section 2.1.21). Prediagnostic serum samples were collected during 1998–2001, and participants (median age, 70 years) were followed for cancer incidence until June 2015. Serum concentrations of PFAS were measured for 172 cases of pancreatic cancer and 999 subcohort participants, and hazard ratios were calculated with adjustment for age and year at blood draw, education, race or ethnicity, smoking, and alcohol use. Hazard ratios (95% CI) for pancreatic cancer per concentration doubling were 0.94 (95% CI, 0.74–1.21) and 0.87 (95% CI, 0.70–1.10) for PFOA and PFOS, respectively. In sex-specific analyses, hazard ratios per PFOA doubling were 0.71 (95% CI, 0.52–0.96) and 1.14 (95% CI, 0.78–1.67) for men and women, respectively, although similar hazard ratios for both sexes were observed for PFOS. [The strengths of this study included prediagnostic serum samples, the relatively large number of cases, and adjustment for potential confounders such as smoking. The study limitations included low-level exposure with a small exposure contrast. In addition, because of its design as a survivor cohort, this study would not have included some people who may have had PFOA- or PFOS-related cancer, especially those who developed cancers earlier in life in a susceptible exposed population. This survivor bias would have biased the results downwards (i.e. towards the null or even towards inverse associations).]

Vieira et al. (2013) conducted two case–control studies of 18 different incident cancers during the years 1996–2005 among residents of 13 counties in Ohio and West Virginia, USA, including both contaminated and non-contaminated water districts near the same polymer-production plant in Parkersburg, West Virginia, USA, that was the source of contamination in the population studied by Barry et al. (2013) (see Section 2.1.22). In the first case–control study, cases and controls (all other cancer cases excluding cancers of the kidney, liver, pancreas, and testis) were compared with regard to residence in a contaminated or non-contaminated water district. The OR for pancreatic cancer was 1.0 (95% CI, 0.8–1.3; 58 exposed cases) after adjustment for age, sex, diagnosis year, insurance provider, and smoking status. In the second case–control study, restricted to the Ohio data because of availability of geocoded street addresses, serum PFOA concentrations were estimated by environmental, exposure, and toxicokinetics models designed by Shin et al. (2011a, b). The ORs for pancreatic cancer in the low, medium, high, and very high exposure categories compared with the unexposed, calculated after adjustment for age, race, sex, diagnosis year, insurance provider, and smoking status, were 1.3 (95% CI, 0.7–2.3; 12 exposed cases), 0.9 (95% CI, 0.5–1.7; 10 exposed cases), 1.1 (95% CI, 0.6–2.3; 9 exposed cases), and 0.6 (95% CI, 0.1–2.5; 2 exposed cases), respectively. [The Working Group noted that the studies by Barry et al. (2013) and Vieira et al. (2013) were overlapping rather than independent studies in

that the same geographical areas and some of the same cases were included in both analyses, although the extent of overlap was unknown. The strengths of this study were the large number of incident cancers from cancer registries and the reasonably large number of exposed cases in the contaminated water districts. The second case–control study based in Ohio benefited from being able to estimate serum levels for individuals on the basis of a validated model. The limitations were the assignment of an ecological exposure (by water district) in the first case–control study and the somewhat arbitrary assumption in the second case–control study that the estimated serum levels 10 years before case diagnosis were the most relevant, as well as the assumption that cases and controls had remained in the same residence for 10 years. Additionally, the control group included cases of other cancers (bladder, brain, female breast, cervix, leukaemia, lung, melanoma, multiple myeloma, NHL, ovary, prostate, thyroid, and uterus), which may not be representative of the source population because of differences in lifestyle and socioeconomic status among cancer cases. In particular, it might bias estimates towards the null, if any of the included cancers were in fact associated with PFOA. Otherwise, the Working Group considered these potential differences in confounders to be unlikely to have substantive effects in this population with a very high exposure.]

2.5.3 Colorectal cancer and other cancers of the digestive tract (other than liver and pancreas)

See Table S2.5 (Annex 4, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.who.int/636).

Five occupational cohort studies (Alexander et al., 2003; Leonard et al., 2008; Lundin et al., 2009; Consonni et al., 2013; Steenland et al., 2015; Girardi and Merler, 2019) and three studies from communities surrounding a plant from which there had been environmental release of PFOA and contamination of public and private water supplies (Barry et al., 2013; Vieira et al., 2013; Li et al., 2022a) investigated the association between PFOA or PFOS (or both) and cancers of the colorectum and other digestive organs (oesophagus and stomach).

Olsen et al. (2004) studied workers at two manufacturing plants between 1993 and 1998 in Decatur, Alabama, USA. "Episode of care" was identified using health claim data between 1993 and 1998 and was compared between 652 workers at a fluorochemical-production plant (exposed group) and 659 workers at a film plant (non-exposed group). [Episode of care is not a definitive measure of risk because it could include cases of incident cancer, prevalent cancer, and tentatively diagnosed cancer. Mortality in the same company was reported in a study by Alexander et al. (2003) included in the present monograph. Therefore, the study by Olsen et al. (2004) was judged to be uninformative.]

Innes et al. (2014) conducted a cross-sectional study to examine the association between serum concentrations of PFOA and PFOS and self-reported colorectal cancer diagnosis, verified by chart review for 47 359 participants in a comprehensive health survey between 2005 and 2006 by the C8 Health Study Project. [Since the participants in this study overlapped with those in a cohort study by Barry et al. (2013), and since prevalent cases were used as the case group and the serum concentrations of these participants were influenced by the presence and/or treatment of cancer, the study was judged to be uninformative.]

Among the occupational cohort studies was a study by Lundin et al. (2009) of mortality among of 3993 workers at an APFO-production plant in Cottage Grove, Minnesota, USA, between 1947 and 1997, with follow-up until 2002 (see Section 2.1.1). Using rates for the state of Minnesota as a referent, SMRs were calculated

according to classification of jobs by exposure to APFO. For colon cancer, SMRs for "never", "ever probable/never definite", and "ever definite" exposure groups were 1.30 (95% CI, 0.75–2.12; 16 deaths), 0.88 (95% CI, 0.42–1.62; 10 deaths), and 1.07 (95% CI, 0.13–3.86; 2 deaths), respectively. For rectal cancer, SMRs for "never" and "ever probable/never definite" exposure groups were 0.40 (95% CI, 0.01–2.22; 1 death) and 1.28 (95% CI, 0.26–3.76; 3 deaths), respectively (0 deaths in the "ever definite" category). For oesophageal cancer, SMRs for "never", "ever probable/never definite", and "ever definite" exposure groups were 0.59 (95% CI, 0.07–2.13; 2 deaths), 0.31 (95% CI, 0.01–1.70; 1 death), and 1.54 (95% CI, 0.04–8.57; 1 death), respectively. For stomach cancer, SMRs for "never" and "ever probable/never definite" exposure groups were 0.74 (95% CI, 0.15–2.15; 3 deaths) and 1.06 (95% CI, 0.29–2.71; 4 deaths), respectively (0 deaths in the "ever definite" category).

Alexander et al. (2003) studied the mortality of a cohort of 2083 production workers who were exposed to PFOS at a plant in Decatur, Alabama, USA, that produced speciality films and fluorochemicals, and who had worked for ≥ 1 year at the plant between 1961 and 1997 (Section 2.1.2). Using rates for the state of Alabama as referent, SMRs for all cohort members were 0.30 (95% CI, 0.01–1.66; 1 death) for colon cancer and 1.76 (95% CI, 0.21–6.35; 2 deaths) for oesophageal cancer. In addition, the SMR for cohort members ever employed in a low-exposure job, but never a high-exposure job, was 1.43 (95% CI, 0.04–7.94; 1 death) for colon cancer.

Leonard et al. (2008) investigated mortality among 6027 workers exposed to PFOA at a polymer-production plant in Parkersburg, West Virginia, USA (see Section 2.1.3). Eligible workers were employed at the plant for ≥ 1 day between 1948 and 2002 and were followed for mortality from 1948 to 2002. SMRs were computed in comparison to the US population, the West Virginia state population, and an eight-state regional employee population from the same company on the basis of 17 deaths from colon cancer, 5 from rectal cancer, 4 from oesophageal cancer, and 3 from stomach cancer. SMRs estimated using three different reference populations were less than unity except for that for rectal cancer using the reference population of workers from the other regional facilities within the same company (SMR, [1.321]; 95% CI, [0.429–3.082]). Steenland and Woskie (2012) reported an extension of this study by an additional 6 years of follow-up and comprehensive quantitative exposure assessment. Steenland et al. (2015) conducted an incidence study of a subset of the PFOA-exposed workers (n = 3713) in Steenland and Woskie (2012). Rate ratios for quartiles of cumulative serum PFOA level estimated by JEM were calculated by adjusting for age, year of birth, sex, race, education, BMI, and time-varying smoking and alcohol consumption. Compared with those in the lowest quartile, the rate ratios in the second, third, and highest quartiles were 0.58 (95% CI, 0.18–1.87), 1.43 (95% CI, 0.49–4.19), and 1.20 (95% CI, 0.39–3.62), respectively, on the basis of 41 cases of incident colorectal cancer (P for trend, 0.68).

The C8 Health Study (Section 2.1.5) included a total of 32 254 community residents and workers exposed to PFOA from a polymer-production plant in the Mid-Ohio Valley, USA (Barry et al., 2013). Cumulative serum PFOA concentrations were estimated for community residents and workers, taking into account community and occupational exposure, and cancer diagnosis was assessed through self-reported questionnaire and validation through medical-record review and cancer registry data (Barry et al., 2013). Hazard ratios per unit natural log-transformed estimated cumulative PFOA serum concentration were 0.99 (95% CI, 0.92–1.07; 264 cases) for incident colorectal cancer, 0.96 (95% CI, 0.70–1.32; 15 cases) for incident oesophageal cancer, and 0.72 (95% CI, 0.45–1.14; 12 cases) for incident stomach cancer, after adjustment

for time-varying smoking, time-varying alcohol consumption, sex, education, birth year (5-year calendar intervals), and age.

In the pooled international TFE cohort study, follow-up was conducted for mortality (1950–2008) of 5879 male workers who were ever employed or employed for a minimum of 6 or 12 months at one of six TFE-production sites in North America and Europe between 1950 and 2002 (Section 2.1.6). Among the subset of workers who had ever been exposed to APFO (n = 4205), the SMR using national rates as the referent was 1.44 (95% CI, 0.72–2.57) for cancer of the oesophagus, whereas SMRs for cancers of the stomach, colon, and rectum were below or around unity (Consonni et al., 2013). In addition, SMRs for oesophageal cancer for groups of low, medium, and high cumulative APFO exposure were 1.62 (95% CI, 0.44–4.14; 4 deaths), 1.54 (95% CI, 0.42–3.93; 4 deaths), and 1.16 (95% CI, 0.24–3.39; 3 deaths) (P for trend, 0.60).

Girardi and Merler (2019) reported on mortality among 462 male employees who had worked for ≥ 6 months before 2009 at a factory manufacturing PFOA, PFOS, and other chemicals in Trissino, Veneto, Italy (Section 2.1.9). They were followed for mortality from 1970 to 2018. SMRs were calculated in comparison with the regional mortality rates, and mortality risk ratios were estimated by a Poisson regression model using rates from non-exposed workers in other plants. For colon cancer, the SMR was 1.72 (95% CI, 0.72–4.14) and the mortality risk ratio was 2.84 (95% CI, 0.74–10.9), based on 5 deaths; for oesophageal cancer, the SMR was 2.31 (95% CI, 0.68–6.50) and the mortality risk ratio was 3.62 (95% CI, 0.59–22.3), based on 3 deaths; and for stomach cancer, the SMR was 1.30 (95% CI, 0.42–4.02) and the mortality risk ratio was 2.43 (95% CI, 0.54–10.9), based on 3 cases.

[The strengths of the incidence study by Steenland et al. (2015) included use of estimated average annual serum PFOA concentrations and adjustment for several potential confounders such as smoking, alcohol drinking, and BMI. In contrast, the five occupational cohort studies of cancer mortality (Alexander et al., 2003; Leonard et al., 2008; Lundin et al., 2009; Consonni et al., 2013; Girardi and Merler, 2019) included small numbers of deaths (fewer than 17) and lack of adjustment for important confounders such as smoking, alcohol drinking, and BMI. The strengths of the study by Barry et al. (2013) included a relatively large number of cases of colorectal cancer and control for potential confounders such as smoking, but the small number of cases of oesophageal and stomach cancer was a limitation of this study. In addition, Consonni et al. (2013) studied work-related exposure to TFE and APFO and noted high correlations between exposure to TFE monomer (IARC Group 2A, IARC, 2016) and PFOA, which precluded evaluation of the effects of the individual compounds.]

The Ronneby Register cohort (Section 2.1.13) comprised 60 507 individuals who had ever lived in the Ronneby municipality during a period when drinking-water was contaminated with a mixture of PFAS, mainly PFOS, PFHxS, and PFOA (1985–2013), and incidence data were linked to Swedish Cancer Register (1985–2016) (Li et al., 2022a). Using the regional external population as the referent, SIRs for rectal cancer among residents who had ever lived in the contaminated area were 1.25 (95% CI, 0.89–1.69; 41 cases) for men and 1.33 (95% CI, 0.91–1.88; 32 cases) for women. SIRs for stomach cancer were 1.10 (95% CI, 0.70–1.64; 24 cases) for men and 1.03 (95% CI, 0.55–1.76; 13 cases) for women. For colon and oesophageal cancer, SIRs were below or around unity for both men and women. The group of residents who had ever lived in the contaminated area was subdivided by the number of years living at an ever-high area, and calendar year-, age-, and sex-adjusted hazard ratios were calculated, comparing the ever-high group with the never-high group of residents who had never lived in the contaminated area. Hazard ratios for

the ever-high group were 1.25 (95% CI, 0.95–1.64) for rectal cancer and 1.14 (95% CI, 0.79–1.66) for stomach cancer. In addition, hazard ratios for short-high (1–10 years) and long-high (≥ 11 years) exposure were 1.16 (95% CI, 0.80–1.69) and 1.34 (95% CI, 0.94–1.90) for rectal cancer, respectively, and 0.86 (95% CI, 0.51–1.46) and 1.56 (95% CI, 0.95–2.55) for stomach cancer, respectively. [The strengths of this study included the large general population sample with complete ascertainment and follow-up, owing to the high-quality Swedish population registers with complete population coverage, and the strong documented exposure contrast. The study limitations were the mixed exposure profile without the possibility to single out effects caused by specific compounds, the small numbers of cases, and the lack of information on important confounders such as smoking, alcohol drinking, and BMI. Additionally, SIRs from the external comparisons might be viewed as ecological comparisons.]

