



RAPID RESPONSE REPORT

SUPPLEMENT

**SCREENING FOR PFAS EXPOSURE IN
HUMANS**

2 JULY 2025

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■ LIST OF ABBREVIATIONS

ABBREVIATIONS

DEFINITION

AAP	American Academy of Paediatrics
ACOG	American College of Obstetricians and Gynaecologists
AHA	American Heart Association
AMSTAR	Assessing the Methodological quality of SysTemAtic Reviews
ATSDR	Agency for Toxic Substances and Disease Registry (USA)
BMH-Wal	Human biomonitoring – Wallonia
CIM	Interministerial Public Health Conference (Belgium)
CIRC/IARC	Centre International de Recherche sur le Cancer - International Research Centre on Cancer
CNGE	National College of Teaching GP - Collège National des Généralistes Enseignants (France)
CSI	Independant Scientific Advisory Board - Conseil Scientifique Indépendant (Walloon region)
DEGAM	Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin - German society for General Practice and Family Medicine
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency (USA)
ESRO	Expedited scientific research and reporting
EU-PARC	European partnership for risk assessment of chemical products
FLEHS	Flemish Environment and Health Studies
HBM	Human Biomonitoring
HBM-C	German commission of human biomonitoring
IARC	International Agency for Research on Cancer
INAMI	National Institute for Health and Disability Insurance (Belgium)
ISO/IEC	International Organization for Standardization (ISO) / International Electrotechnical Commission (IEC)
ISSeP	Scientific Institute for Public Service - Institut Scientifique de Service Public (Wallonia)
MeFOSAA	N-methylperfluorooctane sulfonamidoacetic acid
NASEM	National Academies of Sciences, Engineering, and Medicine (USA)
NTP	National Toxicology Program (USA)
OECD	Organisation for Economic Co-operation and Development
PFBS	Perfluorobutanesulfonic acid
PFDA	Perfluorodecanoic acid
PFHpS	Perfluoroheptanesulfonic acid
PFHxS	Perfluorohexanesulfonic Acid
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctanesulfonic acid

PFOSA	Perfluorooctanesulfonamide
PFUnDA	Perfluoroundecanoic acid
POP	Persistent Organic Pollutants
R³	Rapid Respond Report
RCGP	Royal College of General Practitioners (UK)
RIVM	National Institute for Public Health and Environment (Netherlands)
SIGN	Scottish Intercollegiate Guidelines Network
SSMG	Scientific Society for General Practice - Société Scientifique de Médecine Générale (Belgium)
TFA	Trifluoroacetic acid
UK NSC	National Screening Committee (UK)
USPSTF	US Preventive Services Task Force

1 PFAS ASSOCIATION WITH CANCER

1.1 Evidence on the association between PFAS and kidney cancer

KEY POINTS TABLE

- The consensus report of the *National Academies of Sciences, Engineering and Medicine* (NASEM, 2022) assessing the link between PFAS, and kidney cancer is primarily based on one high-quality case-control study conducted in the general population. In addition, four earlier studies of populations living in PFAS-contaminated areas were considered. Based on the consistency of the magnitude and direction of the effects observed, the NASEM deemed that there was sufficient evidence to establish an association between PFAS and kidney cancer.
- Following the report of the NASEM, two additional case-control studies with a similar design were conducted in the general population not overexposed to PFAS. Their findings were more heterogeneous, showing no clear overall association, but revealing an increased likelihood of kidney cancer within certain sub-populations (sex, ethnic groups).
- Apart from these studies conducted in the general population, most of the current scientific evidence derives from populations residing near PFAS-contaminated areas. Results of these studies were overall inconsistent, with some reporting non-statistically significant associations between PFAS exposure and kidney cancer. Although an association between the highest levels of PFAS exposure and kidney cancer is reported in some studies (particularly in those conducted in the contaminated areas in the Mid-Ohio Valley), considerable uncertainty persists. Many factors contribute to the overall heterogeneity of the studies, complicating interpretation and comparison:

Exposure and timeframe:

 - Exposure assessment methods vary across studies: general population studies used single PFAS serum measurements (collected in the 1990s or 2000s), while studies on highly exposed groups used pharmacokinetic models, or proxies (environmental monitoring data).
 - The levels of PFAS exposure, ranges of concentrations and the types of exposure vary considerably across studies.
 - The description of the techniques used to measure PFAS serum concentrations is often lacking.
 - The duration of exposure varies considerably between studies.

Quality of data and risk of bias:

 - The overall methodological quality of the identified studies is low. Studies are prone to several sources of bias including selection bias (e.g. attrition, “healthy worker effect”), immortal bias, lag bias, or confounding bias.
 - Sample sizes and the number of kidney cancer cases varied widely across studies. Given the rarity of such type of cancer, statistical power may be limited.

Synthesis of evidence: estimating a pooled effect is challenging due to heterogeneity of exposure levels, differences in the reported outcomes, potential **duplication** of participant data across studies, characterisation of the reference group, and variation in adjustment variables.

- The extant body of evidence provides informative, though limited, insights into a potential association between PFAS exposure and kidney cancer. However, the precise magnitude of excess risk at the individual level, as well as the exposure thresholds associated with increased risk, remain insufficiently defined. While the NASEM have concluded that there is sufficient evidence to support an association, such statement cannot yet be fully supported by the existing literature and should be further explored. Our findings align closely with the conclusions outlined in the recent report from the IARC, concluding that while epidemiological evidence suggests a plausible link between PFOA exposure and kidney cancer, the association lacks consistent support from the most informative studies, and the influence of chance, bias, or confounding by other PFAS cannot be confidently excluded.

1.1.1 Evidence considered in the National Academies report – 2022

The *National Academies of Sciences, Engineering and Medicine* (NASEM) evaluation deemed that there was sufficient evidence to establish an association between PFAS and kidney cancer.¹ This assessment was primarily informed on the study from Shearer *et al.* published in 2021², and four earlier studies.³⁻⁶ No assessment of the quality of studies was performed. The NASEM stated that the study from Shearer *et al.*² was sufficiently robust and adjusted for main confounders (see Table 1).

Additionally, they noted a strong exposure-response trend with the highest PFAS exposure exhibiting a heightened association. The consistency of the magnitude and direction of the effects observed in earlier studies led them to the conclusion that there is *sufficient evidence* to support a link between PFAS and an increased risk of kidney cancer.

The following section provides a comprehensive and pragmatic description of the studies included in the NASEM report, with a focus on the essential elements of their design and results (Figure 1) was retrieved from the NASEM's evaluation and showed the measures of this association through studies. More details can be found in Table 1).

Figure 1 – Association between PFOA exposure and kidney cancer through the studies considered by the consensus report from National Academies of Science (2022)

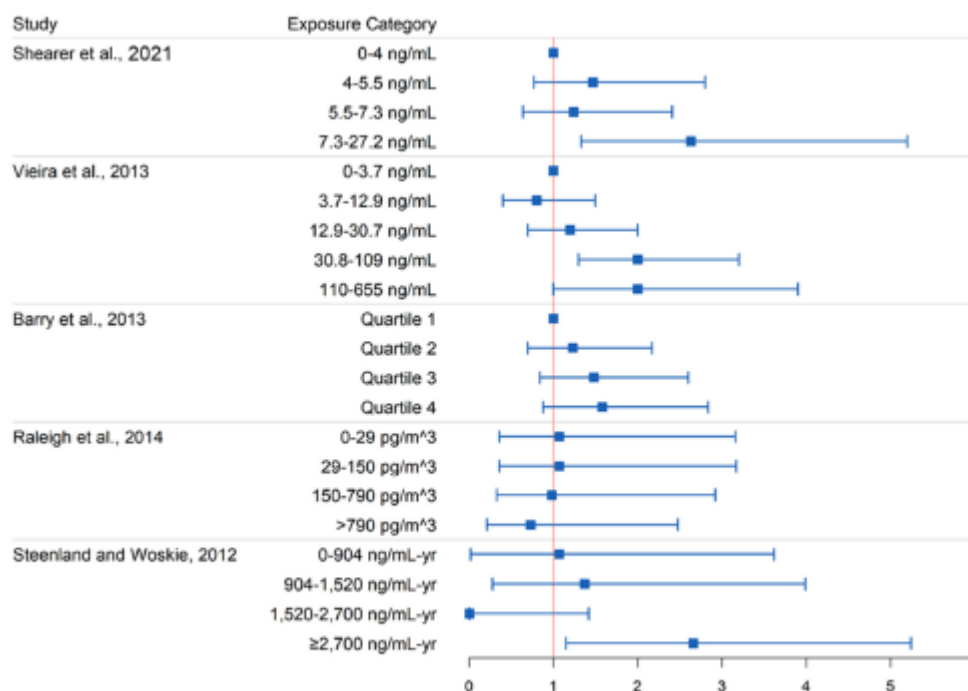


FIGURE 3-8 Kidney cancer adjusted rate ratios and 95% confidence intervals by study and PFOA exposure category.

Source: National Academies of Science - 2022 ¹

- In 2021 Shearer *et al.* published a nested case-control analysis within the “Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial” (see Box 1) to examine the association between pre-diagnostic serum concentrations of PFOA and seven other PFAS with the risk of renal cell carcinoma, in the general population.² There was only one serum sample per individual, and this was collected between 1993 and 2001^a. The study included 324 cases and 324 matched controls. Among the participants included in the screening arm of the PLCO study, with available prediagnostic samples, those with kidney cancer were identified and retrieved as cases. Controls were individually matched to cases, on the bases of age at enrolment, sex, race and ethnicity, study centre and study year of blood draw. Cases of kidney cancer were diagnosed between 2 and 18 years after serum collection (mean 8.8 years). PFAS serum concentrations were measured on a single blood sample per each participant. Category cut-off limits were determined based on the quartiles of serum PFAS concentrations among the control group. The findings revealed that the odds of PFAS exposure was significantly higher in the carcinoma group than in the control group, only in the highest concentration quartile. Specifically, individuals in the highest quartile of PFOA concentration exhibited a more than twofold increased risk of developing kidney cancer compared to those in the lowest quartile, but no statistically significant association was observed with the other quartiles. In addition, when considered as a continuous variable^b and after adjustment for the presence of other PFAS in the serum, the odds ratio for renal cell carcinoma was 1.71 for the increase of one unit in PFOA concentration (on a log₂ scale). Conversely, after

^a Among the available blood samples collected over time in the setting of the study, the earliest ones were used (personal communication from authors).

^b The incremental unit was a log base 2 scale: 1 unit increase in serum PFAS concentration on the log base 2 scale corresponds to an approximate doubling in analyte levels.

mutual adjustment for other PFAS than PFOA, only the association with PFOA remained statistically significant (see Appendix 1.1). In addition, no statistically significant interactions with PFOA were observed with PFOS and PFHxS. Sensitivity analysis (e.g. exclusion of participants with altered kidney function) did not reveal any discrepancies. It is important to emphasize that the distribution of PFAS concentrations among controls were similar to those observed in participants in the National Health and Nutrition Examination Survey (NAHNES) study^c, that have shown that the vast majority of the US population were reported to have detectable concentrations of PFAS in their blood.⁷

Box 1 – PLCO cancer screening trial

Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial was a study designed and sponsored by the National Cancer Institute (NCI) and conducted on men and women aged 55 to 74, enrolled between 1993 and 2001. The main goal of the study was to determine the effects of cancer screening through biomarkers or specific procedures (e.g. sigmoidoscopy) on cancer-related mortality. To this end, 74 000 participants were assigned to the screened and non-screened arms. The design included a baseline questionnaire, regular follow-up procedures, and blood samples collection which were then cryopreserved and biobanked.⁸

Vieira *et al.* conducted a case-control study to explore the association between PFOA exposure and the incidence of 18 cancer types. Cancer cases were identified using data from two cancer registries in Ohio and West Virginia near the *DuPont Teflon* manufacturing facility, including areas with PFAS drinking water contamination, as well as unexposed geographic areas. Cases participants were compared to a control group including individuals having a cancer different from liver, kidney, testicular or pancreatic.⁶ Analyses were performed on two different sets of data: the contamination of the water district and secondly, the estimated PFOA serum concentration. The determination of serum PFOA concentrations was achieved through the use of a methodology that integrated environmental exposure (based on the residence at time of diagnosis), and pharmacokinetic models^{d,9}. Levels of exposure to PFOA were categorised as ‘very high’, ‘high’, ‘medium’, ‘low’ and ‘unexposed’, based on the distribution in the study population (tertiles breaks of distribution were utilised as cutoffs). Based on these categories of PFOA exposure, the analysis^e revealed a positive association between PFOA exposure and kidney cancer, among individuals in the very high and high exposure quartile, assuming 10-year residency (see Table 1).

In the second part of the analysis, based on the water district contamination^f, the analysis comparing exposed and unexposed zones showed a non-statistically significant aOR of 1.1 (95%CI: 0.9-1.4). However, the subgroup analysis of several districts located in the exposed zones further revealed a statistically significant association between kidney cancer and PFOA concentrations in one exposed district including 23 cases (Tuppers Plains – see Table 1) when compared to non-exposed areas.

Barry *et al.* investigated the association between PFOA exposure and cancer incidence among residents in the same region as Vieira *et al.*⁶ (Ohio, in an area affected by emissions from a nearby *DuPont* chemical plant).³ The cohort consisted of adult community residents who resided in contaminated water districts or were employed at the local plant (no controls). Participants took part in a 2005–2006 baseline survey, during which serum concentrations of PFOA were measured (in the setting of the *C8 Health Project*).¹⁰ The same technique of estimation of cumulative serum concentration as in Vieira *et al.* was used.⁹ It is important to acknowledge that the concentrations demonstrate considerable variability. The cohort was interviewed in 2008-2011 on incidence of

^c <https://www.atsdr.cdc.gov/pfas/data-research/facts-stats/index.html>

^d PFOA concentrations were categorised on the distribution of the annual PFOA serum concentration among the exposed study population, assuming a 10-year residency. Values are presented in Table 1.

^e Adjusted odds ratio were calculated for exposure categories, with the category ‘unexposed’ serving as the reference group.

^f Cases living in contaminated water district area were identified. Cases outside the contaminated water districts were assigned to the unexposed group. Adjusted odds ratio were calculated for kidney cancer with contaminated districts versus unexposed water districts.

cancers^g. The analysis revealed an association between higher PFOA exposure (logged estimated cumulative PFOA concentration^h) and increased incidence of kidney cancer (hazard ratio > 1), but this trend was not statistically significant (see Table 1). Specifically, individuals in the highest exposure quartile exhibited a higher risk compared to those in the lowest quartile, though this did not reach statistical significance. It is important to note that the main limitation of the study is the likelihood that individuals could have died before inclusion.

The research by Steenland *et al.* reported on excess mortality rates among employees at the *DuPont* chemical plant in the same region as the studies described above (West Virginia).⁵ Using a model of estimation of the cumulative serum concentration, they estimated an average annual serum PFOA concentration of 350 ng/mL among the cohort, using historical data^{i,11}. The study then compared mortality outcomes^j against two reference groups: other *DuPont* workers in the region, and the general U.S. population. The number of cases of kidney cancers was limited to 12 cases. A modestly elevated standardised mortality ratio (SMR) for death from kidney cancer was observed when compared to the reference populations: it was 1.28 (95% 0.66-2.24) when the reference group was the workers of the region, while it was 1.09 (95%CI: 0.56-1.90) when the reference was the US population. However, the analysis by quartile of cumulative serum concentration of PFOA revealed an association of kidney cancer mortality and the highest quartile of PFOA estimated exposure^k (see Table 1 and Figure 1). The present study was an update of an earlier study (Leonard *et al.*¹²) which is also presented in Table 1 and described below.

Leonard *et al.* investigated mortality patterns among employees at the US *DuPont* chemical plant manufacture with the goal of determining if occupational exposure was associated with increased mortality risks, particularly focusing on several conditions (heart disease, diabetes and cancers).¹² Causes of death were retrieved from a local register (*DuPont Epidemiology Registry*), or through the *US National Death Index* (NDI Plus). This preliminary study was subsequently updated and published by Steenland *et al.*⁵ The cohort included individuals who had been employed at the plant between 1948 and 2002. Excess mortality analysis (SMR) was used to compare observed deaths in the cohort to expected deaths based on three reference populations (see Table 1). The number of cases of kidney cancer was small and a non-statistically significant increase of SMR kidney cancer was observed.

Raleigh *et al.* assessed the mortality and cancer incidence among employees from facilities involved in the production of ammonium perfluorooctanoate (APFO) in Minnesota.⁴ The study compared the data from these facilities with the mortality data from the population of Minnesota, and from data of another unexposed plant (incident cancer cases were identified through the consultation of cancer registries at the state level). First, global SMRs (i.e. all cancers as cause of death), and cancer-specific SMRs of the exposed and unexposed plants did not differ from the overall mortality rate in Minnesota^l. Second, by comparing APFO exposure quartiles to the non-exposed population, there was no statistically significant association between exposure to APFO and an increased the risk of cancer (see Table 1).

^g Incidence of cancer at any time. The self-reported information was confirmed using cancer registry and medical folders for those who underwent cancer before 1992.

^h The interpretation of the log cumulative exposure coefficient means that an increase of one unit of log cumulative exposure results in a relative risk of e^{β} .

ⁱ The job exposure matrix was based on serum data from 1 308 workers from 1979 to 2004. The estimated average serum PFOA level was 350 ng/mL.

^j Deaths were recorded until 2008 via the National Death Index or from death certificate data prior to the start of the National Death Index in 1979.

^k A similar result was observed in analysis with a 10 year lag (see Table 1).

^l Kidney cancer SMR was: 0.53 (95 %CI: 0.20 -1.16) in one plant and 1.23 (95%CI: 0.73 - 1.95) in the other one (see Table 1).

Table 1– Evidence table including studies from the consensus report from the NASEM

Author, year, country	Study design	Study period	Type of exposure (population characteristics)	Assessment of exposure	Types of PFAS	Outcome(s)	Main findings	Adjustment
Shearer ² , 2021, USA	Nested case control in the PLCO Cancer Screening Trial (324 cases of kidney cancer/324 matched controls)	1993-2001 Kidney cancers diagnosed from 2 to 18 years after blood collection	Environmental US (background exposure, i.e. no known PFAS contaminated area) Age: 55-70+ years	Measured pre-diagnostic serum concentration of PFAS; single blood sample	PFOA, PFOS, PFHxS PFUnDA, PFNA, EtFOSAA, MeFOSAA, PFDA Quartile of serum concentrations (µg/L): PFOA - Q1: <4 - Q2: ≥ 4 -5.5 - Q3: <5.5- 7.3 - Q4: >7.3- 27.2 PFOS - Q1: ≤ 26.3 - Q2: >26.3- 38.4 - Q3: >38.4- 49.9 - Q4: >49.9-154.2 PFHxS - Q1: ≤ 2.2 - Q2: >2.2- 3.4 - Q3: >3.4-5.5 - Q4: >5.5- 37.4	Kidney cancer incidence	aOR (95%CI) kidney cancer, quartile 2 to quartile 4 (reference: quartile 1): PFOA - Q2: 1.47 (0.77-2.80) - Q3: 1.24 (0.64-2.41) - Q4: 2.63 (1.33-2.37) <i>Trend p-value 0.007</i> PFOS - Q2: 1.67 (0.84-3.30) - Q3: 0.92 (0.45-1.88) - Q4: 2.51 (1.28-4.92) <i>Trend p-value 0.009</i> PFHxS - Q2: 1.41 (0.75-2.64) - Q3: 1.14 (0.59-2.20) - Q4: 2.07 (1.06-4.04) <i>Trend p-value 0.04</i> aOR (95%CI) kidney cancer, continuous value of PFAS (log-2 scale incremental unit) *: - PFOA: 1.71 (1.23-2.37) - PFOS: 1.39 (1.04-1.86) - PFHxS: 1.27 (1.03-1.56) <i>* : values for other PFAS are available on demand</i>	Age at enrolment, sex, BMI, tobacco, hypertension, renal function (eGFR), previous freeze-thaw cycle of the samples, years from blood collection to kidney cancer diagnosis
Vieira ⁶ , 2013, USA	Mixed design (for the analysis based on serum levels: 246 cases of	1996-2005	Environmental, proximity to PFAS contaminated zone (resident living near the	Modelled cumulative serum PFOA concentration (5 categories), based on	PFOA Categories of modelled concentrations of annual PFOA serum exposure (µg/L):	Kidney cancer incidence	aOR (95%CI) kidney cancer , based on estimated serum levels (in the region surrounding the plant- Ohio, 246 cases; 59 with 'detectable PFOA', compared to 'unexposed'):	Age, race, sex, diagnosis year, insurance provider,

	kidney cancer in contaminated and non-contaminated zones/controls from cancer registry: all other cancers except kidney, pancreas, testicular, liver; for analysis based on water district results: 751 cases of kidney cancer). Analyses based on: PFOA estimated serum levels and water district analysis		<i>DuPont Teflon</i> manufacturing) US, and surrounding unexposed zones	residence at time of diagnosis	• Very high: 110-655 • High: 30.8-109 • Medium: 12.9-30.7 • Low: 3.7-12.8		• Very high (n=9): 2.0 (1.0-3.9) • High (n=22): 2.0 (1.3-3.2) • Medium (n=17): 1.2 (0.7-2.0) • Low (n=11): 0.8 (0.4-1.5) aOR (95%CI) kidney cancer, based on water district analyses, comparing 94 cases of kidney cancer in exposed zones with 657 cases in unexposed population: Overall comparison between water contaminated and non-contaminated areas: 1.1 (0.9-1.4) Subgroup analysis of districts: • <i>District Little Hocking: 1.7 (0.9-3.3)</i> • <i>District Lubeck: 0.7 (0.4-1.3)</i> • <i>District Tupper's Plains: 2.0 (1.3-3.1)</i> • <i>District Belpre: 1.4 (0.8-2.3)</i> • <i>District Mason: 0.9 (0.6-1.3)</i>	smoking status
Barry ³ , 2013, USA	Longitudinal study (32 254 residents with 113 cases of kidney cancers), no comparison group	2008-2011	Environmental (contaminated area; N=28 541) and occupational (workers from the plant; N= 3 713) Mean age: 53 years	Modelled lifetime cumulative serum PFOA concentration based on self-reported residential history	PFOA Median serum PFOA concentration measured in 2005-2006 (range): • Community: 24.2 (0.25- 4 752) ng/mL • Workers: 112.7 (0.25- 22 472) ng/mL Estimated annual PFOA serum levels:	Kidney cancer incidence	aHR (95%CI) for the effect of logged estimated cumulative PFOA concentration on the incidence of kidney cancer: 1.10 (0.98-1.24) aHR (95%CI) kidney cancer by PFOA quartiles 2 to 4 (reference quartile 1), whole cohort (environmental and occupational), no lag: • 1.23 (0.70-2.17) • 1.48 (0.84- 2.60) • 1.58 (0.88- 2.84) <i>Trend p-value 0.18</i>	Tabacco, alcohol consumption , education, 5-year birth period

					• Community: 19.4 (2.8- 9 217) ng/mL • Workers: 174.4 (5.2- 3 683) ng/mL Cut-off values of quartiles not provided		aHR (95%CI) kidney cancer by PFOA quartiles 2 to 4 (reference quartile 1), whole cohort (environmental and occupational), 10-year lag: • 0.99 (0.53-1.85) • 1.69 (0.93- 3.07) • 1.43 (0.76- 2.69) <i>Trend p-value 0.34</i>	
Steenland ⁵ , 2012	Cohort study N= 5 791 exposed workers, compared to general population, and regional worker population—12 cases of kidney cancer	1952-2008	Occupational (DuPont chemical workers)	Modelled cumulative serum PFOA concentration (workplace and residential drinking water) using historical serum concentrations	PFOA Mean estimated annual average PFOA serum concentration: 350 ng/mL Quartiles of exposure: • Q1: 0- < 904 ppm-years • Q2: 904- <1520 ppm-years • Q3: 1520—<2700 ppm-years • Q4: ≥2700 ppm-years <i>*pound per million</i>	Kidney cancer mortality	SMR for kidney cancer mortality: • 1.28 (0.66-2.24)- Ref group: other workers in the region • 1.09 (0.56-1.90)- Ref group: US population SMR for kidney cancer mortality by PFOA quartiles: • 1.07 (0.02-3.62) • 1.37 (0.28-3.99) • 0 (0.00-1.42) • 2.66 (1.15-5.24) <i>Trend p-value 0.02</i> SMR for kidney cancer mortality in Analyses with a 10-Year Lag, by PFOA quartiles: • 1.05 (0.13-3.79) • 0.87 (0.11-3.15) • 0.44 (0.01-2.44) • 2.82 (1.13-5.81) <i>Trend p-value 0.02</i>	Not specified
Leonard ^{1, 2} , 2008, USA	Cohort study N= 6 027 exposed workers,	1948-2002	Occupational (DuPont workers)	All individuals who ever worked at the plant at any time	PFOA	Mortality from kidney cancer	SMR (95%CI) for kidney cancer mortality in 3 external reference populations: • US: 1.51* (0.74-2.649) • West Virginia: 1.51* (0.78-2.637)	/

	compared with 3 reference populations: US, West Virginia and region workers population – 12 cases of renal cancer			between plant start-up on January 1, 1948, and December 31, 2002			Region workers: 1.81* (0.935-3.162) * Values were <i>originally expressed in percentage format and were reported in decimal format (e.g. 151 corresponds to SMR 1.51)</i>	
Raleigh ⁴ , 2014, USA	Cohort study N= 4 668 exposed workers (16 cases of kidney cancer), and 4 359 unexposed workers. Comparison with regional mortality (state of Minesota).	1947-2008 (mortality analysis limited to deaths occurring between 1960 and 2008; incidence analysis started in 1988)	Occupational (ammonium production plant worker- air contamination) Age at follow-up: 63.2 (exposed) - 68.8 (non-exposed)	Modelled cumulative PFAS serum concentration (task-based job exposure matrix to estimate exposure)	APFO Quartile cut points (SMR) in the air: 2.6 10⁻⁵ µg/m³ years 1.4 10⁻⁴ µg/m³ years 7.3 10⁻⁴ µg/m³ years Quartile cut points (HR): 2.9 10⁻⁵ µg/m³ years 1.5 10⁻⁴ µg/m³ years 7.9 10⁻⁴ µg/m³ years	Mortality from kidney cancer and incidence of kidney cancer	SMR (95%CI) death from kidney cancer , comparison with mortality in the state of Minnesota: - Exposed: 0.53 (0.20-1.16) - Non-exposed: 1.23 (0.73-1.95) HR (95%CI) for the incidence of kidney cancer by APFO quartiles compared to the non-exposed population: - Q1: 1.07 (0.36-3.16) - Q2: 1.07 (0.36-3.17) - Q3: 0.98 (0.33-2.92) - Q4: 0.73 (0.21- 2.48) - Q1-Q2: 1.07 (0.46-2.46) - Q3-Q4: 0.85 (0.36- 2.06)	SMR: age, sex and calendar period HR: age, year of birth