Vieira et al. (2013) conducted two case–control studies among residents of 13 counties in Ohio and West Virginia, USA (Section 2.1.22). In the first case–control study, after adjustment for age, sex, diagnosis year, smoking status, and insurance provider, the odds ratio for colorectal cancer was 0.9 (95% CI, 0.8–1.0; 383 exposed cases). In the second case–control study, restricted to the Ohio data, and after adjustment for age, race, sex, diagnosis year, smoking status, and insurance provider, ORs for colorectal cancer for the categories with low, medium, high, and very high exposure compared with the unexposed were 1.0 (95% CI, 0.8–1.3; 72 exposed cases), 0.9 (95% CI, 0.7–1.2; 64 exposed cases), 1.3 (95% CI, 1.0–1.7; 63 exposed cases), and 0.6 (95% CI, 0.3–1.0; 13 exposed cases), respectively. [The strengths of the study by Vieira et al. (2013) also included the large number of incident colon cancers from cancer registries and the reasonably large number of exposed cases in the contaminated water districts.]

2.6 Cancers of the brain and lymphatic and haematopoietic tissue

2.6.1 Cancers of the eye and brain, and other cancers of the nervous system

See Table S2.6 (Annex 4, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.who.int/636).

The Working Group identified four cohort studies and two case–control studies investigating the risk of brain cancer associated with PFOA or PFOS exposure. Two of the cohort studies included occupational cohorts (Lundin et al., 2009; Consonni et al., 2013), one of the cohort studies included the C8 Health Project cohort (Barry et al., 2013), and one of the cohort studies included the Ronneby Register cohort (Li et al., 2022a). The case–control studies were population-based (Vieira et al., 2013). In addition, the Working Group reviewed one case–control study on retinoblastoma (Chen et al., 2024).

(a) Cohort studies

A cohort study was conducted on mortality among 3993 employees of an APFO-manufacturing facility located in Cottage Grove, Minnesota, USA (Lundin et al., 2009) (see Section 2.1.1). During the follow-up until 2002, 807 decedents were identified. Using the rates for the state of Minnesota as the referent, SMRs were calculated for different jobs classified by exposure to APFO (the ammonium salt of PFOA). Only 7 deaths were observed for cancer of the central nervous system, with 5 deaths assigned to the "ever probable/never definite" exposure group and 2 deaths assigned to the "never" exposure group. The SMRs for the "ever probable/never definite" exposure group and the "never" exposure group were 1.16 (95% CI, 0.37–2.70) and 0.44 (95% CI, 0.05–1.59), respectively. [The Working Group noted that the significant limitations of

the study included the small occupational cohort with a limited number of deaths and the crude exposure assessment by job classification, which made this study uninformative for cancers of the central nervous system.]

Barry et al. (2013) focused on PFOA exposure and incident cancers among community residents and workers exposed to PFOA from a chemical plant, using the C8 Health Project cohort in combination with the cohort of workers from the polymer-production plant in Parkersburg, West Virginia, USA (see Section 2.1.5). The study population comprised 28 541 community members and 3713 workers, with 32 254 participants in the entire cohort. Cancer cases were captured by self-report by the participant and confirmed by medical chart review or state cancer registry matching in Ohio and West Virginia. The number of reported cases of primary brain cancer was 33. The analysis included 17 cases of validated primary brain cancer for whom there was complete covariate information. The authors calculated cumulative PFOA serum concentration estimates for each community participant on the basis of regional historical data. For participants who had ever worked in the polymer-production plant in Parkersburg, a JEM was applied to estimate occupational exposure levels and combined with estimated serum levels from residential exposure to contaminated drinking-water. A proportional hazards regression model was applied in a stratified analysis adjusting for age, time-varying smoking, time-varying alcohol consumption, sex, education, and birth year. Risk estimates based upon models in which exposure was unlagged or lagged 10 years were similar. The hazard ratios for a 1-unit increase in natural log-transformed cumulative exposure in relation to brain cancer were 1.13 (95% CI, 0.84–1.51) for unlagged exposure and 1.06 (95% CI, 0.79–1.41) for exposure lagged by 10 years in the whole cohort. For community residents, increased exposure to PFOA was associated with a slightly increased risk of brain cancer (HR, 1.14; 95% CI, 0.78–1.65; 13 cases), whereas for the workers, there was no clear evidence of a trend in risk of brain cancer (HR, 0.82; 95% CI, 0.26–2.59; 4 cases). [The Working Group noted as strengths the large cohort, strong exposure contrast, assessment of individual cumulative PFOA exposure, and lagged analyses. Limitations included the self-reported cancer cases, no evaluation of co-exposure to other PFAS in residents, and wide confidence intervals in the estimate for occupational workers.]

The association between occupational exposure to PFOA and mortality from brain cancer was investigated in the pooled international TFE worker cohort, in which data were pooled from workers from one or more of six TFE-production sites in North America and Europe (Consonni et al., 2013) (see Section 2.1.6). The epidemiology departments or the local health unit performed ascertainment of vital status and cause of death through record linkage or individual follow-up procedures. Exposure assessment was performed by a personal semiquantitative estimate using a JEM. There were 4 cases of brain cancer among 4205 men who had ever been exposed to PFOA, and the SMR for brain cancer associated with exposure to PFOA was 0.64 (95% CI, 0.17–1.63), using national rates as the referent. [The Working Group noted as strengths the inclusion of all TFE-production sites worldwide, and the complete enrolment and follow-up data. Limitations included the high correlations between TFE and PFOA exposure and the small number of cases of brain cancer observed, which limited the informativeness of this study.]

Li et al. (2022a) investigated cancer incidence in the Ronneby Register cohort, a community of residents with high-level environmental exposure to a mixture of PFAS, in Sweden. By the end of the follow-up (31 December 2016), the study had identified 150 cases of incident brain cancer (80 men and 70 women) (see Section 2.1.13). All information on brain cancer diagnosis was

obtained from the nationwide Swedish Cancer Register. To facilitate comparison, Ronneby residents were assigned to mutually exclusive groups, "never-high" and "ever-high", based on whether they were exposed to PFAS-contaminated water at their residence. When comparing the study population to the general population of Blekinge County excluding Ronneby, the incidence of brain cancer was increased in the "ever-high" group among men (SIR, 1.29; 95% CI, 0.83–1.93) but decreased in the "never-high" group among women (SIR, 0.73; 95% CI, 0.55–0.96). In internal comparisons, the "ever-high" group was further subdivided by the time period of high exposure ("early-high" in 2004 or earlier, "late-high" in 2005 or later) and duration of time in a high-exposure area ("short-high" for ≤ 10 years, and "long-high" for ≥ 11 years). Hazard ratios for early-high and late-high were 1.20 (95% CI, 0.78–1.84) and 1.31 (95% CI, 0.76–2.26), respectively, and those for short-high and long-high were 1.06 (95% CI, 0.66–1.69) and 1.50 (95% CI, 0.92–2.44), respectively. [The Working Group noted as strengths the large study population, strong exposure contrast, and unbiased inclusion. The main limitations included the small number of cases, the crude exposure assessment (not including individual water intake or other sources of exposure than drinking-water), the mixed exposure profile, and the limited information on potential confounders such as smoking habits, BMI, and occupational exposure.]

(b) Case–control study

A case–control study was conducted using cancer registry data for residents of counties in Ohio and West Virginia surrounding the polymer-production plant in Parkersburg, West Virginia, USA, from which PFOA had been emitted into drinking-water sources (Vieira et al., 2013) (see Section 2.1.22). The study included incident cancer cases drawn from registry data from 1996 through 2005. Controls comprised all other cancers in the study data set, except cancers of the kidney, pancreas, testis, and liver. There were 506 cases of brain cancer in the final data set, of which 150 came from Ohio. All people with a cancer diagnosis were classified as exposed (living within a contaminated water district) or unexposed (not living in contaminated water districts) using geocoding. The AORs varied among the water districts exposed to contaminated water, with the AOR for the overall exposure risk being 1.0 (95% CI, 0.8–1.3). In a second case–control study, the authors restricted the analysis to Ohio participants for whom annual PFOA serum concentrations could be estimated on the basis of an existing PFOA exposure prediction model. Individual-level annual exposure was categorized as very high, high, medium, low, and unexposed. Using the unexposed group as the reference category, the AORs for high, medium, and low individual-level exposures were 0.6 (95% CI, 0.2–1.6), 1.8 (95% CI, 1.1–3.2), and 1.5 (95% CI, 0.8–2.7), respectively. No cases of brain cancer occurred in the group with very high exposure. Findings were similar in various sensitivity analyses (e.g. using cumulative PFOA serum exposure instead of annual exposure; using exposure level for exposure estimates that did not account for latency; including cases of kidney, liver, pancreatic, and testicular cancer in the control group). [The Working Group noted that the strengths of the study included its focus on a population with high PFOA exposure, the strong contrast in exposure levels, and the estimation of individual-level exposure for a subset of the population. Limitations included the use of other cancers as the reference group and the potential for exposure misclassification (reliance on the address at the time of diagnosis rather than a complete residential history in analyses among Ohio participants). However, both these limitations would be expected to have resulted in a bias towards the null.]

A population-based case–control study was conducted that included 501 children aged < 5 years with a diagnosis of retinoblastoma

between 1983 and 2013 identified and randomly selected from the California Cancer Registry (Chen et al., 2024). Controls (n = 899) were selected from California birth rolls and frequency-matched to cases on year of birth. For cases and controls, neonatal dry blood samples were available, collected from the newborn heel-stick test, which is done 12–48 hours after birth for neonatal genetic screening. This sampling is a routine procedure, for > 99% of all neonates in California, and samples are stored by the California Newborn Screening Program for genetic disease. The blood spot was used for quantification of PFOA, PFOS, and PFNA. Outliers for PFAS measurement identified through a principal component analysis were excluded (n = 10), leaving a total of 497 cases and 893 controls for the analysis. Children with a PFOA concentration above the mean, compared with those with a concentration below the mean, had a higher risk of retinoblastoma (OR, 1.16; 95% CI, 0.90–1.50), particularly so for those born from US-born mothers (OR, 1.41; 95% CI, 1.00–2.02). Children with a neonatal heel-stick PFOS concentration of above the mean, compared with those with a concentration of below the mean, had a 29% higher risk of retinoblastoma (OR, 1.29; 95% CI, 1.00–1.67), with risk being elevated in both US-born and Mexico-born mothers. When restricting to unilateral retinoblastoma cases, the OR for a PFOS concentration of above the mean versus below the mean was 1.42 (95% CI, 1.03–1.97), whereas for bilateral retinoblastoma cases the OR was 1.14 (95% CI, 0.82–1.62). [The Working Group noted the limited sample size for the stratified analysis by mother's birthplace. The population-based design and the use of prediagnostic samples collected for medical reasons unrelated to the case status was a strength of this study, since it minimized selection bias and provided a measurement of PFOA and PFOS exposure unrelated to diagnosis or treatment. Such measurements are probably representative of fetal exposure; however, uncertainty remained concerning the capture of the relevant window of exposure for cancer development. In addition, PFAS were measured by a semiquantitative non-targeted method, which limited comparability across studies.]

2.6.2 Cancers of lymphatic and haematopoietic tissue and other cancers

See Table S2.6 (Annex 4, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.who.int/636).

Five occupational cohort studies have investigated mortality for cancers of lymphatic and haematopoietic tissue, melanoma, lung, or mesothelioma (Alexander et al., 2003; Leonard et al., 2008; Lundin et al., 2009; with later follow-up of mortality for selected cancers by Steenland and Woskie, 2012; Consonni et al., 2013; Steenland et al., 2015, Girardi and Merler, 2019). Two cohort studies (Barry et al., 2013; Li et al., 2022a) and one case–control study (Vieira et al., 2013, partly overlapping with Barry et al., 2013) addressing highly exposed community residents have investigated the incidence of cancers of lymphatic and haematopoietic tissues and melanoma according to PFOA and/or PFOS exposure. A large US case–cohort study of the general population with low background exposure examined a range of cancers of lymphatic and haematopoietic tissue (Winquist et al., 2023). A small case–control study with cross-sectional sampling of exposure data by Lin et al. (2020) examined associations between germ cell tumours in preschool children and maternal serum concentrations of PFOA and PFOS. [The Working Group noted the unclear methods used for control selection and some very high PFOA measurements that were not discussed. This study was considered uninformative for the evaluation of human cancer hazard and was not considered further.]

Lundin et al. (2009) conducted a mortality study among 3993 workers at an APFO-production plant in Cottage Grove, Minnesota, USA, between 1947 and 2002 (see Section 2.1.1). Using the rates for the state of Minnesota as the referent, SMRs were calculated according to classification of jobs by exposure to APFO (the ammonium salt of PFOA) in three categories: never, ever probable/never definite, and ever definite. Of 29 deaths from cancers of lymphatic and haematopoietic tissue, only one was among those definitely exposed to APFO (SMR, 0.37; 95% CI, 0.01–2.08) and 14 were probably, but never definitely exposed (SMR, 0.96; 95% CI, 0.53–1.61). None of the 3 deaths from lymphosarcoma-reticulosarcoma or 13 deaths from other lymphatic and haematopoietic cancers were among the definitely exposed, but 2 deaths (SMR, 1.80; 95% CI, 0.22–6.51) and 5 deaths (SMR, 0.71; 95% CI, 0.23–1.66), respectively, were among the probably, but never definitely, exposed for these cancer types. The single death from Hodgkin lymphoma was observed in the group of workers who had never been exposed. For leukaemia, 7 of 12 deaths were among the probably but never definitely exposed (SMR, 1.27; 95% CI, 0.51–2.61) with only 1 death among the definitely exposed (SMR, 0.96; 95% CI, 0.02–5.34). [The Working Group noted that this study was focusing on mortality, and its informativeness with respect to specific, relatively rare, cancers was limited by the small numbers and the crude exposure assessment that did not allow for analysis of cumulative exposure or lagged analyses.]

Alexander et al. (2003) studied mortality from cancers of lymphatic and haematopoietic tissues combined and melanoma between 1961 and 1998 among 2083 workers enrolled from 1961 through 1997 at the PFOS facility in Decatur, Alabama, USA (see Section 2.1.2 for a full description). The median duration of follow-up was 25.9 years, and a total of 4 deaths from lymphatic and haematopoietic cancer, 3 deaths from melanoma, and 15 deaths from respiratory system cancers were identified. Workers were classified as highly exposed to PFOS (and PFOA) according to a company-specific JEM based upon a survey of PFOS serum measurements and included a subset of workers in the chemical division, whereas workers in the film-producing division were unexposed at work. The geometric mean serum PFOS concentration for chemical division employees was 0.9 ppm [900 ng/mL] and for film division employees it was 0.1 ppm [100 ng/mL]. Using the Alabama state population as the referent, SMRs for lymphatic and haematopoietic cancers were not increased in the entire cohort including both chemical and film divisions, or in ever potentially highly exposed employees (Table S2.6, Annex 4, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.who.int/636). The SMR for melanoma was increased in both the entire cohort and exposed employees, but estimates were based on few (≤ 3) exposed cases. Mortality was not elevated from respiratory system cancers (all trachea, bronchus, and lung) overall or in any exposure category.