Legend: aHR: adjusted hazard ratio; aOR: adjusted odds ratio; 95% CI: 95% confidence interval; HR: hazard ratio; ppm: pound per million; N: number; Q 1,2 3 4: quartiles 1,2,3,4; SMR: standardised mortality ratio; SIR: standardised incidence ratio

1.1.2 Search for new evidence

1.1.2.1 Method

With the aim to update the evidence that had been identified through the report from the *National Academy of Science* retrieved in the scoping phase, a search was conducted for publications that had been issued subsequently (new primary studies or systematic reviews). In this regard, the approach adopted for the update was consistent with the method for updating systematic reviews outlined in the ESRO methods developed by KCE.^{m13}

In brief, the initial step involves identifying a recent, high-quality systematic review that is appropriately aligned with the current research question. If the identified review meets quality standards, an update is considered. In the absence of a satisfactory review, a search for newly published studies or additional evidence regarding the association of interest is undertaken, following the structured framework outlined hereunder:

- **P:** human individuals exposed to PFAS
- **E:** PFAS (all types)
- **O:** kidney cancer (incidence, related mortality, associated excess mortality)
- **S:** cohort studies, case-control; no case report or limited case series
- **T:** 2020-2025 (the year 2020 was selected as the cut-off point and not 2022 (date of the consensus report from *National Academy of Science*) to consider an overlap between the new search and the search arising from this report).

The search was performed on March 7, 2025, only in PubMed with the following strategy: ("PFAS"[All Fields] OR "PFOA"[All Fields] OR "PFOS"[All Fields]) AND ("kidney"[MeSH Terms] OR "kidney"[All Fields] OR "kidneys"[All Fields] OR "kidney s"[All Fields]); Filter: 2020-now.

1.1.2.2 Results

SEARCH FOR A GOOD-QUALITY SYSTEMATIC REVIEW

The search in PubMed yielded 181 results. A systematic review/meta-analysis (SR/MA) published in 2023ⁿ was identified. This study included nine studies examining the association between PFAS exposure (PFOA, PFOS) and kidney cancer incidence or mortality^{o,14}. The findings indicated a significant association between overall PFAS exposure (occupational and environmental) and kidney cancer incidence or mortality, with a risk ratio (RR) of 1.18 (95%CI: 1.05-1.32) (see Figure 2). The quality of the included studies was assessed using a modified version of Newcastle-Ottawa scale (NOS) (see Appendix 1.2): 6 were rated as 'low quality', defined as NOS score <8 (the description of the quality of studies is presented in Appendix 1.3). A sensitivity analysis and meta-regression of the pooled risk ratio on study quality scores did not indicate a statistically significant association between the pooled effect estimate and study quality. Nevertheless, the pooled risk ratio derived from high-quality studies was itself not statistically significant (Pooled RR: 1.24; 95%CI: 0.93-1.65).

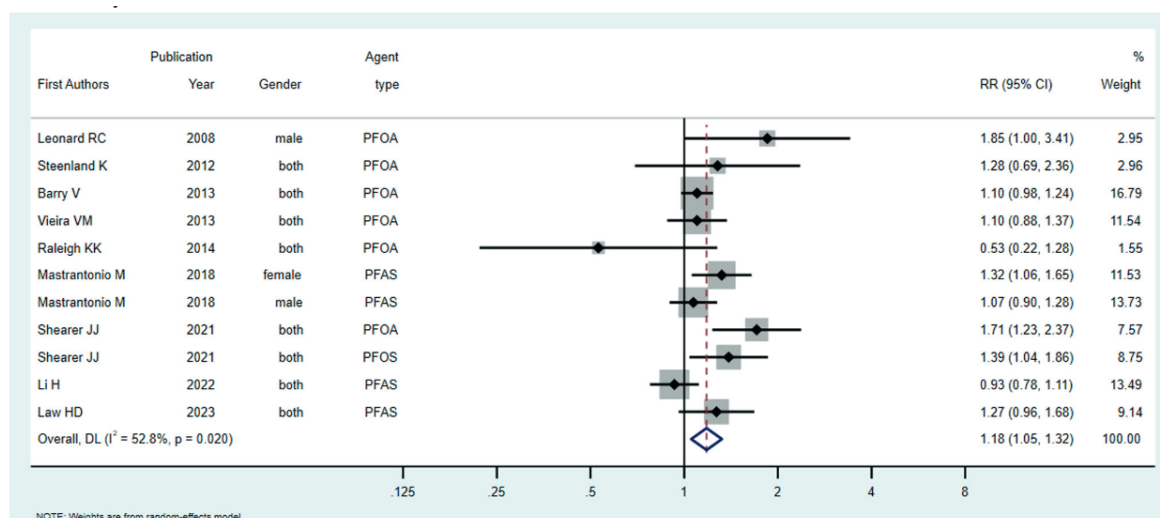
The quality assessed by AMSTAR 2 tool was rated as low (details of the analysis are provided in Appendix 1.4). In addition, several methodological limitations were identified, including the pooling of results across different types of PFAS, the inclusion of overlapping populations among different studies, and the combination of kidney cancer incidence and mortality estimates within a single meta-analysis to derive an overall effect estimate. Consequently, this article was discarded.

^m <https://kce.fgov.be/en/publications/all-reports/expedited-scientific-research-and-reporting-esro-at-kce>

ⁿ The search was performed on 8 July 2023.

^o All the studies referenced in the report from the *National Academies of Science* were included in this meta-analysis.

Figure 2 – Meta-analysis on the association between PFAS (PFOA, PFOS) and kidney cancer



Source: Seyeddsalehi *et al.*, 2023¹⁴

Search for updated evidence

Among the other articles different from the SR/MA from Seyeddsalehi *et al.*,¹⁴ 10 publications specifically addressed kidney cancer. These include three cohort studies, two case control studies, and a secondary analysis of two occupational mortality studies previously published (the study from Steenland *et al.*⁵ and another study not addressing kidney cancer). Additionally, one systematic review without meta-analysis, one scoping review and one critical review (along with related comments) were identified. The list of the studies is presented in Table 2.

The studies included in both the SR and the scoping review were examined, and one primary study – published prior to the timeframe of our search strategy and not included in the report from the NASEM – was identified.¹ The retrieved primary studies are briefly summarised below and described in Table 3.

Table 2 – Results from the update of the evidence (March 2025)

Included study, year	Design
Hanvoravongchai ¹⁵ , 2024	Systematic review in PubMed and Scopus (1990-2024) to examine the association between PFAS and kidney diseases (no meta-analysis for kidney cancer). Histological and molecular outcomes were included.
Steenland ¹⁶ , 2021	Scoping review: search Pubmed until 2020 on cancers and PFAS in general ^P
Bartell ¹⁷ , 2021	Critical review
Stevenson ¹⁸ , 2021	Comments on the review from Bartell <i>et al.</i>
Biggeri ¹⁹ , 2024	Ecological study
Law ²⁰ , 2023	Ecological study
Li ²¹ , 2022	Ecological study
Rhee ²² , 2023	Nested case-control study
Winquist ²³ , 2023	Case-control study
Park ²⁴ , 2023	Analysis of two previous occupational mortality studies

^P Types of studies included in the scoping review: 16 cohort, 10 case control, 1 cross sectional, 1 ecologic study

DESCRIPTION OF THE PRIMARY STUDIES

The included studies are described below, focusing on the essential elements of their design and results; more details can be found in Table 3.

- The nested case-control study by Rhee *et al.*²² was conducted in the multi-ethnic cohort MEC study (Multi-ethnic study; see Box 2), and extended the study by Shearer *et al.* Authors sought to replicate their findings obtained with the PLCO database² to a multi-ethnic cohort. The association between PFAS and the subsequent development of kidney cancer was evaluated by the measure of pre-diagnostic serum concentration of nine PFAS^q among participants who developed a kidney cancer (incident cases through 2018), and matched controls. Overall, in contrast to their previous studies including mainly White participants (Shearer *et al.* study²), PFOA was not associated with kidney cancer. Nevertheless, suggestive positive associations were observed in white participants and in participants who had blood drawn before 2002, but this was not statistically significant. On the other side, PFNA was associated with kidney cancer among African American participants (see Table 3).

Box 2 – MEC cancer screening trial

The Multiethnic Cohort (MEC) study is a large, population-based research that follows over 215,000 men and women in Hawaii and California, aged 45–75 at the study's inception. Five distinct racial and ethnic groups are represented: Japanese Americans, African Americans, European Americans, Latinos, and Native Hawaiians. These groups exhibit varying levels of risk for chronic diseases. The study involves an extensive biorepository, which includes blood and urine samples. These samples are linked to comprehensive, long-term data on lifestyle factors, including diet, smoking, and physical activity, as well as biomarkers and clinical records.²⁵

- Winquist *et al.* designed a case control study on the associations between PFAS and selected cancers, using the *American Cancer Society's Cancer Prevention Study II (CPS-II) LifeLink Cohort*^r in which participants provided a blood sample and completed a brief survey.²³ The study included a randomly selected sub-cohort of 999 individuals (500 men and 499 women) without prior cancer diagnoses at the time of serum collection as a control group, and all participants with incident selected cancers: breast (n= 786), kidney (n= 158), pancreas (n= 172), prostate (n=1 610). Samples were collected between 1998 and 2001, and the median follow-up was 14.3 years (range: 1 month- 17 years). Overall, there was no clear association between PFAS and cancer, but in stratified analysis, an association of PFOA exposure and the histological subtype 'renal cell carcinoma' was observed exclusively among women (see Table 3).
- Li *et al.* conducted an ecological study in Sweden that compared the incidence of kidney cancer in regions with PFAS-contaminated drinking water (the use of firefighting foams at a military airport led to significant PFAS contamination in the local water supply) with non-contaminated areas within the same county.²¹ Individual exposure metrics were derived from residential addresses and water distribution data. Information on cancer diagnoses was retrieved from the Sweden Cancer Registry from 1985 to 2016. Two different statistical approaches were used. Firstly, an external comparison was performed by calculating sex, age and calendar year standardised incidence ratios (SIR) for overall and specific cancers, in which the "exposed" and "non-exposed" groups were compared with a regional Swedish population. In a secondary step, hazard ratio (HR) were calculated between "exposed" and "non-exposed" groups. Overall, there was no statistically

^q The list of PFAS is presented in Table 3.

^r Additional information on the study: <https://www.cancer.org/research/population-science/cancer-prevention-and-survivorship-research-team/acs-cancer-prevention-studies/cancer-prevention-questionnaires.html>

significant increase in the risk of kidney cancer: the SIRs for overall cancer were similar between the 'exposed and 'non-exposed groups, across both male and female individuals^s (see Table 3).

- Law *et al.* conducted an ecological study in Australia examining cancer incidence and mortality rates, comparing PFAS-contaminated regions to non-exposed areas.²⁰ Standardized incidence ratios (SIRs) were calculated using national health databases to evaluate differences in cancer occurrence between exposed and non-exposed groups. Results were heterogeneous with one region exhibiting and increased risk (SIR 1.82; 95%CI: 1.04-2.96), while the two others did not (See Table 3).
- The study by Mastrantonio *et al.* was an Italian ecological study comparing mortality rates, from 1980 to 2013, between municipalities with PFAS-contaminated drinking water, and those with uncontaminated supplies^t.²⁶ In January 2014, a significant PFAS contamination was detected in the Veneto Region's drinking water, primarily attributed to discharges from a manufacturing company operating since 1964. Sex-specific SMRs for causes of death were compared between contaminated and uncontaminated municipalities. An excess mortality was found for kidney cancer exclusively among women. There was also suggestive evidence of an association between PFAS and kidney cancer for men, but this was not statistically significant (see Table 3).
- The study by Biggeri *et al.* had an ecological design and was conducted in the region of Veneto, Italy.¹⁹ It compared mortality rates in areas with known PFAS contamination (30 municipalities) to those in the broader region (three provinces), focusing on all-cause mortality, cardiovascular diseases, and various cancers. In the contaminated region, they observed an absolute excess mortality of 3 890 deaths during the period 1985-2018^u, representing an excess of 115 deaths/year. Regarding cancer mortality, an increasing trend was observed by calendar period in both sexes: considering the 1980-1989 period as a reference, there was an excess mortality during the periods 1990-2009 and 2010-2018 (see Table 3). The excess mortality attributed to kidney cancer was elevated in the exposed populations, particularly more pronounced in the area where there was a contamination of the water and the ground simultaneously^v.

^s SIR of 1.04 for men (95% CI: 0.96–1.12) and 0.89 for women (95% CI: 0.82–0.96)

^t The classification of contaminated areas was based on the limits set by the Italian National Health Institute (ISS): PFOS ≤ 30 ng/L, PFOA ≤ 500 ng/L, and other PFAS ≤ 500 ng/L.

^u A total of 51 621 deaths instead of 47 731 deaths according to the mortality rates in the considered provinces.

^v A group of 30 municipalities formed an area of maximum exposure for a total of 153 525 inhabitants. Among these, authors made the distinction between the area that was served by a contaminated aqueduct and also located on the groundwater contamination plume and the other area including municipalities served by the contaminated aqueduct but not located on the groundwater contamination plume.

Table 3 – Evidence table including studies identified in the update of the evidence

Author, year, country	Study design	Study period	Type of exposure (population characteristics)	Assessment of exposure	Types of PFAS	Outcome(s)	Main findings	Adjustment
Rhee ²² , 2023, USA (same study than Shearer et al in a multi-ethnic cohort)	Nested case-control study N= 428 cases/428 controls	1993-2018 (inclusion of all incident cases of kidney cancer diagnosed through 2018)	Environmental Median age (blood collection): 67 years	Measured pre-diagnostic serum concentration of PFAS; single blood sample	PFOA, PFOS, PFHxS, PFUnDA, PFNA, EtFOSAA, MeFOSAA, PFDA Quartile of serum concentrations (µg/L): PFOA • Q1: ≤ 3.27 • Q2: > 3.27-4.47 • Q3: > 4.47-6.22 • Q4: >6.22 PFOS • Q1: < 16.65 • Q2: 16.65- < 25.05 • Q3: 25.05- < 36.40 • Q4: ≥ 36.40 PFHxS • Q1: < 1.6 • Q2: 1.6- <2.4 • Q3: 2.4- <3.55 • Q4: ≥ 3.55	Kidney cancer incidence	aOR (95%CI) kidney cancer per quartile of blood concentration (reference: quartile 1): PFOA • Q2: 1.09 (0.73-1.64) • Q3: 1.05 (0.70-1.56) • Q4: 0.88 (0.58-1.35) <i>Trend p-value 0.46</i> PFOS • Q2: 0.90 (0.60-1.35) • Q3: 0.89 (0.57-1.37) • Q4: 0.83 (0.53-1.30) <i>Trend p-value 0.44</i> PFHxS • Q2: 0.94 (0.64-1.38) • Q3: 0.65 (0.44-0.98) • Q4: 0.79 (0.52-1.21) <i>Trend p-value 0.27</i> PFNA • Q2: 0.88 (0.59- 1.32) • Q3: 0.90 (0.57- 1.42) • Q4: 1.29 (0.78- 2.12) <i>Trend p-value 0.04</i> aOR (95%CI) kidney cancer, continuous value of PFAS*: • PFOA: 0.87 (0.73-1.05) • PFOS: 0.92 (0.79-1.07)	BMI, eGFR, smoking status, hypertension

							• PFHxS: 0.84 (0.74-0.96) • PFNA: 1.03 (0.85- 1.24) * : values for other PFAS are available on demand <u>NB</u>: in stratified analysis: - aOR (95%CI) for PFOA in white participants: 2.12 (0.87-5.18) - aOR (95%CI) for PFNA in: ○ African Americans: 3.69 (1.33-10.25) ○ Native Hawaiians: 2.24 (0.70-7.19) ○ Whites: 1.98 (0.92-4.25)	
Winqvist ²³ , 2023	Case-control study N= 999 (sub-cohort from ACS-CPS II study including 500 men/499 women who had no previous cancer diagnosis) and 158 kidney cancers cases	1998-2017	Environmental	Measured pre-diagnostic serum concentration of PFAS, single blood sample Median age at blood collection: 71 years (men), 69 years (women)	PFOA, PFOS, PFNA, PFHxS, PFHpA Median serum concentrations (P25-P75) in cases vs controls, ng/mL: • PFOA: 5.20 (3.90-7.30) vs 5.20 (3.90-6.90) • PFOS: 18 (13-26) vs 18 (13-25) • PFNA: 0.68 (0.51-1.00) vs 0.67 (0.49-0.98) • PFHxS: 3.30 (2.10-4.90) vs 3.10 (2.00-5.10)	Kidney cancer incidence	aHR for kidney cancer (95%CI), quartile 2 to quartile 4 (reference: quartile 1): PFOA • Q2 (3.9- < 5.2 ng/mL): 0.93 (0.56-1.56) • Q3 (5.2- <7.3 ng/ml): 0.83 (0.49-1.40) • Q4 (≥ 7.3 ng/mL): 1.20 (0.71-2.04) PFOS • Q2 (13 - <18 ng/mL): 0.92 (0.54-1.57) • Q3 (n18 - <26 g/ml): 0.97 (0.58 -1.63) • Q4 (≥ 26 ng/mL): 1.14 (0.67-1.92) PFNA • Q2 (0.51- <30.68ng ng/mL): 1.15 (0.69-1.92) • Q3 (0.68 - <1.00 ng/ml): 1.01 (0.60 - 1.69) • Q4 (≥ 1.00 ng/mL): 1.25 (0.74-2.11) PFHxS • Q2 (2.1- <3.3 ng/mL): 1.13 (0.67-1.93) • Q3 (3.3 - <4.9 ng/ml): 1.35 (0.80-2.27)	Sex, year of serum sample collection, age at serum collection, race and education from the 1982 baseline survey, smoking status, alcohol consumption from 1997 survey (or earlier surveys)

					PFHpA: 0.11 (0.07-0.19) vs 0.10 (0.06-0.20)	- Q4 (≥ 4.9 ng/mL): 1.12 (0.66- 1.89) aHR (95%CI) kidney cancer, continuous value of PFAS: - PFOA: 1.08 (0.88-1.33) - PFOS: 1.03 (0.84- 1.26) - PFNA: 1.07 (0.90-1.28) - PFHxS: 1.06 (0.91-1.24) NB: in stratified analysis, aHR (95%CI) PFOA for histological subtype RCC within women: 1.54 (1.05-2.26)	
Li ²¹ , 2022, Sweden	Ecological study N= 60 507 (inhabitants on contaminated vs non-contaminated areas) – 122 cases of renal cancer, in total	1985-2016	Environmental (contaminated area- drinking water contamination)	Exposure was based on data on yearly residential address and water distribution	PFPeA , PFHxA, FHpA , PFOA, PFBS, PFHxS, PFHpS, PFOS Exposed zone (3 084 people, collected in 2014-2015), geometric mean (range), ng/mL: - PFOS: 199 (0.68-1868) - PFHxS: 176 (0.23-1658) - PFOA: 11 (0.04-92) Non-exposed zone (226 persons, collected in 2016), ng/mL: - PFOS: 40 (0.58-839) - PFHxS: 30 (0.14-974)	Incidence of kidney cancer (standardised incidence rate and HR) HR (95%CI) for kidney cancer, between exposed and non-exposed groups: 1.27 (0.85 –1.91) SIR (95%CI) of kidney cancer in male participants, comparison with reference population (Blekinge county): - Unexposed: 0.67 (0.49-0.90) - Exposed: 0.86 (0.50-1.38) SIR (95%CI) of kidney cancer in female participants comparison with reference population (Blekinge county): - Unexposed: 1.17 (0.84- 1.57) - Exposed: 1.47 (0.84- 2.39)	Age, sex

					PFOA: 3.5 (0.04-49)			
Biggeri ¹⁹ , 2024; Italy	Ecological study N= 57 621 deaths in contaminated areas, compared with mortality in the population in the three provinces where the contaminated area is located	1980-2018	Environmental (contaminated area- drinking water): - area connected with the PFAS contaminated aqueduct (30 municipalities) - area connected with the PFAS contaminated aqueduct and contaminated ground water (13 municipalities)	Resident in the municipalities of contaminated areas	PFOA, PFBA, PFBS, PFPeA, PFHxA, PFHxS, PFHpA, PFDaA, PFOS	Mortality from kidney cancer	Absolute excess mortality (90%CI) from 1985 to 2018: 51 621 death vs 47 731 expected; SMR (90%CI)**: 1.08 (1.07-1.09)* * values were <i>originally expressed in percentage format and were reported in decimal format (e.g. 108 corresponds to SMR 1.08)</i> Evolution of overall cancer mortality estimated by mortality rate ratio (90%CI), considering 1980-1989 period as reference: - Period 1990-2009: 1.05 (1.01-1.08) - Period 2010-2018: 1.08 (1.04-1.12) Kidney cancer-specific mortality estimated by SMR** (90%CI) in the period 2015-2018: Zone connected with the PFAS contaminated aqueduct[#]: - Males: 128 (98-165) - Females: 123 (83-176) Zone connected with to the PFAS contaminated water + contaminated ground water[#]: - Males: 175 (124-241) - Females: 169 (102-264) ** <i>expressed in percentage format rather than in decimal format (e.g. 128 corresponds to SMR 1.28)</i> [#] <i>see more details within the text in section 0</i>	Age, sex

Law ²⁰ , 2023, Australia	Ecological study N= 318 887 (54 343 exposed compared with 264 544 individuals who never had an address in the exposed areas) – 47 cases of renal cancer	1983- 2019	Environmental (contaminated area)	Exposure (or non- exposure) was based on data on residential address	Mix of PFAS	Incidence of kidney cancer	SIR (95% CI) for kidney cancer: in the exposed populations (by regions), compared with non-exposed populations: • Northern Territory: 0.77 (0.28-1.67) • New South Wales: 1.15 (0.74-1.69) • Queensland: 1.82 (1.04-2.96)	Age, sex, calendar time
Mastrantonio ²⁶ , 2018, Italy	Ecological N= 143 605 individuals in contaminated area and 588 012 in non- contaminated area – 1176 cases of death from kidney cancer in total	1980- 2013	Environmental (contaminated area; drinking water)	Exposure to contaminated area versus non- contaminated area (based on residency); PFAS exceeding at least one of the following limits in drinking water: PFOS > 30 ng/L, PFOA > 500 ng/L, other PFAS > 500 ng/L	PFOA, PFBA, PFDeA, PFHpA, PFPeA, PFUnA PFOS, PFBS, PFDoA, PFHxA, PFNA	Mortality from kidney cancer	Ratio of SMRs* (95%CI) for kidney cancer mortality: • Overall: 1.07 (0.93-1.23) • Men: 1.07 (0.90-1.28) • Women: 1.32 (1.06-1.65) <i>* Ratio between SMR contaminated area/SMR uncontaminated area (reference: Italian population)</i>	Sex

NARRATIVE SYNTHESIS OF THE EVIDENCE

Following the comprehensive review of the current literature on the association between exposure to PFAS and renal cancer, a narrative summary of the results was undertaken, focusing exclusively on studies reporting the incidence of renal cancer. This choice is justified by the fact that studies of mortality are subject to various confounding factors, such as the fact that kidney cancer mortality depends on how early the diagnosis is made and the quality of medical care, both of which may vary between the areas, and countries compared. Ecological studies were excluded due to their high risk of bias, including the lack of individual-level exposure and outcome data, and limited ability to control for confounding factors, all of which undermine the validity of estimating a causal association between PFAS exposure and renal cancer incidence. As part of this summary, the quality of the selected studies was also assessed, using the SIGN (Scottish Intercollegiate Guidelines Network)^w methodology for case-control (checklist 4), and cohort (checklist 3) studies (details of the analysis are available in Appendix 1.5).