[The Working Group noted that this study had complete data for a highly exposed occupational cohort with long follow-up, but numbers of less-frequent cancers, such as cancers of lymphatic and haematopoietic tissue and melanoma, were low and did not allow estimation of an association with PFOS with reasonable precision. The exposure assessment was rather crude, without assessment of cumulative exposure, and co-exposures to potential carcinogens and other fluorochemicals were likely. Therefore, the Working Group considered that this study provided limited information for the evaluation of cancers of lymphatic and haematopoietic tissue, melanoma, or respiratory system cancers.]

Leonard et al. (2008) studied mortality from several specific cancers of lymphatic and haematopoietic tissue and from melanoma among 6027 workers (men, 81%) who had ever worked at the polymer-production facility in

Parkersburg, West Virginia, USA, between 1948 and 2002. With follow-up until 2002, mortality was not elevated for melanoma (3 deaths) for workers versus any of the three reference groups considered. A later follow-up until 2008 was published by Steenland and Woskie (2012) (see Section 2.1.3 for a full description). Only the latest follow-up data for NHL, leukaemia, lung cancer, and mesothelioma are reported here (Steenland and Woskie, 2012). The latest follow-up for melanoma is also reported in Table S2.6, as in Steenland et al. (2015). The mean follow-up was 30 years, and 14, 14, 84, and 6 deaths from NHL, leukaemia, lung cancer, and mesothelioma, respectively, were observed. SMRs were computed using the US population and an eight-state regional employee population from the same company (other workers in the same company and region) as referents.

Compared with other workers in the same company and region, increases were not observed for NHL (SMR, 1.05; 95% CI, 0.57–1.76), leukaemia (SMR, 1.05; 95% CI, 0.57–1.76), or lung cancer (SMR, 0.78; 95% CI, 0.62–1.64) in the PFOA-exposed cohort. SMRs according to individual cumulative PFOA exposure estimates without a lag did not indicate dose–response associations for these causes of death. Mortality from mesothelioma was elevated in the cohort (SMR, 2.85; 95% CI, 1.05–6.20), especially in the fourth quartile of cumulative PFOA exposure (5 deaths).

[The Working Group noted that this was the largest of the three US occupational PFAS cohorts (partly because there was no restriction with respect to duration of employment) and was characterized by a high degree of completeness of case ascertainment and cohort follow-up. A major strength of the updated follow-up was estimation of individual cumulative serum PFOA levels. The magnitude of occupational exposure to suspected or known human carcinogens such as asbestos was not quantified, but some co-exposure could not be ruled out.]

Barry et al. (2013) evaluated the risk of cancers of lymphatic and haematopoietic tissue and of melanoma in 28 541 community residents in the Mid-Ohio Valley, USA, who were exposed to PFOA in drinking-water as a result of emissions from the polymer-production plant in Parkersburg, West Virginia, and in 3713 employees working at this plant (a total of 32 254 individuals; men, 46%) (see Section 2.1.5). The average duration of follow-up after age 20 years was 33 years and during this period 66, 136, 241, and 108 cases of incident leukaemia, lymphoma, melanoma, and lung cancer, respectively, were identified. Adjusted hazard ratios for selected cancers of lymphatic and haematopoietic tissue and melanoma were computed by proportional hazard regression by estimated cumulative PFOA exposure (continuous variable). The risk of leukaemia, lymphoma (type not specified), melanoma, and lung cancer did not increase with increasing estimated cumulative exposure (Table S2.6, Annex 4, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.who.int/636). Risk estimates based upon models where exposure was unlagged, lagged 10 years, or lagged 20 years were similar (data for a 20-year lag were not reported in the manuscript). Results based on all self-reported cancer cases were similar to those for based on validated cases only (the results of the analysis using validated cases only were not reported in the manuscript). [The Working Group noted that these findings in this large community cohort with individual assessment of cumulative exposure did not consistently indicate that PFOA is associated with increased risk of these cancers at exposure levels encountered in a community with mainly high environmental exposure.]

Consonni et al. (2013) investigated cause-specific mortality rates in an international occupational cohort of 5879 male TFE workers of whom 4205 were also exposed to APFO (see Section 2.1.6). An individual semiquantitative

estimate of cumulative TWA airborne exposure was assigned from a study-specific JEM. In total, 49 deaths from lung cancer and 19 deaths from lymphatic and haematopoietic cancer were identified during follow-up from 1950 to 2008 in workers who had ever been exposed to APFO.

Using national rates as the referent, SMRs for lymphatic and haematopoietic tissue cancers combined, for NHL, and for multiple myeloma were not elevated in male workers who had ever been exposed to APFO. Mortality from leukaemia was increased (SMR, 1.61; 95% CI, 0.88–2.88), but without indications of increasing risk with increasing cumulative exposure. Lung cancer mortality was lower in workers than in the reference population (SMR, 0.73; 95% CI, 0.54–0.97).

[The Working Group noted that this cohort included all TFE-production sites worldwide during the entire period of production and benefited from almost complete enrolment and follow-up data. The informativeness of this study was limited. Internal analyses were not performed. Analyses stratified by level of cumulative exposure only included few cases (e.g. 3 or 4 cases of leukaemia in tertiles of cumulative exposure).]

Girardi and Merler (2019) reported mortality from cancers of lymphatic and haematopoietic tissue and lung in 1970–2018 among 462 male employees enrolled from 1960 through 2008 at a factory manufacturing PFOA, PFOS, and other chemicals in Trissino, Veneto, Italy (see Section 2.1.9 for details). A cohort of railroad workers from the geographical region constituted the reference group. For the factory-worker and railroad-worker cohorts, the mean duration of employment was 12.5 and 9.7 years, respectively, and the mean length of follow-up was 31.7 and 34.3 years, respectively. Loss to follow-up was < 3%. The geometric mean for PFOA was 4048 ng/mL, highest among PFOA operators (geometric mean, 8826 ng/mL; range, 335–86 300 ng/mL).

Using both regional and reference factory data as referents, mortality from cancers of lymphatic and haematopoietic tissue (7 deaths) was increased in the entire factory-worker cohort and increased with increasing estimated cumulative level of PFOA exposure, as indicated by tertile analysis (Table S2.6, Annex 4, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.who.int/636). Mortality from lung cancer (6 deaths) was not elevated in the factory-worker cohort compared with either reference group.

[The Working Group noted that this study had the advantage of complete data for an occupational cohort with high-level exposure, long follow-up, biological monitoring data, and estimates of cumulative exposure to PFOA. Subsets of employees seemed to have the highest recorded levels of PFOA among the available PFAS cohorts so far. Major limitations were that few samples were available to model some job categories; the small size of the factory-worker cohort with only 7 deaths from cancers of lymphatic and haematopoietic tissue among 462 employees followed for about 32 years, resulting in imprecise confidence intervals; inability to distinguish the effects of different PFAS compounds and other potential carcinogenic co-exposures; and limited confounding control. Factory workers were exposed to several chemicals in addition to PFOA and PFOS.]

Li et al. (2022a) reported sex-stratified risk estimates for the most common specific cancers of lymphatic and haematopoietic tissue, melanoma, and lung cancer among 60 507 residents (15 811 highly exposed; men, 52%) of Ronneby municipality, Sweden, reporting on follow-up from 1985. PFOA constituted only a minor proportion of the PFAS (mainly PFOS and PFHxS) that contaminated the drinking-water (for details, see Section 2.1.13).

The SIR, adjusted for sex, age and calendar year, for NHL was not increased in male or female

Ronneby residents who had ever been exposed to highly contaminated drinking-water, but the internal analysis within the Ronneby municipality revealed an elevated hazard ratio for residents with high-level exposure for > 10 years and for residents with high-level exposure during the latest period, where contamination levels were assumed to be higher, relative to residents who had never been exposed to highly contaminated water. The latter risk estimates were uncertain, with broad confidence intervals including unity.

The SIRs for multiple myeloma and chronic lymphocytic leukaemia were not increased in residents who had ever been exposed (men or women), and no consistent increase in risk was seen according to time or duration of exposure in residents ever living in a highly contaminated district. The SIR for chronic myeloid leukaemia was increased in Ronneby residents with low-level (only men) or high-level exposure, but numbers were low and precluded more detailed analysis.

The SIR for melanoma was increased in Ronneby residents with low-level (only men) or high-level exposure, and internal analysis indicated higher risk among residents with high-level exposure for > 10 years and especially for residents with high-level exposure during the latest period (HR, 1.54; 95% CI, 1.09–2.19).

[The Working Group noted that major strengths included complete registration of the cohort, no loss to follow-up, and a long follow-up period. Major limitations were the crude ecological exposure assessment, without individual estimates related to PFOS exposure.]

Winquist et al. (2023) conducted a case–cohort study within the ACS prospective CPS-II LifeLink Cohort, with measurement of PFOA, PFOS, and several other PFAS in prediagnostic serum samples collected during 1998–2001. Overall, there was no increase in the incidence of lymphatic and haematopoietic cancers associated with serum PFOA or PFOS serum concentrations. [The Working Group noted several strengths, including the case–cohort design, large sample size, good cancer ascertainment via registries and examination by histological subtype, and prediagnostic serum samples. Limitations were mainly the low exposure levels, narrow exposure contrast, and probable attenuation of risk estimates because of delayed blood sampling relative to time of enrolment.]

Vieira et al. (2013) conducted a case–control study to investigate the risk of 18 cancers in a community sample with relatively high exposure to PFOA because of contamination of drinking-water by the polymer-production plant in Parkersburg, West Virginia, USA. Using all other cancers except kidney, testicular, liver, and pancreatic as controls, odds ratios were estimated for exposed versus unexposed and for subsets of exposed across districts (see Section 2.1.18).

The odds of NHL were elevated among exposed residents in contaminated water districts (152 cases) relative to the unexposed, but the excess was limited to the very-high and medium exposure categories. Leukaemia (72 exposed cases), multiple myeloma (36 exposed cases), and melanoma (168 exposed cases) were not associated with exposure in contaminated water districts, and the odds of these cancers did not increase with increasing exposure category.

Lung cancer (632 exposed cases) was associated with exposure to contaminated water (OR, 1.2; 95% CI, 1.1–1.3), but the elevation was observed only in the high-exposure category and not in the very-high exposure category.

[The Working Group noted that this was a relatively large study population with a strong exposure contrast and with estimates of individual-level exposure for a subset of the population. Limitations included the use of other cancers as controls, which may cause bias towards the null if PFAS exposure is a risk factor for the cancers in the control group, or the opposite if PFAS exposure is associated with risk factors – for instance, smoking and alcohol consumption – that are probably more prevalent in the cancer controls than in the background population.

Individual-level exposure misclassification was most likely to be independent of the cancer outcome, with probable bias towards the null as a result.]

2.7 Cancer of all sites combined

See Table S2.7 (Annex 4, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.who.int/636).

There were seven cohorts that contributed evidence on PFOA and/or PFOS exposure and the risk of cancer overall. Five of these were occupational cohorts that used JEMs to estimate exposure and were focused primarily on men and on cancer mortality. In contrast, Li et al. (2022a) examined overall cancer incidence in residents with high environmental exposure, and Wen et al. (2022) evaluated serum PFOA and PFOS levels in relation to mortality using NHANES, which was more representative of exposure levels in the general US population. All these studies used data linkages to ascertain cancer outcomes, most commonly using information from death certificates. [The Working Group noted that although this approach had the benefit of often providing very complete outcome data, the focus on cancer mortality did not provide much information on the relation between PFAS exposure and specific cancers that have a longer survival time after diagnosis. Additionally, the studies in this section considered all cancer diagnoses as a single outcome, a heterogeneous category that may mask important associations with individual cancer outcomes.]

Raleigh et al. (2014) evaluated overall cancer mortality in an occupational cohort that included 4668 workers exposed to PFOA at an APFO factory in Cottage Grove, Minnesota, USA, between 1947 and 2002 and a comparison group of 4359 employees who were unexposed workers at a tape and abrasive production facility in Saint Paul, Minnesota (see Section 2.1.1, PFOA-production workers). Individual inhalation exposure was estimated using a JEM created from expert evaluation and industrial hygiene data. Mortality information was obtained from the NDI. There were 332 cancer deaths identified among the exposed workers. Overall cancer mortality for individuals working at the exposed plant (Cottage Grove, SMR, 0.87; 95% CI, 0.78–0.97) was lower than that for workers at the unexposed location (Saint Paul, SMR, 1.04; 95% CI, 0.95–1.13). Higher APFO exposure was not associated with a higher SMR for overall cancer mortality (quartile 4, SMR, 0.92; 95% CI, 0.71–1.16). [The Working Group noted that although this study had individual cumulative air exposure assessment with some evidence of this exposure metric being correlated with serum level, unlikely co-exposure to TFE, and a relatively higher number of overall cancer mortality cases compared with the individual cancer types, the heterogeneous nature of the outcome limited the inference from these findings. The study also lacked data on workers who left Minnesota or Wisconsin or on potential confounding factors such as smoking, which, if associated with occupational exposure, may have led to residual confounding.]

Alexander et al. (2003) studied a population of 3512 PFOS-exposed production workers at a plant in Alabama, USA (see Section 2.1.2, PFOS-production workers). 2083 participants were identified who had worked for ≥ 1 year between 1961 and 1997. Mortality follow-up was conducted using linkage to the NDI. The individual's PFOS exposure was estimated on the basis of job history and information from a subset (n = 232) for whom blood samples had been collected in 1998 and PFOS levels measured. Based on this subset, all workers were categorized according to their possible exposure (no workplace exposure, low potential exposure, or high potential exposure). Of the 2083 workers who met the criterion of working ≥ 1 year at the plant, 39 cancer deaths (total deaths, 145) were observed. The SMR for all

cancer deaths was 0.72 (95% CI, 0.51–0.98). It was similar when limiting to employees who were ever employed in a high-exposure job (SMR, 0.84; 95% CI, 0.50–1.32; 18 deaths), as well as for those who were ever employed in a low-exposure job but never in a high-exposure job (SMR, 0.52; 95% CI, 0.19–1.14), or those who worked in a high-exposure job for ≥ 1 year (SMR, 0.84; 95% CI, 0.46–1.41). [The Working Group noted that this study used a JEM informed by a subset of workers with blood measurements and had a strong exposure contrast but few deaths and no cancer incidence data. This study evaluated mortality using an NDI linkage, which would have underestimated associations with specific cancer types that have more favourable survival after diagnosis. The heterogeneous nature of the outcome limited the inference from these findings. Furthermore, the study was conducted predominantly in men and had limited control for confounding by factors such as smoking, which, if associated with occupational exposure, may have led to residual confounding.]