CASE-CONTROL STUDIES

- Three nested case-control studies investigating the incidence of kidney cancer were selected.^{2, 23, 27} Two were categorised as ‘high quality’, and one was rated ‘acceptable to high’ (see Table 4). Each study used data from large-scale databases focused on cancer prevention and involved population with environmental exposure to PFAS.
- The findings across the three studies were inconsistent. Among them, only the study by Shearer *et al.* reported a statistically significant association between environmental exposure to perfluorooctanoic acid (PFOA) and kidney cancer.² The other two studies did not demonstrate statistically significant associations.^{23, 27} In the study by Rhee *et al.*, no statistically significant association was observed in the subgroup analysis limited to white participants^{x, 27} Likewise, the study by Winquist *et al.* identified an association between PFAS exposure and the histological subtype renal cell carcinoma, but only among female participants in stratified analyses.²³ It is worth noting that all three studies relied on a single blood sample collected approximately 20 years ago. Furthermore, for the two studies using the PLCO database, although the study protocol indicated that multiple blood samples were collected over time, only one sample per individuals was used for the analyses. Results are summarised in Table 4.

LONGITUDINAL AND COHORT STUDIES

- Three studies assessing the incidence of kidney cancer were selected. In the three studies, PFAS exposure was estimated through a modelling approaches.^{3, 4, 6} The quality was rated ‘acceptable’ for all three. Two studies were conducted in West Virginia and Ohio (the Mid-Ohio Valley Study) and involved workers and residents of environmental contaminated areas.^{3, 6} The participants were overlapping between both studies. The study by Barry *et al.* included workers exposed to PFOA and residents of PFAS-contaminated areas. The other study by Vieira *et al.* involved participants living in the same contaminated areas and used a multifaceted design incorporating modelled serum concentrations of PFAS and an ecological comparison of cancer incidence between areas with and without PFAS-contaminated water (notably, the control group consisted of cancer patients identified through a cancer registry, including individuals with malignancies other than kidney cancer). The last study focused exclusively on employees of a facility in Minnesota that produced ammonium perfluorooctanoate (APFO), a salt derived from PFOA.⁴
- One study conducted in the Mid-Ohio Valley reported a statistically significant association between PFOA exposure and kidney cancer incidence among individuals in the high and very high exposure quartiles, although the number of observed cases was limited.⁶ In contrast, a complementary analysis based on water district contamination levels revealed a non-statistically

^w <https://www.sign.ac.uk/using-our-guidelines/methodology/checklists/>

^x A statistically significant association between PFNA and kidney cancer was observed in African American individuals subgroup (See Table 3).

significant association. The other study conducted in the Mid-Ohio area found no statistically significant relationship between PFOA exposure and kidney cancer incidence.³ Lastly, a third study focusing on occupationally exposed workers reported no association between exposure to per- and polyfluoroalkyl substances (PFAS) and the incidence of kidney cancer.⁴ Results are summarised in Table 4.

Table 4 – Summary of the results of studies assessing kidney cancer incidence

Author, year, country	Study design	Type of exposure	PFAS exposure assessment	Narrative summary of the main results	Quality (SIGN methodology)
Shearer ² , 2021,	Nested case-control	Environmental	Single blood sample taken on average 8.8 years before the diagnosis	• Association between kidney cancer incidence and PFOA exposure (particularly in the highest serum concentration quartile corresponding to concentrations ranging between 7.3 and 27.2 ng/mL – adjusted OR (95%CI) fourth <i>quartile vs first quartile</i>: 2.63 (1.33-2.37) • No association between kidney cancer incidence and other PFAS	High
Rhee ²² , 2023, USA	Nested case-control	Environmental	Single blood sample	• No association between kidney cancer incidence and PFAS exposure	High
Winquist ²³ , 2023	Nested case-control	Environmental	Single blood sample	• No association between kidney cancer incidence and PFAS exposure • In a stratified analysis, statistically significant association between PFOA and the incidence of the histological subtype 'renal cell carcinoma' in women and not in men	Acceptable to high
Vieira ⁶ 2013, USA	Mixed design (cohort and environmental)	Environmental, (proximity to PFAS contaminated zone)	Modelling technique	• Statistically significant association between kidney cancer and high-serum PFOA exposure category: aOR (95%CI) for kidney cancer (number of cases): ○ Very high [110-655 µg/L] (n=9): 2.0 (1.0-3.9) ○ High [30.8-109 µg/L] (n=22): 2.0 (1.3-3.2) ○ Medium [12.9-30.7 µg/L] (n=17): 1.2 (0.7-2.0) ○ Low [3.7-12.8 µg/L] (n=11): 0.8 (0.4-1.5) • No statistically significant relation between PFOA exposure and kidney cancer based on water district results (contaminated and non-contaminated areas)- aOR (95%CI): 1.1 (0.9-1.4). Separate districts analysis showed heterogeneous results.	Acceptable
Barry ³ , 2013, USA	Longitudinal	Environmental (proximity to PFAS contaminated)	Modelling technique	Non statistically significant association between modelled cumulative PFOA serum concentration and kidney cancer incidence:	Acceptable

		zone) and occupational		• aHR (95%CI) logged estimated cumulative PFOA serum concentration: 1.10 (0.98-1.24) • aHR (95%CI) by PFOA quartiles 2 to 4 (reference= quartile 1), no lag: ○ 1.23 (0.70-2.17) ○ 1.48 (0.84- 2.60) ○ 1.58 (0.88- 2.84)	
Raleigh ⁴ , 2014, USA	Cohort	Occupational	Modelling technique	No association between modelled cumulative AFPO serum concentration and kidney cancer incidence	Acceptable

1.1.3 Discussion and conclusion

The association between PFAS exposure and kidney cancer has received growing attention, particularly in light of the *National Academies of Science* consensus report, which concluded that sufficient evidence exists to support such a link.¹ This conclusion was based primarily on a high-quality case-control study conducted in the general population, along with findings from earlier studies conducted in populations exposed to high exposure to PFAS. The consistent direction and magnitude of the associations observed across these studies were key in supporting the conclusion of the *National Academies of Science*.

Following the conclusions of the *National Academies of Science* consensus report, our review identified a body of literature predominantly focused on populations exposed to high levels of PFAS. Notably, two additional case-control studies conducted within the general population yielded more heterogeneous findings compared to the study by Shearer *et al.*^{22, 23} While these studies did not establish a strong overall association between PFAS exposure and kidney cancer, stratified analyses indicated elevated likelihood of kidney cancer among specific subgroups. This variability highlights the complexity of evaluating environmental carcinogens such as PFAS within heterogeneous populations exposed to different levels of exposure, and the potential of individual intrinsic characteristics of subgroups.

In this context, although the study by Shearer *et al.* is methodologically robust, a key limitation lies in its exposure assessment, which relied on a single blood sample to estimate PFAS levels.² While the authors posited that a single measurement may serve as a reasonable proxy for long-term exposure, emerging evidence suggests that the biological half-lives of the most commonly studied PFAS in humans are limited.²⁸

In addition to studies conducted within the general population, our pragmatic literature search predominantly identified studies involving populations residing in proximity to PFAS-contaminated areas. The findings from these studies were generally inconsistent, with many reporting associations between PFAS exposure and kidney cancer that did not reach statistical significance. Although some studies did suggest a dose-exposure relationship, this association was typically limited to individuals with the highest levels of exposure (e.g. those in the upper quartiles of serum PFAS concentrations), and the number of cases was limited. It is important to emphasize that several methodological and population-specific characteristics across these studies likely contributed to the observed heterogeneity. These factors are critical for interpreting the variability in reported associations and for interpreting the results:

EXPOSURE AND TIMEFRAME

- Exposure assessment methods across studies are highly heterogeneous, presenting challenges for direct comparison. In studies involving general population cohorts, exposure was typically estimated using single serum PFAS measurements obtained from biobanked samples collected during clinical studies conducted in the 1990s or 2000s. In contrast, studies focusing on populations with elevated PFAS exposure employed more complex approaches, including pharmacokinetic modelling based on historical biomonitoring data, residential history as a proxy for cumulative exposure, and environmental monitoring data, or based on the levels of PFAS detected in the environment (e.g., drinking water, contaminated air, soil contamination).
- Levels of PFAS exposure and types of exposure vary considerably across studies. Most of the studies identified in our literature search report on populations residing in highly contaminated environment, with markedly elevated estimated serum levels of PFAS.
- The description of measurements techniques performed in the laboratory are often lacking. This makes it difficult to compare results with the techniques currently in use.

The duration of exposure varies considerably between studies. As this is an important determinant of cumulative serum concentrations, Bartell *et al.* suggested a method facilitating the comparison between studies and consisting of dividing the cumulative serum PFAS concentration by the duration of observation to estimate average PFOA serum concentrations.¹⁷ The authors explained that such an approach is more appropriate for facilitating comparisons across studies. Accordingly, the results

of four studies were converted into an average effect size per 10 ng/mL increase in serum PFOA concentration, and were subsequently included in a meta-analysis.^{2, 3, 5, 6} This analysis found a 16%(95%CI: 3-30) increase in kidney cancer risk per 10 ng/mL increase in serum PFOA. It is important to acknowledge that, given the overall low incidence of kidney cancer over time, such an increase would have only a limited impact on the overall risk.

QUALITY OF DATA AND RISK OF BIAS

The overall methodological quality of the studies included in the identified meta-analysis was generally low. Among them, the case-control study conducted by Shearer *et al.* was the most rigorously designed.² In contrast, the cohort studies assessing the relationship between PFAS exposure and kidney cancer were subject to several inherent sources of bias including selection bias (e.g. loss to follow-up, proportions of “volunteers” for study participation, “healthy worker effect”), immortal bias, lag bias, or confounding bias. Furthermore, sample sizes and the number of kidney cancer cases varied widely across studies (with occupational studies typically featuring smaller cohorts). Given the rarity of such type of cancer, statistical power may be limited.

SYNTHETISING DATA

The meta-analysis identified in our review was rated as low quality, owing to several methodological limitations. Conducting quantitative synthesis through meta-analytic techniques in this context presents substantial challenges, primarily due to inconsistencies in the comparability of exposure levels, the potential duplication of participant data across studies, differences in the reported outcomes, and the considerable variation in the covariates used for statistical adjustment. In addition, the reference groups were variable including unexposed populations or low-exposure populations.

In conclusion, the existing research offers useful, albeit limited, understanding of a potential association between PFAS exposure and kidney cancer risk – an association that warrants careful consideration and should not be dismissed. However, the precise magnitude of excess risk at the individual level, as well as the exposure thresholds associated with increased risk, remain insufficiently defined. Although the NASEM have concluded that there is sufficient evidence to support an association, such statement cannot yet be fully unravelled by the existing literature and should be investigated in the light of the development of more longitudinal research incorporating more standardized exposure definition and outcome definitions, while also integrating the regulatory standards and exposure mitigation strategies. Our findings are largely consistent with those reported in the recent publication from IARC. Authors stated that, although epidemiological evidence supports the plausibility of a positive association between PFOA exposure and kidney cancer, this association has not been consistently observed in the most informative studies. The report further notes that the potential influence of chance, bias, or confounding by other PFAS compounds cannot be ruled out with reasonable confidence.²⁹

1.2 Evidence on the association between PFAS and breast cancer

KEY POINTS TABLE

- The consensus report of the US *National Academies of Science, Engineering and Medicine* (NASEM, 2022) assessing the link between PFAS, and breast cancer included seven studies, all case-control studies conducted in the general population. Overall, the studies showed inconsistent findings, with weak positive as well as negative associations, and oftentimes non-significant. However, the NASEM concluded there is *limited or suggestive evidence* of an association of PFAS with breast cancer, mainly based on a French nested case control study of postmenopausal women suggesting a dose-response relationship with PFOS (and not PFOA) and hormone receptor positive breast cancer.³⁰
- The US Environmental Protection Agency (EPA) 2024 reports on PFOA and PFOS concluded that the results on risk of breast cancer were mixed.
- Two more recent systematic reviews (Chang et al 2024³¹ and Seyyedsalehi et al 2024³²) performed meta-analyses (MA) including 9 and 19 individual studies, respectively. They included different study designs in their meta-analyses, and neither showed a significant association or clear trend.

Chang et al. 2024, a MA with a moderate to high quality, focused on case-cohort, case-control studies with background exposure and individual level blood measurements.³¹ The authors concluded that *current epidemiological evidence is inadequate to conclude on the PFAS-breast cancer relationship*.