Steenland and Woskie (2012) conducted a mortality study among a cohort of PFOA-exposed workers at the polymer-production plant in Parkersburg, West Virginia, USA (see Section 2.1.3). There were 5791 workers who were employed for ≥ 1 day between 1948 and 2002 and who had sufficient work histories to allow for estimation of PFOA exposure. PFOA exposure was estimated using information on work history and from a subset with serum PFOA measurements. This cohort was highly exposed, with estimated serum PFOA concentrations that were two orders of magnitude higher than those in the general population. SMRs were calculated comparing workers in the cohort to workers at other factories in the same company in a similar geographical region and to the general US population. A total of 1084 deaths were observed during follow-up from 1952 to 2008; of these, 304 were determined to be cancer-related, ascertained via linkage to the NDI or from death certificate data. Relative to workers at other factories within the same region and company, mortality for all cancer types in participants in the Parkersburg polymer-production plant cohort was not elevated overall or when considering quartiles of estimated exposure to PFOA (e.g. quartile 4, SMR, 0.94; 95% CI, 0.76–1.16). The consideration of either a 10-year lag (e.g. quartile 4, SMR, 0.92; 95% CI, 0.73–1.15) or 20-year lag (data not reported) did not alter conclusions. [The Working Group noted that this study included a highly exposed cohort with long follow-up period and used a comparison group that included other workers, which may have attenuated any healthy-worker effect. Another strength of the study was the detailed exposure assessment using an enhanced JEM with serum exposure levels based on measurements from workers. However, the study did not evaluate the incidence of all cancers combined. Using cancer mortality data from linkages may underestimate associations with specific types of incident cancer, particularly those with more favourable survival after diagnosis. The heterogeneous nature of the outcome was a main limitation. There was limited control for confounding, which could have led to residual confounding if lifestyle factors such as smoking were related to occupational status in the cohort.]

Consonni et al. (2013) evaluated cancer mortality in a cohort of workers who were employees at six TFE-production sites in North America and Europe and were exposed to APFO (the ammonium salt of PFOA) as part of the manufacturing process between 1950 and 2002 (see Section 2.1.6). Job-specific exposure matrices based on the potential for exposure were used to estimate semiquantitative exposure to both TFE and PFOA. Vital status was obtained until 2008 using a variety of methods and linkages across the various geographical locations where the factories were located. Among 4205 workers who had ever been exposed to APFO, there were a total of 534 deaths, including 159 deaths from cancer. Overall, there was no association

between all-cancer mortality and cumulative estimated APFO exposure, when comparing with a national referent (e.g. highest cumulative exposure, SMR, 0.78; 95% CI, 0.59–1.02). Co-exposure to high levels of TFE and high levels of APFO was also not associated with an elevated SMR (0.81; 95% CI, 0.60–1.06). [The Working Group noted that although this study was a comprehensive population of international TFE workers at the time it was conducted, it used a semiquantitative exposure assessment with no validation of estimated exposures. The study was limited to men and did not include information on potential confounding factors such as smoking status, which, if associated with occupational exposure, could have led to residual confounding. It was also difficult to discern whether any observed effects in this study would be caused by TFE (IARC Group 2A, IARC, 2016), if present, or by PFOA, given the high correlation between the exposures. Using cancer mortality data from linkages may underestimate associations with specific types of incident cancer, particularly those with more favourable survival after diagnosis. The heterogeneous nature of the outcome limited the inference from these findings.]

Girardi and Merler (2019) investigated mortality in a cohort of 462 PFAS-exposed workers at a factory in Trissino, Veneto, Italy, and compared mortality rates with those for regional general populations and 1383 railroad workers who were not exposed to PFAS compounds (see Section 2.1.9). PFAS exposure was estimated using a JEM, which was informed in part by serum PFOA concentrations. Exposure was categorized into tertiles of estimated PFOA and was also evaluated on the basis of categories of exposure (ever at PFAS department, never at PFAS department, and in offices). Vital status was obtained from death certificates, for deaths between 1970 and 2018. This was a highly exposed occupational cohort (n = 120 with measured PFOA; geometric mean, 4048 ng/mL), with 107 deaths observed, 42 of which were from cancer. There was no excess mortality observed when compared with regional rates for comparison overall (all cancers, SMR, 1.00; 95% CI, 0.74–1.36) although the overall cancer mortality risk was elevated when compared to that for the railworkers (risk ratio, 1.32; 95% CI, 0.91–1.91). There was little evidence of association with categorical estimates of PFAS exposure, with imprecise increases in the SMR for the highest estimated tertile of PFOA (SMR, 1.22; 95% CI, 0.79–1.87) and among those ever working in a PFAS department (SMR, 1.46; 95% CI, 0.85–2.51), when using regional rates as the referent. However, the estimate for the highest tertile of PFOA was more pronounced when the railroad workers were used as the referent (risk ratio, 1.65; 95% CI, 1.02–2.65), and an increase was also evident for those ever working in a PFAS department (risk ratio, 1.97; 95% CI, 1.10–3.54). [The Working Group noted that this was a highly exposed cohort, for which serum levels were used in conjunction with a JEM to inform the exposure classification. The population was limited to men and although the study did not include any information on confounders such as smoking, it used both national rates and an unexposed worker population to reduce the impact of the healthy-worker effect, which may also limit residual confounding. However, despite a long follow-up period, there were few cancer-related deaths, and the use of death certificates to ascertain cancer mortality data may underestimate possible associations with specific types of incident cancer, particularly those with more favourable survival after diagnosis. The heterogeneous nature of the outcome limited the inference from these findings.]

Li et al. (2022a) examined overall cancer incidence in more than 60 000 individuals who lived in Ronneby municipality in Sweden in 1985–2013 (see Section 2.1.13). This study population included approximately one third who were exposed to water contaminated with a mixture of PFAS compounds, mainly PFOS, PFHxS, and, to a lesser extent, PFOA. The exposure assessment

was based on annual residential addresses and information on drinking-water supply, and cases were identified using cancer registry linkage until 2016. There were 5702 cases of cancer identified. There was no evidence that exposure to highly contaminated PFAS drinking-water was associated with excess incidence, as SIRs were around or below the null. SIRs were also similar for both the "never-high" and "ever-high" exposure groups, defined on the basis of living at an address supplied with PFAS-contaminated water, compared with an external reference group. In the internal cohort comparison analysis, there was little difference in the hazard ratios for overall cancer incidence according to estimated exposure duration or timing of exposure, although there may have been a slight increase for high exposures between 2005 and 2013 (late period) (HR, 1.09; 95% CI, 0.99–1.20) but not for high exposures between 1985 and 2004 (early period). Li et al. (2022a) also conducted sensitivity analyses further adjusting for highest education attained. Potential confounding by smoking was partly accounted for, since duration of education and smoking are highly correlated (Eek et al., 2010). [The Working Group noted that this study had a large general population sample with a high environmental level of PFAS exposure and near-complete registry-based case identification. Other strengths included the use of both an external reference group and internal comparisons. However, the exposure assessment was limited by not having any individual-level measurements of exposure and by including areas that were contaminated by multiple PFAS, which limited inferences regarding associations with individual compounds. The minimal information on individual-level confounders, except for education (which was included in sensitivity analyses), may not be as important in this context, given that exposure was determined on the basis of the water distribution system.]

Wen et al. (2022) evaluated the association between mortality and serum measurements of PFOA and PFOS using data from NHANES, which is a continuously conducted and nationally representative cross-sectional survey designed to represent the non-institutionalized US population (see Section 2.1.15). Blood samples were collected in 1999–2014, and participants were followed up for mortality using linkage to the NDI until the end of 2015. Of the 1251 deaths that occurred during the study follow-up period, 248 were from cancer. Increasing serum PFOA levels were not related to higher incidence of cancer-related mortality (PFOA tertile 3 versus tertile 1, HR, 1.06; 95% CI, 0.68–1.71). In contrast, increasing PFOS level was related to higher adjusted hazard ratio for overall cancer-related mortality in a dose–dependent manner (PFOS tertile 2 versus tertile 1, HR, 1.26; 95% CI, 0.75–2.06; PFOS tertile 3 versus tertile 1, HR, 1.75; 95% CI, 1.10–2.83), adjusting for the other measured PFAS in addition to sex, age, race or ethnicity, education, smoking status, physical activity, hypertension, healthy eating index, creatinine clearance rate, serum total cholesterol, and serum cotinine. [The Working Group noted that the strengths of this investigation were the use of a nationally representative population with serum measurements of PFOS and PFOA, with probable complete ascertainment of cancer mortality. Despite relatively good control for potential confounders, including other PFAS, the Working Group noted that the analysis did not adjust for calendar time, which is important given temporal trends in PFAS concentrations. Other limitations included the short follow-up time for some of the participants, which may not reflect the relevant etiological window, and, for some individuals, the blood sample may have been collected after cancer diagnosis and treatment, since participants with cancer at baseline were not excluded. There was also a relatively small number of cancer-related deaths, and the focus on overall cancer mortality, a heterogeneous outcome, may mask associations for individual cancer types.]

2.8 Evidence synthesis for cancer in humans

This section provides a synthesis of the epidemiological evidence on cancer in humans exposed to PFOA or PFOS. The synthesis is based upon a total of 36 epidemiological studies available to the Working Group.

The first epidemiological study addressing risk of cancer associated with exposure to PFAS was an occupational mortality study in a cohort of workers manufacturing APFO (the ammonium salt of PFOA), in the Cottage Grove plant in Minneapolis, Minnesota, USA (Gilliland and Mandel, 1993). This study was published more than five decades after large-scale manufacture of PFOA was initiated.

2.8.1 Studies evaluated

The epidemiological evidence on the carcinogenicity of PFOA and PFOS in humans is available from studies with three different exposure settings. First, occupational exposure of workers in chemical plants manufacturing or using PFOA or PFOS; second, high environmental exposure in communities contaminated by emissions from chemical plants or other specific sources, such as the use of aqueous firefighting foam; and last, background exposure of the general population. Studies within these three settings typically have different epidemiological designs with different strengths and limitations; thus, comparing findings for a particular cancer site across the various exposure settings may assist causal inference. The studies that the Working Group considered the most informative and hence to which the most weight was given when balancing the evidence for carcinogenicity in humans were large cohort and nested case–control studies from all three major exposure settings.

(a) Occupational cohort studies

Chemical plants manufacturing or using PFOA or PFOS were established at three major sites in USA and some facilities in Europe from the late 1940s onwards, and follow-up studies of worker cohorts from these sites contributed substantially to the evidence on human carcinogenicity of PFOA and, to a lesser degree, of PFOS. The three US cohorts were the PFOA-manufacturing facility in Cottage Grove, Minnesota (Gilliland and Mandel, 1993; Lundin et al., 2009; Raleigh et al., 2014), the polymer-production plant in Parkersburg, West Virginia (Leonard et al., 2008; Steenland and Woskie, 2012; Steenland et al., 2015), and the fluorochemical-production facility in Decatur, Alabama (Alexander et al., 2003; Alexander and Olsen, 2007). A number of plants in Europe and the Parkersburg polymer-production facility were included in the pooled international TFE cohort (Consonni et al., 2013), and a small PFAS-manufacturing plant in the Veneto region, Italy, contributed data on workers with extremely high PFOA serum concentrations (Girardi and Merler, 2019).

The occupational cohort studies were distinguished by PFOA or PFOS serum concentrations that were up to two orders of magnitude higher in workers than in the background population, with exposure contrasts facilitating the evaluation of exposure–response relations. The occupational cohorts generally had several decades of follow-up since first exposure, and exposure profiles were dominated by only a few PFAS compounds, depending on manufacturing processes. Thus, occupational exposures to either PFOA and PFOS were usually confined largely to one or the other, without being mixed. However, co-exposure to other PFAS and TFE was possible in some studies. Some occupational cohorts had information on blood concentrations of PFOA and/or PFOS, which were used to develop company-specific JEMs estimating serum levels

across time and jobs. This provided reliable information, given that blood levels represent an internal dose resulting from all exposure routes and may be superior to exposure metrics based on air concentrations that account for exposure only by the inhalation route.

A major limitation of occupational cohort studies is their relatively small sample sizes for specific cancers, inability to address cancers of the breast and female genital tract (since most chemical-plant workers are men), and the use of mortality rather than incidence by most of the studies. Mortality studies provide weaker data on etiology and generally smaller sample sizes than do incidence studies, especially for cancers with a low fatality rate. Another concern with occupational studies is that some are based on cross-sectional samples excluding workers at risk before cohort enrolment, although this will affect cancers with a low fatality rate to a lesser extent and may create only a rather weak downward bias for cancers with a high rate of fatality. Moreover, mortality studies often lack histological data, which might lead to attenuation of risk estimates for all cases combined if the risk is associated only with certain histological subtypes. Despite these caveats, the Working Group considered three occupational studies to be particularly informative, i.e. those by Alexander and Olsen (2007), Raleigh et al. (2014), and Steenland et al. (2015). All three used incidence data and provided risk estimates for a range of cancers according to cumulative quantitative exposure metrics, although the study by Alexander and Olsen (2007) still suffered from small numbers.

(b) Studies of high environmental exposure

These studies can be particularly informative because, like occupational studies, they may enable detection of health effects that may be less marked in general population studies with low exposures. Only three high-level environmental exposure studies were available: Barry et al. (2013), Vieira et al. (2013), and Li et al. (2022a). Exposure levels and contrasts in these settings were between the low background levels of the general population and the very high occupational levels. They benefited from large study populations, resulting in more precise risk estimates and high comparability of exposed and unexposed people recruited from the same geographical regions.

The C8 Science Panel Project included a group of workers (11.5% of the cohort) with occupational exposure to primarily PFOA at a polymer-production plant in Parkersburg, West Virginia, USA, and residents in the Mid-Ohio Valley USA, which was contaminated by emissions from this facility from the late 1940s until about 2005 (Barry et al., 2013). This Mid-Ohio Valley cohort had an important strength in its modelling of individual cumulative serum PFOA concentrations from birth onwards based on a large number of parameters, including plant emission data, measured drinking-water levels, residential histories, individual consumption of tap water, and toxicokinetic data for PFOA in humans. The estimated PFOA serum concentrations correlated well with a large number of PFOA measurements made in 2005 and 2006. The serum concentrations of PFOA, PFHxS, and PFNA were elevated by about 500%, 75% and 40%, respectively, compared with US background levels, whereas the PFOS serum concentration was not increased (Frisbee et al., 2009).

The case–control study of West Virginia and Ohio residents (Vieira et al., 2013) somewhat overlapped the C8 Science Panel study. Since this non-nested case–control study was based upon cancer registry records from a longer period and from larger geographical areas, the total number of cancer cases was higher than those of the analyses by Barry et al. (2013). This provided more accurate risk estimates, which is particularly important when considering rare cancer types. However, a limitation was the reference group that comprised people with other cancers

(except pancreatic, kidney, testicular, and liver cancer), which may attenuate risk estimates if these other cancers are also associated with PFAS. Also, exposure misclassification was of some concern, because the residential address used to assign exposure based on the same model used in Barry et al. (2013) was known only at the time of diagnosis (for details, see Section 2.1.22). However, since the error could mostly be of Berkson type, exposure misclassification might not cause substantial attenuation of risk estimates (Armstrong, 1998).