The MA of Seyyedsalehi et al. combined several study designs and also included studies conducted in contaminated areas with proxy measurements of exposure (such as residency).³² The authors concluded there is *evidence suggesting a possible link between PFAS exposure, especially PFOA and the incidence of breast cancer*.

- The literature update identified four recent primary studies with variable designs and variable results:
 - A USA case-cohort study, with a low risk of bias, but in an older postmenopausal population with prediagnostic blood sampling, showed *no increased risk of breast cancer*.²³
 - A Chinese nested case control study, with a low risk of bias, showed *increased risk of breast cancer, more pronounced in premenopausal women*.³³
 - A US cross-sectional study showed *no increased risk for breast cancer* based on PFAS serum concentrations.³⁴
 - A Swedish study in a contaminated area where exposure was measured via residency, showed no association.³⁵
- The body of evidence for the association of PFAS and breast cancer risk in terms of number of individual studies is quite large (> 20) and encompasses predominantly studies **in the general population (with background exposure)** and a minority in contaminated populations. An important factor impeding the analysis and even combining individual studies in a meta-analysis, is the large heterogeneity:
 - In study designs. The majority of studies are (nested) case-control or case cohort studies.
 - In population (e.g. premenopausal, or postmenopausal women)

- Exposure assessment (single blood samples or residential history as a proxy for cumulative exposure; in case of individual blood samples, different types of PFAS are measured with predominantly PFOS and PFOA) and timing (whether it is pre-diagnostic and sufficient follow-up or whether it is concomitantly with the diagnosis)
- Levels of PFAS exposure and types of exposure: even in the background exposure studies the range of PFAS concentrations in blood differs between studies. For example for PFOS, a median of around 2 ng/ml PFOS in a Chinese study,³³ and around 18 ng/ml PFOS in an American study,²³ 17ng/ml in a French study,³⁰ and 32ng/ml in another American study³⁶. Most of the time the highest tertile/quartile/quintile is compared to lowest.
- However, both the individual studies and available meta-analyses show inconsistent findings which impedes concluding on an association of PFAS with breast cancer.
- More epidemiological studies, especially well-designed prospective studies with more standardized exposure definition with attention to the timing and duration of exposure assessments and detailed breast cancer information (e.g. hormone receptor status) are necessary to establish a clearer understanding of a possible relationship

1.2.1 Evidence considered in the NASEM report – 2022

The consensus report by the US *National Academies of Sciences, Engineering and Medicine* (NASEM, 2022) was considered as a starting point,¹ and stated that there is *limited or suggestive evidence of an association* of PFAS with breast cancer. In total, seven case-control studies were considered (Bonefeld-Jorgensen study of 2011 and 2014, Wielsøe et al 2017, Cohn et al 2020, Hurley et al 2018, and Tsai et al 2020, Mancini 2020).^{30, 36-41} All the studies analysed the exposure in a general population (no focus on a contaminated area). Three studies reported no evidence of an association with breast cancer, with some even suggesting an inverse association (Bonefeld-Jorgensen 2014, Hurley et al 2018, Cohn et al., 2020). Cohn et al is a nested case control study but where the exposure is measured as blood concentration in the mother (maternal serum) and where the breast cancer is self-reported.³⁶ The case control study in Inuit population in Greenland by Wielsøe and colleagues (2017) is an update of the 2011 Bonefeld Jorgensen study, and found positive associations with PFAS and breast cancer. The serum PFAS level was determined at the time of diagnosis. The case-control study from Tsai et al 2020, which was rated as high risk of bias,^y showed a significant association in the subset of Taiwanese women 50 years or younger, with a stronger association in oestrogen receptor-positive tumours. A case control study nested in the French E3N cohort (Mancini 2020), rated with a low risk of bias did not identify a significant association between breast cancer risk and PFOS or PFOA exposure, though it suggested a linear dose-response relationship between PFOS serum concentrations in postmenopausal women and the risk of developing hormone receptor-positive breast cancer.³⁰ Figure 3 shows an overview of the study results focused on PFOS.

^y Assessed in the report of National Academies: high risk of bias because the exposure was measured after the cancer diagnosis had been made

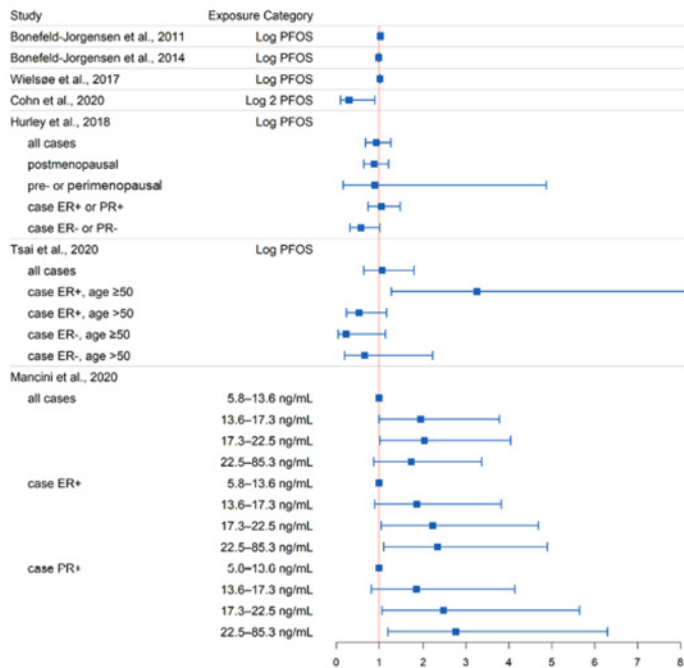
Figure 3 – Forest plot on risk of breast cancer and PFOS exposure in NASEM analysis¹

FIGURE 3-10 Breast cancer adjusted rate ratios and 95% confidence intervals by study and PFOS exposure category.

NOTE: ER = estrogen receptor; PR = progesterone receptor.

DATA SOURCES: Bonefeld-Jorgensen et al., 2011; Cohn et al., 2020; Hurley et al., 2018; Mancini et al., 2020; Tsai et al., 2020; Wielsoe et al., 2017.

1.2.2 Evidence considered in the US EPA 2024 report

In 2024, the US Environmental Protection Agency (EPA) published two reports, one on PFOA and one on PFOS.^{42, 43} The analysis of EPA is based on epidemiological evidence in humans, animal studies and mechanistic evidence. Here we focus on epidemiological evidence.

1.2.2.1 PFOA

In 2016, EPA concluded there was no association between PFOA exposure in the general population and breast cancer. In the C8 Health Project cohort, Barry et al. (2013)³ observed a significant inverse association with breast cancer for both unlagged and 10-year lagged estimated cumulative PFOA serum concentrations.

Seven general population studies published since the 2016 assessment examined breast cancer (Itoh et al., 2021; Omoike et al., 2021; Cohn et al., 2020; Mancini et al., 2020; Tsai et al., 2020; Hurley et al., 2018; Ghisari et al., 2017)^{30, 36, 38, 39, 44-46} of which four were considered medium confidence (Cohn et al., 2020; Mancini et al., 2020; Hurley et al., 2018; Ghisari et al., 2017). All studies were case-control studies (with some nested designs), except for one cross-sectional NHANES-based study (Omoike et al., 2021)⁴⁶. Compared to the studies considered in the National Academies analysis, two more recent studies were considered, the cross-sectional US NHANES study from Omoike concluding on increased odds of developing ovarian and breast cancers on the one hand, and the Japanese case-control showing inverse relationships with breast cancer incidence.⁴⁵ The overall conclusion was that the studies had **mixed results**.

1.2.2.2 PFOS

Overall, there is no clear conclusion based on the epidemiological studies as the **results are mixed**. A case-control study of breast cancer among Inuit females in Greenland with similar serum PFOS levels to those of the Danish population (1.5–172 ng/mL) reported an association of low magnitude that could not be separated from other perfluorosulfonated acids, and the association was not confirmed in a Danish population (Bonefeld-Jørgensen et al., 2014;³⁷ Bonefeld-Jørgensen et al., 2011)⁴¹. The literature update identified nine studies: Li et al., 2022;²¹ Itoh et al., 2021; Omoike et al., 2021; Cohn et al., 2020; Mancini et al., 2020; Tsai et al., 2020; Hurley et al., 2018; Ghisari et al., 2017; Wielsøe et al., 2017. The study by Li et al. studied exposure via residency in the contaminated Swedish Ronneby area.²¹ Three studies were considered low confidence (Itoh et al., 2021; Omoike et al., 2021; Tsai et al., 2020) because of concerns about temporality of exposure measurements and breast cancer development, the control status was not confirmed via examination or medical records (Tsai et al., 2020), and potential for residual confounding due to SES, lifestyle factors and exposure to other PFAS

1.2.3 Recent systematic reviews

1.2.3.1 Chang et al 2024

During the scoping phase of the literature review, a preliminary pragmatic search in PubMed identified a recent, moderate to good quality (as assessed by AMSTAR see appendix 2.1) systematic review (SR), including a meta-analysis.³¹ This SR included 17 unique studies (18 articles) in total, including also all the seven studies referenced by the National Academies.

The quality of the individual studies was rated with a specific tool for environmental health research (Risk of Bias Tool for Human and Animal Studies – see Box 3). Five studies were rated with a high risk of bias (Wielsøe 2017,⁴⁰ Velarde 2022,⁴⁷ Li 2022,²¹ Raleigh 2014,⁴ and Omoike 2021⁴⁶).

Only studies with an individual level serum concentration of PFAS (and not via an estimated formula, or proxy) were considered for the meta-analyses. Of the 11 eligible studies, the data of nine were included as one of the studies was a follow-up study (Ghisari 2017⁴⁴ is the follow-up of Bonefeld-Jørgensen 2014) and one Chinese study had missing data (Li 2022)⁴⁸. However, the Chinese study was a study that concluded on a statistically significant association with PFOA and PFNA. All 11 studies were nested case-control or case-cohort studies examining background exposure (no contaminated areas). There were meta-analyses that reported a relative risk per natural log-unit increase in serum/plasma (see Figure 4), as well as meta-analyses where the relative risk is based on comparing the highest versus lowest category of serum/plasma PFAS concentrations (see Figure 5). The meta-analysed RRs showed no clear relationship between serum/plasma and overall breast cancer (see Figure 4 and 5), although the authors highlight the high heterogeneity. One aspect is the effect of timing of blood sample collection. Four studies assessed exposure prior to diagnosis where the time between blood sampling and follow up ranged from around 5.6 years as a median in Chang 2023,⁴⁹ 9.6 years in Feng 2022,⁵⁰ around 10–15 years in the Danish cohort,⁴⁴ and the French study reported a maximum follow-up of 20 years.³⁰ For the majority of studies assessing exposure at or after diagnosis there is no assessment of the exposure during the relevant timing for breast cancer, considering its long latency. This raises the possibility that reverse causality may influence the results. The studies with prediagnostic blood samples showed positive but imprecise associations with smaller heterogeneity, for PFOA and PFNA, compared to studies collecting post diagnostic samples (Figure 4). The conclusion of this SR and MA is that the body of **current epidemiological evidence is inadequate to conclude on the PFAS-breast cancer relationship**. Additionally, some possible signals of heterogeneous associations by hormone receptor status in post-menopausal women were observed.³¹ More epidemiological studies, especially well-designed prospective studies with attention to the timing and duration of exposure assessments and detailed breast cancer information, are necessary to establish a clearer understanding of the relationship .

Box 3 – Assessment of risk of bias for environmental studies by Chang et al 2024

Risk of Bias Tool for Human and Animal Studies from the National Toxicology Program Office of Health Assessment and Translation (NTP/OHAT).

Six domains are relevant for epidemiological studies: selection, confounding, attrition/exclusion, exposure, outcome and selective reporting.

Selection, exposure and outcome are the three key domains.

Each domain can be rated as “definitely low”, “probably low”, “probably high”, “definitely high”.

From the moment any of the 3 key domains is scored probably or definitely high, the study is classified as a Tier 3 study (high risk of bias). When all 3 key domains are scored probably or definitely low, it is classified as Tier 1 (low risk of bias).

Studies not classified as Tier 1 or 3 are considered Tier 2

Figure 4 – Forest plot of breast cancer risk per PFAS blood concentration (continuous variable), as reported by Chang et al 2024³¹

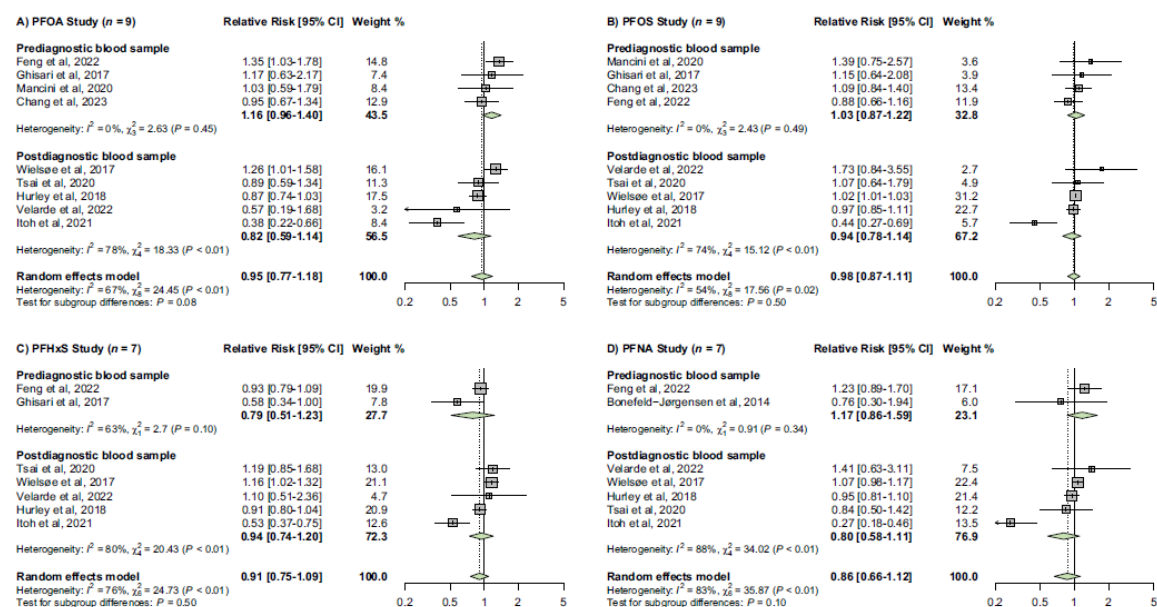
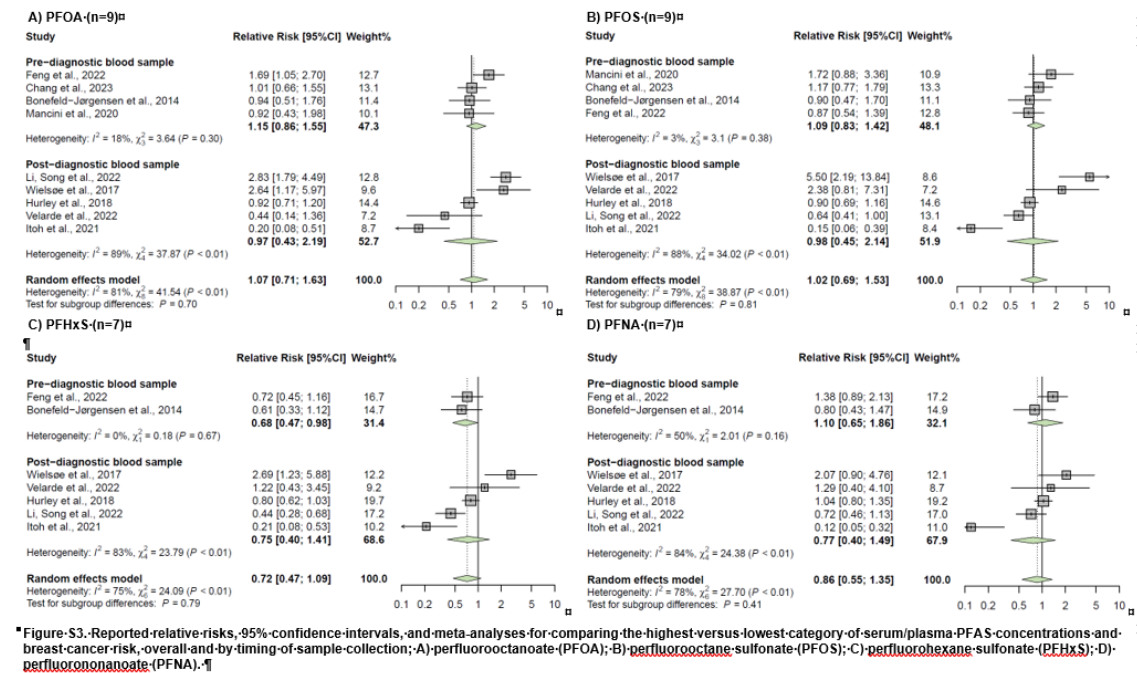


Figure 3. Reported relative risks, 95% CIs, and meta-analyses for per-natural-log-unit increase in serum/plasma per- and polyfluoroalkyl substances (PFAS) concentrations (ng/mL) and breast cancer risk, overall and by timing of blood sample collection, across multiple countries, up to 2023. A) perfluorooctanoate (PFOA); B) perfluorooctane sulfonate (PFOS); C) perfluorohexane sulfonate (PFHxS); D) perfluorononanoate (PFNA). Effect estimates from Chang et al,⁴⁴ Mancini et al,⁵⁰ and Velarde et al⁴⁹ were provided by authors. n, number of studies; I^2 , Higgins and Thompson's statistic; χ^2 , Cochran's Q statistic.

Figure 5 – Forest plot of breast cancer risk per PFAS blood concentration (highest versus lowest category), as reported by Chang et al 2024



1.2.4 Update of the literature

1.2.4.1 Method

Based on the search strategy of the good quality SR by Chang et al. performed in February 2023,³¹ the search was updated on March 17th 2025 (see appendix 2.3). This yielded 42 results with a publication date between Jan 1st 2023 and 17th March 2025.

- **Population:** human individuals exposed to PFAS
- **Exposure:** PFAS (all types), via individual blood measures, model-estimated, job-exposure, residency in contaminated region
- **Outcome:** breast cancer (incidence, related mortality, associated excess mortality)
- **Studies:** cohort studies, case-control, SR/MA; no case report or limited case series
- **Time period:** 2023 (search date of the retrieved good quality systematic review) -2025).

1.2.4.2 Results

Title and abstract screening resulted in 14 full text analyses. Table 5 shows the characteristics, and whether the studies were relevant for further analysis or not. We analysed one more recent systematic review including a meta-analysis (Seyyedsalehi 2024)³² and 4 new primary studies.^{23, 33-35} The study by Winquist et al. was already included in the Seyyedsalehi review and meta-analysis.²³

Table 5 – Result from the update of the evidence on breast cancer (March 2025): full text review

Study, year	Design	Remark
Seyyedsalehi et al 2024 ³²	Systematic review and meta-analysis	Most recent, most comprehensive SR focussed on breast cancer as it also included a more recent case-cohort study (Winqvist 2023) Included older studies that focused on a separate outcome 'mortality'. Is discussed in a separate paragraph.
Hammarstrand et al 2024 ³⁵	An analysis of BC incidence in a subcohort from large cohort (n=24 509) in a high risk zone (Ronneby)	Peculiar study design: from a large cohort a subcohort with the outcome is identified. In the identified BC cases there is categorisation of exposure (either high risk of exposure, or lower/unexposed). The final outcome is the comparison of BC incidence between high risk and lower risk (Harazd ratio)
Dou et al 2024 ³³	nested case control study in the Jinchang Cohort (employees of a factory of which 18 835 women with blood measures)	Four statistical methods were used
Jia et al 2024 ³⁴	meta-analysis of 9 studies + cross sectional study	In addition to a MA based on literature search, also a cross-sectional association study based on the NHANES database (n=1430)
Winqvist et al 2023 ²³	Case-cohort – eligible cohort CPS-LifeLink Cohort	included in the SR/MA from Seyyedsalehi <i>et al</i> Did not observe an association between breast cancer and PFAS
Chang et al 2024 ³¹	Systematic review and meta-analysis	already identified during scoping review and described (see above)
Chang et al 2023 ⁴⁹	Nested case control study	included in MA of Chang et al 2024 and MA of Seyyedsalehi et al 2024
Liu et al 2023	Meta-analysis	Search date of the literature was May 2023. 11 studies were included in the MA and no significant increased risk for breast cancer was identified. Not discussed in detail
Yang et al 2024	SR and dose-response Meta-analysis	The focus is on cancer risk in general. In total there were 40 studies included on all types of cancer and where exposure was measured via serum concentrations of PFAS. Study by Wen et al 2022 has been retracted in April 2025. <i>Wen et al concluded on a positive link between PFAS exposure and mortality.</i> Several analyses were performed: - Combining 13 studies comparing highest versus lowest level of exposure there was no association with breast cancer risk. - Considering PFAS as a continuous variable, pooling data of 6 studies showed elevated PFOA levels (standardised mean difference of 0.41) in breast cancer patients compared to controls.
Zheng et al 2024	Narrative review	Risk of bias as this review only included studies with a positive association between PFAS exposure and breast cancer risk. Therefore not discussed in detail
Feng et al 2024	Case-cohort study	The focus is on the pathophysiology – the role of mitochondrial DNA copy number. Therefore not discussed in detail
Cong et al 2023	Systematic review and meta-analysis	The search date of literature was October 2022, which is not the most recent SR or MA. Included 11 studies, with six studies showing PFAS was a risk factor for breast cancer, 1 study with a negative and 4 with no relation. The MA concluded there is no

		risk association between PFAS and breast cancer. Not further discussed in detail
Sezavar 2024	Meta-analysis	Search date of literature was May 2022, which is not the most recent SR, therefore not discussed in detail. The MA did not show substantial correlation between PFAS exposure and Breast cancer, ovarian cancer, prostate cancer and colorectal cancer.
Iwasaki et al. 2023	Narrative review	Focus on Japanese studies, therefore not discussed in detail

1.2.4.3 Systematic review by Seyyedsalehi et al 2024

Seyyedsalehi's systematic review included 24 studies, with 19 studies on the incidence of breast cancer as well as five older studies on the mortality from breast cancer. The quality of the SR was rated moderate to high (via AMSTAR see appendix 2.1), but interpreting the MA is difficult as it combines so many different study designs (case-controls, cohorts, cross-sectional) and exposure assessments (blood sample, modelled, residency). Moreover, some studies were labelled a wrong study design (Omoike et al 2021⁴⁶ and Cathey et al 2023⁵¹ were actually cross-sectional studies).

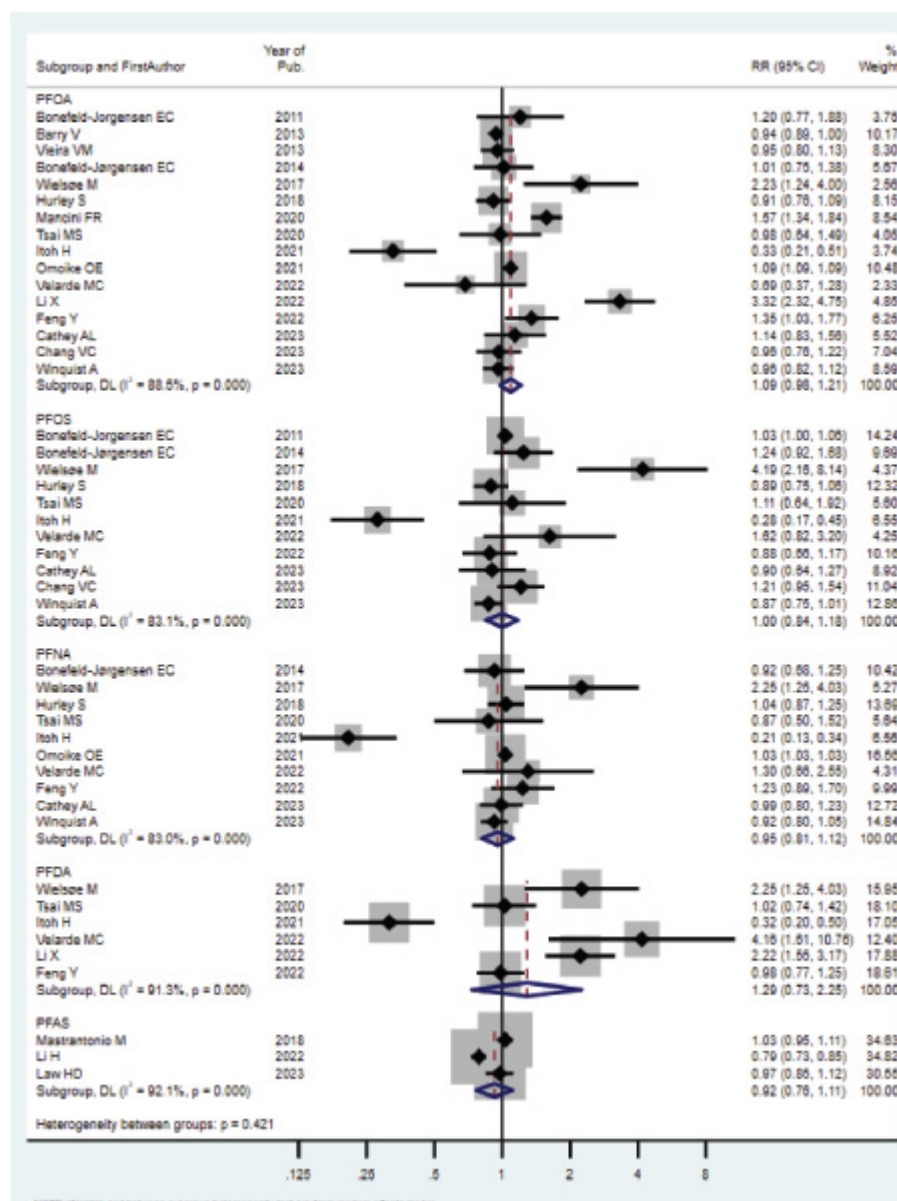
Compared to Chang et al, Seyyedsalehi included some more recent studies: the USA case-cohort study by Winqvist et al 2023,²³ and a cross-sectional study based on the US National Health and Nutrition Examination Survey (NHANES) by Cathey et al.⁵¹ Also an ecological mortality study investigating the impact of PFAS contamination in drinking water on mortality rates in the Veneto Region was included in Seyyedsalehi.²⁶ Seyyedsalehi included several study designs that were excluded from the MA by Chang 2024. For example, Seyyedsalehi included in the meta-analysis, cross sectional studies which are lower in quality as they assess the outcome before the exposure (Cathey et al 2023, Omoike et al 2021).