The third study, in the Ronneby Register cohort, included more than 60 000 community residents living in an area where parts of the population received drinking-water contaminated with PFAS from a nearby airfield (Li et al., 2022a). In contrast to the Mid-Ohio Valley cohort, the Ronneby Register cohort used a crude assignment of exposure based on earlier and current residential addresses, but it was supported by large exposure contrasts in PFAS concentrations in drinking-water across the various water supplies of the municipality. Another limitation of the Ronneby Register cohort, which is in general an issue for most non-occupational PFAS studies, was overlapping exposures to various PFAS. Whereas Ronneby had very high levels of PFOS and PFHxS, levels of PFOA greatly overlapped those of the unexposed Swedish population in the region.

(c) Studies in the general population with background exposure

Studies of subsets of the general population were often case–control studies nested within large cohorts or trials created for other purposes. With this design it is possible to cost-effectively sample large series of cases of a specific cancer; to take advantage of individual data on social, lifestyle, and health issues of particular relevance for a specific cancer; to use frozen blood samples to obtain prediagnostic measurements of contaminants; and to limit potential bias and confounding by matching on relevant characteristics. The main limitation pertaining to population-based studies is low exposure levels, low exposure contrasts, and background exposure to numerous other PFAS. Several chlorinated persistent organic pollutants are also widespread and have even longer biological half-lives than do PFAS, but the two classes of chemicals do not share physicochemical characteristics and in general serum concentrations are not correlated. Positive findings that are not corroborated in studies of high-exposure contrast (e.g. occupational or high environmental exposures) may seem contradictory, although for many carcinogens it has been shown that risk increases greatly with increasing levels at low exposure and then tails off or reaches a plateau at higher exposures (Stayner et al., 2003; Lanphear, 2017; Steenland et al., 2022). Suggested biological explanations include saturation of metabolic pathways, enhanced detoxification, and greater DNA repair efficiency at higher exposure levels (Stayner et al., 2003). Increasing exposure measurement error with increasing level of exposure can also result in the exposure–response relation reaching a plateau (Stayner et al., 2003). Healthy-worker survivor bias may also be a factor reducing the apparent risk in occupational cohort studies.

Despite limitations, several case–control studies nested within large cohorts were considered informative for this evaluation. They included studies based upon the Danish Diet, Cancer, and Health Cohort, addressing associations of PFOA and PFOS with cancers of the urinary bladder, prostate, liver, and pancreas in men (Eriksen et al., 2009); four studies based on the intervention arms in the PLCO Trial, addressing cancers of the kidney (Shearer et al., 2021), breast (Chang et al., 2023), prostate (Rhee et al., 2023a), and pancreas (Zhang et al., 2023); the US Air Force servicemen cohort, addressing testicular cancer (Purdue et al., 2023); two studies based on the US MEC, addressing HCC (Goodrich et al., 2022) and kidney cancer (Rhee

et al., 2023b); a study based in the ATBC Study in Finland, on pancreatic cancer (Zhang et al., 2023); a study of women in the FMC, addressing thyroid cancer (Madrigal et al., 2024); a case–cohort study on the association between PFAS and cancers of the kidney, pancreas, breast, prostate, and lymphatic and haematopoietic tissue among participants in the ACS CPS-II LifeLink Cohort (Winquist et al., 2023); and a small nested case–control study evaluating thyroid cancer in New York, USA (van Gerwen et al., 2023). Finally, four nested case–control studies with prediagnostic PFAS measurements, which addressed risk of breast cancer in population samples with a low level of exposure, i.e. a study of women in the French education system (E3N; Mancini et al., 2020a); the Danish National Birth Cohort (Ghisari et al., 2017); the US Child Health and Development Cohort (Cohn et al., 2020); and the Dongfeng-Tongji cohort of female retirees from a large motor company in China (Feng et al., 2022).

A number of hospital-based and non-nested case–control studies were considered less informative, because the control groups did not clearly represent the same population from which the cases were chosen, resulting in potential unpredictable bias. Moreover, the exposure assessment in these studies was based on postdiagnostic measurements of PFAS in blood samples, which are expected to provide less-reliable information on exposure during the relevant time windows than do prediagnostic baseline samples. Risk estimates may be biased if prodromal disease states, the fully developed disease, or the treatment affect serum concentrations of PFAS (this is labelled reverse causation), but little is known on this issue and the direction of bias, if any, is unpredictable. For these reasons, such case–control studies and one nested case–control study (Hurley et al., 2018) were given less weight when balancing the epidemiological evidence for causal associations for cancers of the breast (Wielsøe et al., 2017; Tsai et al., 2020; Itoh et al., 2021; Li et al., 2022b; Velarde et al., 2022), thyroid (Liu et al., 2022; Li et al., 2023), prostate (Hardell et al., 2014) and liver (Cao et al., 2022).

2.8.2 Exposure assessment quality considerations

Information on individual cumulative exposure to PFOA and/or PFOS that enabled analyses of exposure–response relations including lagged analyses was considered of critical importance for the evaluation of epidemiological studies on the carcinogenicity of PFOA and PFOS. A systematic description and appraisal of exposure assessment in all available epidemiological studies is provided in Section 1.6.1.

Among nine occupational cohort studies in which exposure assessment primarily relied on job history, three studies focusing on PFOA and one study on PFOS used quantitative estimates of cumulative exposure (Alexander and Olsen, 2007; Steenland and Woskie, 2012; Raleigh et al., 2014; Steenland et al., 2015). These estimates were derived from company-specific JEMs informed by industrial hygiene and/or biological measurements and accounted for temporal shifts in exposure levels. In particular, the approach used in the study by Steenland and Woskie (2012) (and Steenland et al., 2015), which incorporated industrial hygiene and biological measurements into modelled serum concentrations, was considered superior to the others.

The inevitable misclassification of exposure related to group-based exposure assignment in these studies may not necessarily cause attenuation of risk estimates towards the null. Depending on the degree of Berkson-type measurement error, it may primarily result in unbiased but less precise risk estimates (Armstrong, 1998). However, errors involved in group mean exposure measurement used in JEMs also could cause bias towards or away from the null. Exposure assessment in the small cohort of PFAS-manufacturing workers in Italy was also modelled via cumulative PFOA serum

concentrations based upon a JEM informed by measurements, but the effects of considerable co-exposure to other PFAS compounds were not accounted for by the analyses (Girardi and Merler, 2019). Other occupational cohort studies applying crude or semiquantitative assignments of exposure levels and without quantitative estimates of individual cumulative exposure were considered at higher risk of exposure misclassification for lifetime exposure and therefore provided less-reliable risk estimates (Alexander et al., 2003; Leonard et al., 2008; Lundin et al., 2009; Consonni et al., 2013).

Among the three studies addressing risk of cancer in residents living in areas contaminated by local PFOS and/or PFOA emissions, one study of the population in the Mid-Ohio Valley, West Virginia, USA, was considered particularly informative because of the modelled annual serum PFOA concentrations from birth onwards (Barry et al., 2013), and another partly overlapping study assessed exposure 10 years before diagnosis, making the exposure assessment slightly less informative (Vieira et al., 2013). The Ronneby Register cohort study in Sweden had well-documented, strong contrasts among residents with respect to PFOS and PFHxS serum concentrations, but the exposure assessment was entirely based upon timing and duration of residence at contaminated and uncontaminated addresses and did not allow estimation of the effects of the individual compounds (Li et al., 2022a).

All studies addressing risk of cancer in general population samples used the concentration of PFAS in at least one blood sample as a proxy for cumulative exposure. This approach is supported by the long biological half-lives of PFOA and PFOS in humans (see Section 4.1 for details) and some indications of high stability of blood concentrations across several years within individuals who provided repeated samples (Blake et al., 2018; Purdue et al., 2023; Rhee et al., 2023a). Furthermore, simulation studies based on available data with repeated measurements up to 8 years apart indicated that bias towards the null because of non-differential misclassification would be modest (Annex 3, Supplementary analyses used in reviewing evidence on cancer in humans, available from: https://publications.iarc.who.int/636).

2.8.3 Co-exposures to other agents of relevance to cancer hazard identification

Mutually independent information on the carcinogenicity of PFOA and PFOS in humans in the available epidemiological studies was obtained by two main approaches.

First, some occupational and environmental settings were associated with exposure to specific PFAS compounds at levels many times as high as background levels, whereby co-exposure to other PFAS compounds above background levels was unlikely, given the characteristics of the production processes and sources of exposure. This applied to the occupational cohorts of workers at the APFO-producing plant in Cottage Grove, Minnesota, USA (Raleigh et al., 2014); the studies of fluoropolymer-production workers in Parkersburg, West Virginia, USA (Steenland and Woskie, 2012; Steenland et al., 2015); and the C8 Science Panel cohort of workers and residents of contaminated areas of the Mid-Ohio Valley, USA (Barry et al., 2013; Vieira et al., 2013). In all these studies, PFOA serum concentrations were substantially elevated above background levels, whereas PFOS serum concentrations were not. Serum concentrations of PFHxS and PFNA were also somewhat above background levels in Mid-Ohio Valley residents, but the correlation with PFOA was modest, indicating that exposure via a source other than the plant in Parkersburg, West Virginia, was likely (Frisbee et al., 2009). Moreover, co-exposure to TFE (classified in IARC Group 2A; IARC, 2016) may have occurred at some European workplaces (Consonni et al., 2013) but was considered unlikely at the plant in

Parkersburg because use was strictly controlled under normal operations (Steenland and Woskie, 2012). For PFOS, there were no occupational or environmental settings without some co-exposure to other PFAS compounds or carcinogens. The occupational cohort of fluorochemical-production workers in Decatur, Alabama was characterized by high exposure to PFOS, but exposure to several other fluorochemicals including PFOA was possible or likely (Alexander et al., 2003; for details, see Table S1.22, Annex 4, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.who.int/636). Likewise, the Ronneby Register cohort was characterized by PFOS exposures an order of magnitude above background levels, but levels of PFHxS were also substantially higher than background levels whereas PFOA levels were not (Li et al., 2022a).

Second, in all studies of general population samples, PFAS exposure was mixed. Most studies estimated exposure by measurement of PFAS compounds in one or more blood samples, and estimates were typically provided for both PFOA and PFOS. In some studies, mutual adjustment was performed for the effects of other PFAS compounds (Cohn et al., 2020; Shearer et al., 2021; Wen et al., 2022; Chang et al., 2023; Purdue et al., 2023; Rhee et al., 2023a, b; Madrigal et al., 2024), which helped to identify individual effects. The correlation coefficients of PFOA and PFOS in the above studies ranged from 0.50 (Wen et al., 2022) to 0.70 (Rhee et al., 2023a), and therefore the possibility of unstable statistical models or overadjustment was unlikely. The same concern applied to correlations between PFOA, PFOS, and other common legacy PFAS (Shearer et al., 2021; Rhee et al., 2023b).

2.8.4 Bias and confounding

Exposure- and outcome-dependent selection into studies was not considered to be an important source of bias in the most informative studies available for this evaluation. Most occupational studies were based upon rosters kept by major companies (Alexander and Olsen, 2007; Raleigh et al., 2014; Steenland et al., 2015), and the large, nested case–control studies mostly used existing independent databases or public registries to define the study populations (see Table 2.1). Selection bias in terms of a healthy-worker effect (sometimes viewed as a confounder) and healthy-worker survivor bias is of concern when considering occupational studies. Both would be expected to lead to downward bias. The former bias can be mitigated by using internal rather than external comparisons, and the latter is of less concern if there is little evidence that high exposure is associated with leaving employment in a highly exposed job or altogether. Furthermore, compared with studies on other chronic diseases, studies on cancer may be less susceptible to both healthy-worker effects and healthy-worker survivor effects.

The C8 Science Panel cohort of workers and residents in the PFOA-contaminated Mid-Ohio Valley area in Ohio and West Virginia was considered particularly informative for this evaluation because of its size, validated estimates of cumulative internal exposure, large exposure contrast, and extensive covariate information. It was mainly based upon a cross-sectional population sample of residents alive at the time of interview and with most at-risk years occurring before baseline interviews. Selection bias was unlikely because the participation rate was about 80%, and the data did not indicate preferential participation of residents from contaminated areas who had a history of cancer (Barry et al., 2013). Moreover, simulation analyses demonstrated that lacking information about fatalities occurring in the population before enrolment would not affect risk estimates (Barry et al., 2015), unless survival after diagnosis was associated with exposure level, judged a priori to be unlikely.

In most studies, case identification and ascertainment were based upon population-wide cancer registries, death certificates, or death registries (or a combination of these), and in one study the additional data from personal recall of cancer were verified by medical records (Barry et al., 2013). The approaches for case identification in general were not expected to introduce major outcome misclassification.

Only a few informative studies distinguished subtypes of specific cancers, mainly for breast cancer (Hurley et al., 2018; Mancini et al., 2020a; Chang et al., 2023). Examples of environmental exposures causing risk of some but not of other specific cancer subtypes are few (e.g. wood dust causes adenocarcinoma but rarely causes squamous cell carcinoma of the sinonasal cavity; IARC, 2012). Considering that PFAS may modulate endocrine regulation and signalling (for details, see Section 4.2.8), there is a rationale for examination of receptor-defined subtypes of, particularly, breast cancer. However, since the effects of PFAS may depend on endogenous hormone levels and may be inhibitory in some situations but stimulatory in others, it is difficult to put forward a priori hypotheses, which complicates the interpretation of epidemiological findings. There is no mechanistic evidence indicating that the main subtypes of testicular cancer (seminoma, and non-seminoma) have different etiologies in young men in whom these tumours develop from carcinoma in situ in cells of developmental origin (Rajpert-De Meyts, 2006). It is disputed whether subtypes of testicular cancer for which incidence peaks later in adulthood have different etiologies (Coupland et al., 1999; Stang, 2009). At present, studies addressing specific cancer subtypes are mainly explorative and foremost of importance as starting points for forthcoming studies.

Demographic characteristics such as race, ethnicity, sex, age, residence area, socioeconomic status and calendar period are strong determinants of cancer and are also associated with PFAS exposure in the general population (Steenland et al., 2009; Eriksen et al., 2011; Buekers et al., 2018; Momenimovahed and Salehiniya, 2019; Rhee et al., 2023b). With few exceptions, these factors were controlled by design and/or analysis in the highly informative studies. Some studies, mainly nested case–control studies (for details, see Table 2.1), also accounted for the effects of smoking, alcoholic beverage consumption, and BMI, based on data collected by personal interview (Barry et al., 2013); however, such information was not available in the occupational cohort studies, the case–control studies by Vieira et al. (2013), and the Ronneby Register cohort study (Li et al., 2022a). In occupational studies, internal analyses and comparisons of exposed with unexposed workers in the same types of jobs from nearby plants during the same calendar period mitigated confounding due to differences in social and lifestyle factors, whereas confounding in studies of heterogeneous populations not accounting for these factors may result in bias in an unpredictable direction. Nested case–cohort and case–control studies designed to address one or more specific cancers often included information on a range of determinants of these specific cancers, such as hepatitis for primary liver cancer (Goodrich et al., 2022); hypertension and possible reduced glomerular filtration for kidney cancer (Shearer et al., 2021); reproductive factors for breast cancer (e.g. Ghisari et al., 2017; Cohn et al., 2020; Mancini et al., 2020a; Chang et al., 2023); or specific occupational exposures for bladder cancer (Eriksen et al., 2009).

As the main potentially confounding factors, sex, age, time, geography, socioeconomic status, and possibly race or ethnicity were measured and analysed with high accuracy, residual confounding by these factors was considered unlikely. Cooking practices such as frying and consumption of a number of food items (such as eggs, potatoes, red meat, snacks, and vegetables) have been associated with serum concentrations of PFOA and PFOS in a number of

studies. In a general population sample, these factors explained 14% and 24% of the variation in concentrations of PFOA and PFOS, respectively (Eriksen et al., 2011). Various foodstuffs have also been associated with some cancers, and therefore confounding by diet (with unpredictable magnitude and direction) cannot be ruled out in the general population studies, whereas confounding by diet was very unlikely in the occupational studies and the studies of communities with high-level exposure, because the dietary intake of PFAS was marginal compared with the main source of exposure.

2.8.5 Specific cancer sites and exposure to PFOA

(a) Kidney cancer

Three partly overlapping studies of workers and residents in West Virginia and Ohio, USA, have consistently shown increased risk of kidney cancer in relation to occupational and/or high-level environmental exposure (Steenland and Woskie, 2012; Barry et al., 2013; Vieira et al., 2013). The occupational mortality study reported an SMR for fluoropolymer workers in the highest exposed quartile of estimated cumulative PFOA serum concentrations compared with unexposed workers of 2.66 (95% CI, 1.15–5.24; 8 deaths) with indications of an exposure–response relation (Steenland and Woskie, 2012). The highly informative cohort study of workers and residents found an increasing risk of incident kidney cancer with increasing cumulative PFOA serum levels, albeit with borderline statistical significance (Barry et al., 2013). The adjusted hazard ratio for the fourth quartile of cumulative PFOA serum concentrations versus the first was 1.58 (95% CI, 0.88–2.84; 105 cases; linear trend test, $P = 0.18$; using the log continuous PFOA serum concentration, $P = 0.10$). Findings were consistent with results of the third partly overlapping study from this geographical area, a register-based case–control study in Ohio that reported an adjusted odds ratio for incident kidney cancer in exposed people in the highest PFOA serum concentration quartile (110–655 µg/L [ng/mL]), versus the unexposed, of 2.0 (95% CI, 1.0–3.9; total, 246 cases) (Vieira et al., 2013). In this study, there was some concern about the appropriateness of the control group, which comprised people with all other cancers excluding those of the testis, liver, and pancreas.

The results of two (less informative) occupational cohort studies did not corroborate or refute the above findings. The cohort study of APFO workers at the Cottage Grove facility in Minneapolis, Minnesota, USA did not find indications of an increased incidence of kidney cancer in exposed workers. The hazard ratio for the fourth quartile versus the unexposed workers (Saint Paul plant) was 0.73 (95% CI, 0.21–2.48; 16 exposed cases) and there was no indication of increasing risk across increasing quartiles of exposure (see Table 2.2). However, the wide confidence intervals were not incompatible with the effects observed in the earlier studies (Raleigh et al., 2014). The exposure metric was based upon air measurements of PFOA, which may be less reliable than biological measurements if exposure occurs through pathways other than inhalation or if there is large variation in pulmonary absorption of PFOA due to, for instance, differential use of respiratory protection equipment or high pulmonary ventilation in some physically demanding jobs. The international study of mortality in TFE-production workers (Consonni et al., 2013) was not informative because of the semiquantitative exposure assessment and the small number of cases ($n = 10$).

Unlike the above five studies of highly exposed populations, two nested case–control studies and a case–cohort study using a single prediagnostic PFOA serum concentration addressed risk associated with the much lower background exposure of the general US population (Shearer et al., 2021; Rhee et al., 2023b; Winquist et al., 2023). The study based upon the

PLCO Trial cohort reported an adjusted odds ratio for RCC (constituting about 80–90% of all kidney cancers) in the highest exposure quartile (> 7.3–27.2 μg/L [ng/mL]) versus the lowest (< 4.0 μg/L [ng/mL]) of 2.63 (95% CI, 1.33–5.20) (Shearer et al., 2021). Adjusted for other PFAS compounds, the OR was 2.19 (95% CI, 0.86–5.61). This relative risk for RCC observed in the general population was similar to that for kidney cancer observed among people with an exposure more than one order magnitude higher. If these associations are causal, this indicates a non-linear exposure–response relation with a steep increase in risk at very low exposure levels, which tails off or even reaches a plateau with higher exposure (Steenland et al., 2022). The other nested case–control study of an ethnically diverse US population with background exposure levels did not find an association between prediagnostic PFOA serum concentrations and risk of incident RCC overall (OR for a 1-unit increase in PFOA serum concentration on the $\log_2$ scale, 0.89; 95% CI, 0.67–1.18), but – consistent with the earlier findings – the risk was elevated in White participants (23% of the study population), albeit with wide confidence intervals (adjusted OR for a 1-unit increment in PFOA serum concentration on the $\log_2$ scale, 2.12; 95% CI, 0.87–5.18; Rhee et al., 2023b). Finally, the case–cohort study conducted within the CPS-II LifeLink Cohort (in which 98% of participants were White) found no increased risk for all kidney cancers (HR for continuous $\log_2$-plasma PFOA concentrations was 1.08; 95% CI, 0.88–1.33, 156 cases; Winquist et al., 2023). For RCC, the hazard ratio was 1.06 (95% CI, 0.83–1.35). Among women (38% of the case–cohort group), for all kidney cancers there was an increased hazard ratio of 1.33 (95% CI, 0.97–1.83; 65 cases) and for RCC it was 1.54 (95% CI, 1.05–2.26; 42 cases). Of note was that this was a "survivor cohort", in which the median age when follow-up started was 70 years, about 8 years after enrolment began in the CPS-II. At age 40–60 years, the rate of RCC is twice as high in men as in women, which could have contributed to a differential survivor effect by sex (Mancini et al., 2020b; NCI, 2023).

The Working Group concluded that increased risks of kidney cancer overall or RCC in relation to PFOA exposure were reported by two independent and highly informative studies (Barry et al., 2013; Shearer et al., 2021). These studies included large study populations and long follow-up, across which there were large exposure contrasts spanning background, high environmental, and extremely high occupational exposure. There was comprehensive individual-level assessment of cumulative exposure in one of these studies (Barry et al., 2013). Exposure–response relations were observed overall in these two independent populations. The findings were not corroborated overall by those of two other less-informative occupational studies (Raleigh et al., 2014; Consonni et al., 2013), and only among subgroups in two other general population studies (Rhee et al., 2023b; Winquist et al., 2023). In the random-effects meta-analysis conducted by the Working Group, which was based on six studies (three of which were from the Mid-Ohio Valley, as well as Shearer et al., 2021, Rhee et al., 2023b, and Winquist et al., 2023) a meta-rate ratio per 10 ng/mL of 1.16 (95% CI, 0.98–1.38; $I^2 = 0.91$) was estimated for PFOA. The limitations of the meta-analysis were estimation of the linear exposure–response relation from two categorical data points, assumptions about the duration of exposure in three studies, assumptions about the midpoint in the high-exposure category in three studies, and lack of independence of three of the studies.

Taken together, the body of epidemiological evidence indicated that a causal association between PFOA and RCC is credible, but the evidence was not considered sufficiently consistent to rule out chance and bias with confidence. The studies did not allow for an evaluation of kidney cancers of non-RCC histology subtype.

(b) Testicular cancer

The cohort study of the highly exposed Mid-Ohio Valley population with PFOA exposure substantially above background levels (Barry et al., 2013) and the nested case–control study of US Air Force servicemen with exposure levels in the range of the general US population (Purdue et al., 2023) were considered the most informative for the evaluation of testicular cancer. Barry et al. (2013) reported an adjusted hazard ratio for incident testicular cancer of 1.34 (95% CI, 1.00–1.79) for a 1-unit increase in natural log-transformed serum concentrations in unlagged analyses. This observation was not corroborated by Purdue et al. (2023), who reported an OR for testicular germ cell tumour (TGCT; the most common type of testicular cancer) of 0.8 (95% CI, 0.5–1.4), comparing the highest exposed quartile with the lowest, based on 530 cases and matched controls. There was no indication of an exposure–response relation (*P* for trend, 0.86), and similar results were observed in an analysis of the second sample collected in a subset of the population. The range of measured serum PFOA levels in 2005–2006 was 0.25–4752 ng/mL (median, 24.2 ng/mL) for residents in the study by Barry et al. (2013) compared with a geometric mean of 5.8 ng/mL for controls in the study by Purdue et al. (2023). Therefore, the higher exposure contrast in the former study may explain the discrepant findings. Moreover, the study of Air Force servicemen did not control for residential area, which may cause bias in an unpredictable direction. Findings in the study by Vieira et al. (2013) were compatible with an increased risk of testicular cancer, but the cancer cases included somewhat overlapped the cases in the study by Barry et al. (2013), and the study offered no improvements in design or analysis.

One additional population was exposed to high levels of PFOA (and to a much lesser extent other PFAS) resulting from industrial contamination in the Veneto region of Italy, and serum concentration data (more than 18 000 measurements in 2016 among those aged 14–39 years) were reported by municipality (n = 21) by Pitter et al. (2020). Orchiectomies by the same groupings of municipality in the Veneto region between 1997 and 2014 were reported separately (Sistema Epidemiologico Regionale, 2016). Orchiectomy was found to have high sensitivity and positive predictive value for testicular cancer in this region (Sistema Epidemiologico Regionale, 2016). The Working Group combined the serum and orchiectomy rate data and observed a strong positive correlation (Spearman correlation, 0.57; P = 0.006; 21 cases) between serum PFOA concentrations and rates of orchiectomy (standardized on age by 5-year age groups from ages 15 to 54 years to the overall regional rate) by municipality.

Few other studies addressed the of the association between PFOA exposure and testicular cancer. Results of two occupational mortality studies were also compatible with an increased risk but were based on very few cases (< 3), not permitting detailed analysis (Steenland and Woskie, 2012; Consonni et al., 2013). Moreover, these studies of mortality were considered less informative, owing to the high survival rate for testicular cancer, since mortality-based risk estimates reflect a mix of etiological and prognostic factors.

The Working Group concluded that there were indications in two independent populations for an increased risk of testicular cancer associated with PFOA serum concentrations in residents with a high level of exposure. In the third informative study, a null association was seen, but exposure levels were at background in this population. Overall, the Working Group concluded that a positive association between PFOA and testicular cancer is credible. However, chance and/or bias could not be ruled out as explanations for these findings, given the small number of cases in the few available studies and that one of the positive studies was of ecological design.

(c) Bladder cancer

Two occupational cohort studies (Raleigh et al., 2014; Steenland et al., 2015), the cohort study of the Mid-Ohio Valley population with high exposure (Barry et al., 2013), and the partly overlapping registry-based case–control study (Vieira et al., 2013) provided data on the incidence of bladder cancer in relation to individual-level estimates of cumulative PFOA exposure. None of these studies that included large study populations with a strong exposure contrast indicated an increased risk of bladder cancer in relation to PFOA exposure, and the results were consistent with those of the Danish Diet Cancer and Health Cohort study (Eriksen et al., 2009) and a large US case–cohort study (Winquist et al., 2023). The former study only addressed low-level background exposure and did not adjust for co-exposure to PFOS, but PFOS was not associated with increased risk. Finally, the international occupational mortality study did not observe an increased risk of fatal bladder cancer (Consonni et al., 2013), and some indication of increased risk of fatal bladder cancer in an occupational cohort study (Steenland and Woskie, 2012) was not corroborated by the subsequent incidence study that had an improved exposure assessment (Steenland et al., 2015).

The Working Group concluded that the epidemiological evidence in aggregate did not indicate a positive association between PFOA at environmental or occupational exposure levels and urinary bladder cancer, but noted that the occupational cohort studies in particular include few exposed cases, limiting informativeness, and that exposure misclassification may have biased associations towards the null.

(d) Prostate cancer

Altogether, six studies on the risk of prostate cancer and PFOA exposure were fairly consistent in reporting null or inverse associations regardless of study design, type of population (background exposure, high environmental or occupational exposure), method of exposure assessment (estimates of external exposure using various approaches or measurements of serum concentration) or outcome (incident cases or mortality) (see Section 2.3.2 for details). This collection of studies included highly informative studies with a large exposure contrast and lifelong estimates of cumulative PFOA serum concentrations (Barry et al., 2013); high comparability of exposed and non-exposed (Rhee et al., 2023a); extensive control for potential confounding, also including education, BMI and diet (Eriksen et al., 2009); a large study size (Winquist et al., 2023); and examination of more aggressive (i.e. fatal) prostate cancer (Steenland and Woskie, 2012; Raleigh et al., 2014), although cases were few in the latter. One study of incident prostate cancer in an occupational cohort found a higher risk in the second to fourth quartiles based on estimated cumulative PFOA exposure, compared with the lowest quartile, but without a consistent exposure–response trend (Steenland et al., 2015).

An inherent issue in all studies of incident prostate cancer was detection bias in populations undergoing different levels of medical surveillance, because of the common occurrence of latent disease that may be detected by blood assays, and which may cause bias in an unpredictable direction.

The Working Group concluded that the results of several studies addressing diverse populations in different countries and with different designs fairly consistently did not indicate an association between exposure to PFOA and prostate cancer, but considering exposure misclassification that most probably caused bias towards the null, issues related to outcome ascertainment, and latency periods of < 30 years in several studies, the epidemiological evidence did not preclude that such associations may exist.

(e) Breast cancer

The available evidence included two occupational cohort studies with high-level exposure to PFOA but with few cases of incident (Raleigh et al., 2014) or fatal (Steenland and Woskie, 2012) breast cancer, one large cohort study addressing high-level environmental exposure of community residents on the basis of modelled estimates of individual cumulative lifelong serum PFOA concentrations (Barry et al., 2013), and a case–control study of Mid-Ohio Valley residents with a high level of exposure (Vieira et al., 2013, partly overlapping Barry et al., 2013). These studies found no associations between PFOA exposure and breast cancer overall but did not separately evaluate pre- and postmenopausal cancer or subtypes of breast cancer. Moreover, three large cohort or nested case–control studies addressing background exposure of the general population did not report increased risk of incident breast cancer with increasing prediagnostic PFOA serum concentrations, either overall or for pre- or postmenopausal breast cancer, when these were analysed separately (Ghisari et al., 2017; Cohn et al., 2020; Chang et al., 2023). These studies extensively controlled for confounders; however, most could not address risk for specific subtypes. A large case–cohort study of female retirees from a motor vehicle company in China (Dongfeng-Tongji cohort; see Section 2.1.14 for details) reported higher risk of incident breast cancer with higher levels of prediagnostic PFOA plasma concentrations (Feng et al., 2022). The hazard ratio for the highest quartile of PFOA serum concentration versus the lowest was 1.69 (95% CI, 1.05–2.70), with a positive trend. It was not clear how this selected sample of retirees compared with the general population of Chinese women and how selection might influence risk estimates. Moreover, a large cohort study in France of primarily teachers (E3N cohort; see Section 2.1.10 for details) found an increased risk with wide confidence intervals for postmenopausal cancer in the second quartile of prediagnostic PFOA serum concentrations (OR, 1.69; 95% CI, 0.89–3.21) but not in higher quartiles (Mancini et al., 2020a). There was no indication of an exposure–response relation, and risk estimates were not adjusted for PFOS, which also was related to risk of breast cancer in this study.

The association between PFOA and breast cancer was also studied in a large, nested case–control study of US teachers (CTS; see Section 2.1.8 for details, Hurley et al., 2018) and five non-nested case–control studies that all evaluated associations with background exposure of the general population (Wielsøe et al., 2017; Tsai et al., 2020; Itoh et al., 2021; Velarde et al., 2022; Li et al., 2022b). In spite of methodological strengths, such as extensive control for potential confounding, including a range of known determinants related to reproduction, lifestyle, and other environmental contaminants in some of the studies, all were based on measurement of PFOA in postdiagnostic blood samples, and only three studies specified whether efforts were made to collect samples before treatment (Tsai et al., 2020; Velarde et al., 2022; Li et al., 2022b). Moreover, several studies were limited by small sample sizes and control groups with questionable representativeness of the population from which cases were recruited. Findings with respect to breast cancer overall in relation to PFOA exposure were diverse in these six studies – some studies provided indications of increased risk (Wielsøe et al., 2017; Li et al., 2022b), others did not (Hurley et al., 2018; Tsai et al., 2020; Itoh et al., 2021; Velarde et al., 2022).

Breast cancer is a heterogeneous tumour type, and subtypes defined by different ER or PR characteristics may have different etiologies (Yager and Davidson, 2006). Therefore, it might assist causal inference to distinguish risk according to tumour subtype – not least because there is evidence that PFAS compounds may interfere with receptor-mediated hormonal signalling (see Section 4.2.8 for details). Five studies of incident

breast cancer in general population samples provided risk estimates according to breast cancer receptor characteristics, but with inconsistent results. The large, nested case–control studies of the E3N cohort (Mancini et al., 2020a) and the PLCO cohort (Chang et al., 2023) both used prediagnostic serum samples and found some indications of increased risk related to all receptor subtypes (Mancini et al., 2020a; ER+, ER–, PR+, PR–) or to some but not others (Chang et al., 2023; ER–, PR–, ER–/PR–) but without an exposure–response relation, with limited statistical power and without adjustment for the effects of other PFAS (except Chang et al., 2023). Among three case–control studies that used cross-sectional sampling of blood specimens, Li et al. (2022b) reported increased risk with an exposure–response pattern for ER+ and PR+, but not for ER– and PR–. Itoh et al. (2021) reported null or reduced risk in all examined receptor type combinations (ER+/PR+; ER+/PR–; and ER–/PR–), and Tsai et al. (2020) found (with one exception) null or reduced risk in ER+ and ER– subtypes. Although some of these studies were distinguished by extensive adjustment for potential confounders, including both known determinants for breast cancer and, in some cases, other persistent organic compounds (Itoh et al., 2021), they had other methodological drawbacks (for details, see Section 2.4 and Table 2.4). A general issue pertaining to many studies examining receptor subtypes was low statistical power, which complicates causal inference. Similarly, the only study with analyses stratified by polymorphisms in selected xenobiotic and metabolizing genes had limited informativeness because of insufficient statistical power (Ghisari et al., 2017). Finally, a systematic review and meta-analysis included 18 papers of which 11 were eligible for meta-analysis (Chang et al., 2024). The summary rate ratio per 1-unit increase in natural log-transformed serum or plasma PFOA concentration was 0.95 (95% CI, 0.77–1.18) in analyses including all risk estimates. Excluding studies that assessed exposure after diagnosis of breast cancer revealed a summary rate ratio of 1.16 (95% CI, 0.96–1.40). There was considerable heterogeneity across studies.

The Working Group concluded that the most informative epidemiological studies showed a slightly elevated but uncertain association with PFOA. Overall, the two most informative studies (Mancini et al., 2020a; Chang et al., 2023) were null overall but were the only prospective studies that examined postmenopausal breast cancer cases by ER/PR receptor status. Both found non-linear positive associations with ER– and PR– postmenopausal breast cancer. The statistical power was low in studies examining associations with specific tumour subtypes or stratified by levels of endogenous hormone levels (pre- or postmenopausal cancer), limiting the ability to identify causal associations. Moreover, there were few data on risk at exposure levels above background. Overall, despite some evidence of associations for certain subgroups, the available epidemiological evidence was not considered sufficiently consistent to permit a conclusion to be made about the presence of a causal association between exposure to PFOA and breast cancer.

(f) Thyroid cancer

The study of residents with high environmental exposure in the Mid-Ohio Valley, USA, included 86 cases of validated incident cancer and was considered the most informative of a total of seven studies providing data on risk of incident cancer of the thyroid gland (Barry et al., 2013). This study found indications of increased risk of incident thyroid cancer overall but no exposure–response relation, attenuated 10-year lagged risk estimates, and wide confidence intervals (HR per unit cumulative serum PFOA concentration, natural log scale, no lag, 1.10; 95% CI, 0.95–1.26). The corresponding hazard ratio in the subset of workers with substantially higher exposure at the polymer-production plant in Parkersburg,

West Virginia, USA, was 1.93 (95% CI, 1.00–3.71) but with strong attenuation in 10-year lagged analyses based on 8 cases (Barry et al., 2013). The partly overlapping case–control studies in West Virginia and Ohio based on 343 cases did not observe an increased risk of incident thyroid cancer in relation to PFOA exposure (Vieira et al., 2013). A case–control study nested within a cohort of nulliparous pregnant women in Finland found no associations overall but weak associations in women aged > 40 years at diagnosis (OR, 1.20; 95% CI, 0.71–2.01) (Madrigal et al., 2024), and a small nested case–control study likewise reported null results (van Gerwen et al., 2023). Two occupational mortality studies of predominantly male workers were considered uninformative because of low numbers and because mortality is a less appropriate outcome measure because of the high survival rate for thyroid cancer (Leonard et al., 2008; Lundin et al., 2009). Finally, two case–control studies in China addressing background exposure levels reported strong inverse associations between postdiagnostic PFOA serum concentrations and risk of thyroid cancer (Liu et al., 2022; Li et al., 2023).

The Working Group concluded that there was no consistent epidemiological evidence for increased risk of thyroid cancer in relation to occupational or environmental exposure to PFOA across the available studies, which generally had small numbers of cases.

(g) Liver cancer

Of the nine studies addressing the association between PFOA and liver cancer, the cohort study of residents with high environmental exposure in Mid-Ohio Valley, USA, (Barry et al., 2013) and the Diet, Cancer and Health Cohort (Eriksen et al., 2009) were considered particularly informative. These cohorts provided incidence data, had large and well-characterized study populations with high completeness of verified cases, validated lifelong estimates of cumulative internal exposure or prediagnostic serum sampling, and meticulous control for confounding, including adjustment for tobacco smoking, alcoholic beverage consumption, and – in one study – occupation as a waiter or cook, which have been associated with risk of liver cancer. These studies found no associations between levels of PFOA exposure and risk of liver cancer. This finding was also consistent with results of the Ohio and West Virginia cancer registry-based case–control studies (Vieira et al., 2013; for details, see Section 2.1.22), which was also in a highly exposed population (overlapping with Barry et al., 2013). Six other studies of liver cancer reported similar essentially null results but were considered less informative. Four of these were occupational cohort studies with very high exposure contrast but with too few cases for causal inference (Steenland and Woskie 2012; Consonni et al., 2013; Raleigh et al., 2014; Girardi and Merler, 2019). A nested case–control study of the MEC was distinguished by its study of non-viral HCC and found no associations with prediagnostic PFOA plasma concentrations (Goodrich et al., 2022). Finally, a hospital-based case–control study in China was less informative because of various methodological limitations (Cao et al., 2022; for details, see Section 2.5.1). The Working Group concluded that most findings for liver cancer were null, and that most studies, including the one positive high-exposure study (Girardi and Merler, 2019), had few cases.

(h) Pancreatic cancer

Two occupational cohort studies of mortality (Steenland and Woskie, 2012; Raleigh et al., 2014) and incident cancer (Raleigh et al., 2014), a cohort study of a community with high environmental exposure (Barry et al., 2013), and the large nested case–cohort or case–control studies addressing background exposures in the general population in Denmark (Eriksen et al., 2009), in the US PLCO cohort (Zhang et al., 2023), and the US CPS-II LifeLink Cohort

(Winquist et al., 2023) found no indications of increased risk of pancreatic cancer in relation to PFOA exposure. In contrast, a case–control study of male smokers nested within a cancer prevention study in Finland reported an overall increased risk of pancreatic cancer (OR per SD increase in PFOA on the $\log_{10}$ scale, 1.27; 95% CI, 1.04–1.56) (Zhang et al., 2023). The reasons for these discrepant findings compared with earlier studies were unknown. Men within the PLCO cohort who had ever smoked did not have an increased risk of pancreatic cancer (Zhang et al., 2023; see Table S2.5; Annex 4, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.who.int/636). Finally, in the international occupational mortality study of TFE synthesis and polymerization workers, the SMR for workers with the highest cumulative exposure estimate versus the national reference rate was 1.84 (95% CI, 0.67–4.00; 10 exposed cases) (Consonni et al., 2013).

The Working Group concluded that the epidemiological evidence on risk of pancreatic cancer at high levels of occupational exposure to PFOA concerned very few exposed cases and that findings in studies addressing high environmental and background levels were generally null.

(i) Colorectal cancer and cancers of the digestive tract other than liver and pancreas

The most informative occupational cohort study that investigated risk of colorectal cancer found increased incidence in the third and fourth quartiles versus the first quartile of estimated cumulative PFOA serum concentrations but with wide confidence limits and without an exposure–response relation (Steenland et al., 2015). The results of four occupational mortality studies were conflicting, but all reported on very few exposed cases (Leonard et al., 2008; Lundin et al., 2009; Consonni et al., 2013; Girardi and Merler, 2019). The case–control study in West Virginia and Ohio, USA, reported an increased incidence of colorectal cancer in participants with high, but not very high, estimated PFOA serum levels (OR, 1.3; 95% CI, 1.0–1.7; Vieira et al., 2013), but these findings were not corroborated by those of the partly overlapping study of Mid-Ohio Valley residents (Barry et al., 2013). Risk of oesophagus and stomach cancer was addressed by the Mid-Ohio Valley study (Barry et al., 2013), with essentially null findings, and by four occupational mortality studies (Leonard et al., 2008; Lundin et al., 2009; Consonni et al., 2013; Girardi and Merler, 2019). The findings of these studies were conflicting but all – except Consonni et al. (2013) – included fewer than 5 exposed cases (see Section 2.5.3 and Table S2.5 for details; Annex 4, Supplementary material for Section 2, Cancer in Humans, online only, available from: https://publications.iarc.who.int/636).

The Working Group concluded that there was no clear or consistent epidemiological evidence for an increased risk of cancer of the colorectum, oesophagus, or stomach in relation to PFOA exposure. There were no studies in low-exposure general populations. In occupational studies or studies on high environmental exposure, there were very few exposed cases, resulting in highly uncertain risk estimates.

(j) Cancers of lymphatic and haematopoietic tissue

The study of residents with high environmental exposure in the Mid-Ohio Valley, USA, found no indications of increased risk of incident leukaemia or non-specified lymphoma (Barry et al., 2013). These findings were fairly consistent with those from a US case–cohort study (Winquist et al., 2023) and with the mortality study of the fluoropolymer worker cohort in the Parkersburg polymer-production plant, which did not find indications of increased risk of fatal NHL or leukaemia in exposed workers (Steenland and Woskie, 2012). In contrast, the case–control studies in West Virginia and Ohio, USA, reported

an increased incidence of NHL among exposed groups and provided some indications of an exposure–response relation. The OR for residents with the highest estimated PFOA serum concentration, assuming 10-year residency and latency, versus unexposed residents was 1.8 (95% CI, 1.0–3.4; Vieira et al., 2013). The reason for this discrepancy was unknown, but the cohort study with modelled and validated lifelong cumulative exposure assessment was considered to be the most informative. Other occupational mortality studies added little to the evidence because of few exposed cases, resulting in very imprecise risk estimates, reporting risk for other subgroups of cancers of lymphatic and haematopoietic tissue, crude exposure assessment, and other methodological issues (Gilliland and Mandel, 1993; Lundin et al., 2009; Consonni et al., 2013; Girardi and Merler, 2019; for details, see Section 2.6.3).

The Working Group concluded that the studies addressing effects at high occupational exposure levels included very few exposed cases of cancers of lymphatic and haematopoietic tissue and that the strongest evidence on risk related to high environmental levels did not indicate an increased risk. Overall, the epidemiological evidence was insufficient to permit causal inference and to exclude the possibility that causal associations between PFOA exposure and cancer of lymphatic and haematopoietic tissue may exist.

(k) Other cancer types

One study of community residents with high exposure found weak indications of increased risk of brain cancer (Vieira et al., 2013), but findings were not corroborated by those of the most informative study of highly exposed Mid-Ohio Valley residents (Barry et al., 2013). Two occupational mortality studies did not find an increased risk, but there were 5 or fewer deaths in exposed people (Lundin et al., 2009; Consonni et al., 2013). No increased risk for melanoma associated with PFOA exposure was reported in the study of residents with high environmental exposure in the Mid-Ohio Valley, USA (Barry et al., 2013; Vieira et al., 2013). Two occupational cohort mortality studies included very few exposed cases of melanoma, resulting in very imprecise risk estimates (Leonard et al., 2008; Steenland et al., 2015). A positive association between PFOA exposure and mesothelioma was reported in one study of a polymer-production plant in Parkersburg, West Virginia, USA (Steenland and Woskie, 2012), but this finding was not replicated in other studies and was likely to be caused by exposure to asbestos at the plant. Some indication of an increased risk of lung cancer in relation to exposure to PFOA was reported in one study (Vieira et al., 2013), but five other studies, including some that were highly informative, did not find an increased risk (Alexander et al., 2003; Steenland and Woskie, 2012; Barry et al., 2013; Consonni et al., 2013; Girardi and Merler, 2019). The available epidemiological evidence base for evaluation of cancer at these organ sites was sparse and generally null. Finally, a case–control study found indications of an increased risk of retinoblastoma (adjusted OR per IQR increase in blood PFOA, 1.03; 95% CI, 0.97–1.09) in a population with background exposure levels (Chen et al., 2024).

(l) All sites combined

Three occupational cohort studies did not find indications of increased mortality from all types of cancers combined in analyses based upon internal comparisons or comparisons with non-exposed workers, which reduce the likelihood that risk estimates were attenuated because of primary healthy-worker selection or healthy-worker survivor bias (Steenland and Woskie, 2012; Consonni et al., 2013; Raleigh et al., 2014). These results are in line with those of the NHANES 1999–2014 cohort addressing general population background exposure, in which cancer mortality was not associated with PFOA serum levels (Wen et al., 2022). In contrast

to these five studies that all had high statistical power, one small study in Italy of perfluorocarbon-production workers who had the highest serum levels of PFOA ever published provided some, but inconsistent, indications of increased mortality from all cancers combined (Girardi and Merler, 2019).

The Working Group noted that null associations observed in studies of overall risk of cancer are of minimal value when it comes to causal inference of cancer etiology, because specific compounds such as PFOA cannot be expected to contribute to the occurrence of all cancer types, and therefore associations with any specific cancer type may be masked by null associations with other cancer types.

2.8.6 Specific cancer sites and exposure to PFOS

(a) Kidney cancer

The Swedish Ronneby Register cohort study of residents with high environmental exposure found some evidence for an increased risk of incident kidney cancer; when comparing with unexposed residents, the hazard ratio for residents with longer exposure was 1.47 (95% CI, 0.87–2.49) and for residents with more recent exposure was 1.85 (95% CI, 1.00–3.40) (Li et al., 2022a). However, the study did not distinguish the effects of PFOS (the predominant PFAS in drinking-water in this population) from those of other PFAS compounds that were also present at exposure levels above background (Li et al., 2022a). Of the two large nested case–control studies of general populations with substantial lower background exposure and with prediagnostic blood samples, one study observed an association in analyses not adjusted for other PFAS; however, neither study observed associations after adjustment for other PFAS (Shearer et al., 2021; Rhee et al., 2023b). A third large nested population-based case–control study also found no association overall, in men or women (Winquist et al., 2023). The only occupational cohort study that primarily addressed PFOS exposure (Alexander and Olsen, 2007) did not report kidney cancer data.

The Working Group considered that the epidemiological evidence on the association between PFOS and kidney cancer was too sparse to permit evaluation.

(b) Testicular cancer

The study of US Air Force servicemen exposed to levels comparable to those in the general population was the only available study with a sufficient number of cases that addressed the risk of TGCT (the most common type of testicular cancer) related to PFOS exposure and adjusted for other PFAS (Purdue et al., 2023). In an analysis that included the entire study population (using first or only samples), the adjusted OR for the highest versus the lowest exposed quartile was 1.8 (95% CI, 0.9–3.6; *P* for trend, 0.15), whereas the OR for the subset of the population with repeated blood samples (second blood sample only; about one third of the participants) was 4.6 (95% CI, 1.4–15.1; *P* for trend, 0.009). These estimates were adjusted for other PFAS. The reasons for these discrepant results – if not due to chance – were unknown. The men with repeated samples had accumulated more exposed years, but PFOS measurement levels were similar between the two samples, and both were similar to background levels (e.g. as measured in NHANES). Both measurements were obtained by analysis of samples collected on average about 5 years before diagnosis. The Ronneby Register cohort study reported a hazard ratio of 1.51 (95% CI, 0.56–4.03; 45 incident cases) among residents with the longest exposure compared with residents in the same municipality who were not exposed to contaminated drinking-water (Li et al., 2022a). Although PFOS was the main contaminant of drinking-water among Ronneby residents, it was not possible to distinguish the effects of PFOS

from those of other PFAS compounds that were also present at levels above background.

The Working Group concluded that in the two available studies, an imprecise or inconsistent positive association was observed between PFOS exposure and cancer of the testis. Overall, the evidence did not permit the evaluation of a causal association between PFOS and testicular cancer because there were too few informative studies, unexplained inconsistencies between findings, or potential confounding by other PFAS compounds (i.e. PFHxS).

(c) Bladder cancer

An occupational cohort study of PFOS-exposed workers at a chemical plant in Alabama, USA, found indications of an increased incidence of bladder cancer in workers with the highest cumulative PFOS exposure in internal comparisons (Alexander and Olsen, 2007), but these included only a small number of cases, and co-exposure to other PFAS was likely. Incomplete registration and ascertainment of diagnoses may have caused non-differential misclassification of the outcome and bias towards the null. The Ronneby Register cohort study reported moderately elevated risks of bladder cancer among residents with later and longer exposure to PFOS-contaminated drinking-water compared with unexposed residents (HR, 1.50; 95% CI, 0.98–2.28; and HR, 1.39; 95% CI, 0.95–2.02; respectively) (Li et al., 2022a). The group-based exposure assessment not accounting for individual variation limited the options to explore risk at the full range of exposure. The Danish Diet, Cancer, and Health Cohort study (Eriksen et al., 2009) and a US case–cohort study (Winquist et al., 2023) did not find increased risk of bladder cancer. Eriksen et al. (2009) applied a more stringent design including detailed adjustment for smoking and several occupations that have been associated with bladder cancer. Although the average exposure was lower than in Ronneby, exposure levels were overlapping. The Working Group concluded that there were findings indicating an increased risk of bladder cancer in two studies of workers and residents with high environmental exposure, but not in two studies of populations with lower (background) levels of PFOS exposure. The Working Group concluded that there were too few studies available to permit a conclusion to be drawn about the association between PFOS and bladder cancer.

(d) Prostate cancer

Two highly informative cohort studies of background exposure levels in the general Danish and US population investigated the association between PFOS and risk of incident prostate cancer (Eriksen et al., 2009; Rhee et al., 2023a). Eriksen et al. reported moderately increased risks of prostate cancer in the three upper quartiles compared with the lowest quartile, but exposure–response analyses did not provide solid evidence for a linear trend (IRR per 10 ng/mL increase in PFOS concentration, 1.05; 95% CI, 0.97–1.14). The US population-based study reported an OR per unit increase on $\log_2$ scale of 0.99 (95% CI, 0.79–1.23) (Rhee et al., 2023a). Other environmentally exposed population studies did not provide substantial additional information (Hardell et al., 2014; Li et al., 2022a; Winquist et al., 2023). In particular, there were no data available from occupational cohorts with much higher exposure levels.

The Working Group concluded that two large cohort studies of the general population found no consistent evidence for increased risk of prostate cancer in relation to PFOS exposure, but there were no available data at higher exposure levels in an occupational setting.

(e) Breast cancer

Almost all the available studies on associations between PFOS and breast cancer were based upon general population samples, which limited causal inference because of the narrow ranges of exposure. Findings in the most informative

nested case–control and case–cohort studies based upon large samples, incident data, prediagnostic serum PFOS measurements, and good confounder control were partly conflicting. The study conducted in the French E3N Cohort (Mancini et al., 2020a) provided some indications of an increased risk of overall breast cancer at higher PFOS exposure levels. This association appeared to be stronger and linear when restricted to hormone receptor-positive breast cancers. Similarly, in the US PLCO cohort (Chang et al., 2023), PFOS appeared to be positively associated only with hormone receptor-positive breast cancers. These results were not confirmed in the case–cohort study conducted in the Dongfeng-Tongji cohort in China (Feng et al., 2022), or in the CPS-II LifeLink Cohort (Winquist et al., 2023); however, these two studies did not explore the association by hormone-receptor tumour subtype. The only informative available study of populations with higher environmental exposure, the Swedish Ronneby Register cohort study, did not find associations between exposure to PFAS (including PFOS) and overall breast cancer risk, but did not investigate associations with specific tumour subtypes (Li et al., 2022a). Findings in several case–control studies were less informative because of methodological issues relating to postdiagnostic or post-treatment PFOS measurements, and potential confounding (for details, see Section 2.4 and Table 2.4).

In summary, there was little evidence of an association between PFOS exposure and breast cancer overall. However, the two most informative studies (Mancini et al., 2020a; Chang et al., 2023), which were the only prospective studies to examine the association by hormone-receptor tumour subtype, found an imprecise but increased risk of hormone receptor-positive breast cancers associated with higher levels of PFOS. This finding was somewhat contradicted by the null findings among postmenopausal women in the Dongfeng-Tongji cohort (Feng et al., 2022) and the CPS-II cohort (Winquist et al., 2023), which did not stratify by receptor status (most postmenopausal breast cancers are hormone receptor-positive). Given the inconsistencies across studies, the Working Group considered that the available evidence on risk of breast cancer associated with PFOS exposure was inconclusive.

(f) Thyroid cancer

The only studies available to the Working Group were the Swedish Ronneby Register cohort study of residents with high environmental exposure (Li et al., 2022a); a case–control study nested within the FMC including nulliparous women from the general population (Madrigal et al., 2024); a case–control nested within the Bio*Me* cohort (van Gerwen et al., 2023); and two case–control studies on risk related to background exposure of the general population (Liu et al., 2022; Li et al., 2023). The Ronneby study reported an increased risk of thyroid cancer (type unspecified) in exposed women (SIR based on regional reference rates, 2.08; 95% CI, 1.19–3.38; 16 exposed cases) but not in men (3 exposed cases). The FMC study did find indications of an increased risk of papillary thyroid cancer among women diagnosed at age < 40 years; however, when adjusted for exposure to other PFAS, the association was greatly attenuated – the OR for serum PFOS increment by $\log_2$ in women aged < 40 years at diagnosis was 1.14 (95% CI, 0.68–1.93; 185 cases). Although PFOS was present at by far the highest concentrations in contaminated drinking-water in the Ronneby municipality, the effects of other PFAS could not be accounted for in this study (Li et al., 2022a), the study by van Gerwen et al. (2023) had very small numbers in the longitudinal subsample, and the two case–control studies were less informative because of postdiagnostic measurements of exposure, potential for bias related to selection of reference groups, or few cases (Liu et al., 2022; Li et al., 2023).

The Working Group noted that there were inconsistent indications of positive associations between PFOS exposure and thyroid cancer in women, but that, overall, studies were too few to permit an evaluation of causal associations.

(g) Liver cancer

Of the five studies addressing the association between PFOS and liver cancer, the nested case–cohort study of the Danish Diet, Cancer, and Health Cohort (Eriksen et al., 2009) was considered particularly informative because of the large well-characterized study population, high completeness of verified cases, prediagnostic serum sampling, and meticulous control for confounding. No association between levels of PFOS exposure and risk of liver cancer was identified. This study was limited by low exposure levels and rather narrow exposure contrast, but its findings were consistent with those of the Ronneby Register cohort study that addressed much higher environmental exposure (Li et al., 2022a). Also, the Ronneby study did not find an increased risk of liver cancer but included < 10 exposed cases. An occupational mortality study was not informative because it included even fewer cases (Alexander et al., 2003). In contrast, the nested case–control study in the MEC, which was distinguished by its study of non-viral HCC, found some indications of an increased, BMI-adjusted, risk for higher plasma PFOS concentrations (> 54.9 ng/mL, corresponding to the NHANES 90th percentile) compared with lower concentrations (OR, 2.90; 95% CI, 0.78–10.00), but without a clear exposure–response relation (Goodrich et al., 2022) and a risk estimate based upon a post-hoc grouping of exposure. Finally, a Chinese hospital-based case–control study was less informative because of various methodological limitations (Cao et al., 2022; for details see Section 2.5.1).

The Working Group concluded that the most informative studies found no associations between PFOS exposure and risk of liver cancer and, overall, the available epidemiological studies were too few to permit an evaluation of causal associations.

(h) Other cancer types

One cohort study of residents with high environmental exposure (Li et al., 2022a) and two large studies of background exposure (Eriksen et al., 2009; Zhang et al., 2023) found no indications of increased risk of pancreatic cancer. An occupational mortality study of PFOS-production workers in Decatur, Alabama, USA, found no increased risk of fatal cancer of the digestive organs and peritoneum combined, but estimates were based on only 5 deaths (Alexander et al., 2003). The Ronneby Register cohort found no significant increase in the incidence of cancer of the colon, rectum, oesophagus, or stomach in residents with high environmental exposure (Li et al., 2022a). The only available study on associations between PFOS and brain cancer was the Ronneby Register cohort study, which found weak indications of an increased risk of incident brain cancer among highly exposed residents (Li et al., 2022a), but risk estimates were imprecise and the effects of PFOS – which was present at highest concentrations in contaminated drinking-water – and other PFAS present at lower concentrations could not be distinguished. Two occupational cohort studies of fatal cancer of lymphatic and haematopoietic tissue in workers with exposure to PFOS were not informative because of the crude exposure assessments and very few cases (Alexander et al., 2003; Girardi and Merler, 2019). The Ronneby Register cohort study had greater statistical power, but lower exposure levels did not reveal any increased risk of several specific types of cancer of lymphatic and haematopoietic tissue, including NHL, multiple myeloma, and chronic lymphocytic leukaemia, whereas residents who had ever been exposed had a higher risk of chronic myeloid leukaemia but with too few cases to allow more detailed analysis (Li et al., 2022a). One occupational

cohort study addressed risk of fatal melanoma, but the few cases resulted in very imprecise estimates (Alexander et al., 2003). The Ronneby Register cohort study had higher statistical power and found some evidence for an increased risk of melanoma in the subset of residents with the latest ever-high exposure to PFAS-contaminated drinking-water (HR, 1.54; 95% CI, 1.09–2.19) but not in those with the longest ever-high exposure (HR, 1.14; 95% CI, 0.80–1.64), compared with those with no exposure. The findings were not corroborated or refuted by other studies. Finally, a case–control study did not find an increased risk of retinoblastoma (adjusted OR per IQR increase in blood PFOS, 1.02; 95% CI, 0.95–1.09) in a population with background exposure levels (Chen et al., 2024).

The Working Group noted that there were too few studies available for the evaluation of associations between PFOS exposure and melanoma, retinoblastoma, and cancers of the pancreas, colon, rectum, oesophagus, stomach, brain, or lymphatic and haematopoietic tissue.

(i) All sites combined

Overall cancer mortality was not increased among PFOS-exposed workers at the PFOS-production facility in Decatur, Alabama, USA (Alexander et al., 2003), and this was consistent with results from the Ronneby Register cohort study in which combined cancer incidence was not elevated in a population of residents with above-background exposure to PFOS in particular, but also PFHxS and PFOA to a lesser degree (Li et al., 2022a). On the other hand, overall cancer mortality was increased among members of the NHANES 1999–2014 cohort who had the highest serum PFOS values compared with the lowest tertile (Wen et al., 2022), and a small study in Italy with low statistical power reported some inconsistent indications of increased all-cancer mortality in workers with very high exposure to PFOS as well as other PFAS (Girardi and Merler, 2019).

The Working Group noted that the results of the few available studies were conflicting and that the number of informative epidemiological studies was too few to permit an evaluation of the evidence on PFOS and PFOA exposure and risk of all cancers combined.

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