Seyyedsalehi also combined studies with different exposure measurements (before diagnosis, after diagnosis, via blood measurement, via estimations by models, via residency in contaminated area), while Chang and co-authors only included studies with individual blood levels. As shown in Figure 6, Seyyedsalehi also performed multiple meta-analyses, for PFOA separately, PFOS, PFNA, PFDA and also one meta-analysis including three studies where PFAS exposure was defined based on living in a contaminated area, and therefore no individual PFAS values were available: Mastrantonio 2018 the study on excess mortality in Veneto region,²⁶ Li 2022 a retrospective cohort of people residing in the contaminated Ronneby area,²¹ and Law 2023 a retrospective cohort of Australian residents in contaminated areas.²⁰

Although the included studies in the meta-analyses from Seyyedsalehi and Chang were different, the results were similar. The meta-analyses per PFAS did not identify a significant association with breast cancer incidence nor with breast cancer mortality, though Seyyedsalehi and co-authors **concluded there is evidence suggesting a possible link between PFAS exposure, especially PFOA and the incidence of breast cancer** (see forest plot in Figure 6). The authors rated the quality of the primary studies with a modified version of the Newcastle-Ottawa Scale. Only studies with a score ≥ 8 were considered as high quality: Gilliland 1993, Raleigh 2014, Barry 2013, Bonefeld-jorgensen 2014, Hurley 2018, Mancini 2020, Cathey 2023, Chang 2023 and Winqvist 2023. A sensitivity analysis excluding the low-quality studies did not change the outcome.

Figure 6 – Forest plot of association between PFAS exposure and breast cancer incidence as reported by Seyyedsalehi et al 2024

A Incidence



Forest plots (random-effects model) categorised per PFAS exposure type.

1.2.4.4 Primary studies

Winquist 2023 is a case-cohort study in the USA Cancer Prevention Study II Lifelink.²³ In this cohort serum samples were collected in 1998-2001. Premenopausal women at the time of sampling were excluded as menstruation is seen as a route of PFAS elimination. The cases are all incident breast cancer cases ($n = 786$). The comparison group is a subcohort of 500 women randomly chosen that did not have cancer at the time of sampling (from these also 11 developed breast cancer and were thus included in both case as control group). Covariates were considered in the statistical analyses. Nor the model with PFAS as a continuous variable (Log2 transformed measures), nor the model with quartiles show an increased risk of breast cancer incidence in higher PFAS measurements (PFHxS, PFNA, PFOA, PFOS). Overall, this study had a low risk of bias according to the Newcastle-Ottawa Scale method (score 10 out of 12, see appendix 2.2). As this was a rather old cohort at the time of serum sampling (only 5% were younger than 60 years), the people most susceptible to PFAS exposure

might already have passed away. This type of selection bias might explain the negative associations, as it is linked to underestimation of hazard ratio's.

Hammarstrand 2024 is a study on breast cancer cases in the cohort of people in the Swedish Ronneby area, which was contaminated with high levels of PFOS and PFHxS in the drinking water.³⁵ The study identified 313 breast cancer cases via the Swedish Cancer Registry. The exposure of the women with BC was categorised based on residency, i.e. whether they lived in a highly exposed water contaminated municipality or in a lower exposed municipality. The exposure status was validated with serum samples for a subset of residents (n=3350). The quality assessment via NOS scale indicated a low to moderate score (6 out of 12- see appendix 2.2). A strength of the study is its long follow-up period with a median time between contamination and diagnosis of 23 years. The hazard ratio for breast cancer incidence for a resident in a highly exposed area compared to a lower exposed area was 0.96 (95%CI 0.75-1.24). In the group of women with hormone receptor-positive breast cancer (n=233), there was also no increased risk in this subgroup (HR=0.84, 95%CI 0.61-1.14).

Dou et al is a Chinese nested case control study in a cohort of employees of the Jinchuan Nonferrous Metals Corporation.³³ A total of 18 835 employees were women with medical examinations and clinical laboratory tests (blood samples from 2011-2013). In this cohort, 135 incident breast cancers were identified and 540 paired controls matched on age, BMI, education level, occupation, income family history of BC, age of menarche. The mean follow-up time for the case group was 5.2 years. The calculation of odds ratios was done via a categorical approach using quartiles, as well as a continuous approach, and showed significant increased risk for most PFAS. The risks were more pronounced in premenopausal women. The quality as assessed by NOS scale indicated a moderate risk of bias (score 8 out of 12). The study concluded that exposure to mixed PFAS was associated with an increased risk of breast cancer. It also showed the positive correlation with a short-chain PFBA. Overall, the levels of PFAS values in the blood were lower compared to other studies.

Jia et al performed a cross-sectional study based on the USA NHANES database with 286 reported breast cancer between 2003 and 2014.³⁴ Based on a 1:4 case-control ratio, 1144 women without cancer were selected. No matching was applied and the cases and controls differed considerably in age, ethnicity, alcohol use, contraceptive use, and menopause status. Adjustment was foreseen for age, ethnicity, education level, marital status, BMI, family income-to-poverty ratio, alcohol user, smoking status, breastfeeding, menarche, pregnancy frequency, contraceptive, menarche, menopause status, Healthy Diet Index(HEI) and survey cycle. All analyses showed no increased risk for breast cancer based on PFAS serum concentrations (all adjusted ORs were close to 1.0 and not statistically significant).³⁴ This study had a low to moderate rating according to the NOS (score 6.5 out of 12)

In addition to the primary study they conducted a meta-analysis including 9 studies (Li et al 2022, Feng et al 2022, Itoh et al 2021, Tsai et al 2020, Hurley et al 2018, Mancini et al 2020, Bonefeld-Jorgensen 2011, Wielsoe 2017, Velarde 2022), and concluded no statistically significant association between PFAS and the risk of breast cancer (OR = 1.04, 95 % CI: 0.88–1.21). They assessed quality via NOS, and concluded that four had a high quality (score ≥ 7 on a total of 9 points),^{38-40, 50} and the other five moderate (all scored 6). They also stressed the high heterogeneity between studies.

Table 6 – Characteristics of recent primary studies on breast cancer identified during the literature update

Primary study, year	Design	Results
Winqvist 2023 ²³	Case-cohort study within the Cancer Prevention Study II Lifelink (USA) All incident breast cancer cases: n= 786 Comparison group is a randomly selected subcohort without cancer at the moment of sampling (500 men, 499 women)	Background exposure Exposure via a serum sample in 1998-2001 To give an idea on exposure: median PFOS=18 ng/ml, median PFOA =5.2 ng/ml, PFNA =0.64 ng/ml PFHxS = 3.10 ng/ml Premenopausal women at the time of sampling were excluded as menstruation is seen as a route of PFAS elimination; therefore a more older population Cancer diagnosis verified Mean follow up in the sub cohort of 499 women was 14.7y. Association between PFAS and incident breast cancer is modelled as continuous as well as quartiles, and does not show an increased risk Risk of selection bias as it is an older cohort including people less susceptible to exposure
Hammarstrand et al 2024 ³⁵	Nested cohort study in a large cohort (n=24 509 women) in a contaminated zone (Ronneby) 313 breast cancer cases of which 224 cases with hormone positive BC	High risk exposure Exposure is a proxy based on residency, though it is validated via blood samples for a subset Diagnosis in the Swedish Cancer Registry Analysis of the incidence of breast cancer in a high risk zone compared to a lower risk zone The group of people with low exposure is still higher than a background exposure, as everyone who lived in Ronneby area before 2013 had been exposed to some extent to PFAS in drinking water, which might result in underestimation of the association. Because exposure is based on residency, a long latency was possible
Dou et al 2024 ³³	Nested case control study in the Jinchang Cohort (employees of a factory of which 18 835 women with blood measures) 135 incident breast cancers 540 paired controls matched	Background exposure Exposure via serum sample in 2011-2013 (mean time between exposure and BC was 5.23 years) Diagnosis via medical record Four statistical methods were used to assess association between PFAS serum concentration and breast cancer incidence risk

		To give an idea on exposure: fourth quartile for PFOS ≥ 3.67 ng/ml PFOA ≥ 3.30 ng/ml PFNA ≥ 0.83 ng/ml PFHxS ≥ 0.34 ng/ml This is lower compared to other studies
Jia et al 2024 ³⁴	Cross sectional study based on NHANES database (30,887 female participants with cancer information and PFAS measurement) 286 with breast cancer and 1144 without cancer	Background exposure Exposure was via serum sample (cross sectional therefore no latency). To give an idea on exposure magnitude Range of third tertile for PFOS 16.5-175 ng/ml PFOA: 3.98-25.4 ng/ml PFNA: 1.3-15.4 ng/ml Diagnosis of breast cancer was self-reported Cases and controls were not matched, but there was adjustment foreseen in the statistical analysis - Higher tertiles were compared with the lowest tertile
Jia et al 2024 ³⁴	in addition, a meta-analysis of 9 studies (eight case-control studies and one case-cohort study) was performed	Meta-analysis of 9 studies: OR = 1.04, 95 % CI: 0.88–1.21, n=2399 breast cancer cases

Table 7 – Overview of case-cohort and case- control studies on breast cancer incidence

Author	Study Design	PFAS exposure	Conclusion
Bonefeld-Jørgensen 2011 ⁴¹	case-control study in Greenlandic Inuit women 31 cases BC 115 controls matched on age and geographical living area (selected from two cross-sectional studies on healthy persons)	Background exposure Exposure measured via serum at time of diagnosis	The BC cases had significant higher PFAS serum concentration PFOS - Adjusted OR=1.03 (95%CI 1.001;1.07) PFOA Adjusted OR=1.20 (95%CI 0.77;1.88)
Bonefeld-Jørgensen 2014 ³⁷	case-cohort study nested	Background exposure	study does not provide convincing evidence for a causal link between PFAS exposures and premenopausal BC risks 10–15 years later

Author	Study Design	PFAS exposure	Conclusion
Ghisari 2017 (followup) ⁴⁴	within the Danish National Birth Cohort (DNBC) including pregnant women 250 cases with BC 233 controls matched on age and parity	Exposure was measured via serum during pregnancy (1996-2002) PFAS serum concentration was categorised in quintiles. Fifth quintile PFOS >39.07 ng/ml PFOA >6.53 ng/ml PFNA >0.64 ng/ml PFHxS >1.35	
Wielsoe 2017 ⁴⁰	Update of Bonefeld Jorgensen 2011 77 cases 84 control matched on age and geographical living area	Background exposure Exposure measured via serum at time of diagnosis	The BC cases had significant higher serum concentration for PFOS, PFHxS SumPFAS - Adjusted OR=1.01 (95%CI 1.00;1.02) EPA classified this as uninformative as there are concerns about selection bias and exposure assessment.
Hurley 2018 ³⁸	case-control nested in the California Teachers Study that provided a blood sample 902 cases 858 controls matched on age, race, residence	Background exposure Exposure measured via serum after diagnosis (on average after 35 months) Median serum concentration in cases PFOS = 6.695 ng/ml PFOA= 2.35 ng/ml PFNA =0.850 ng/ml PFHxS = 1.515 ng/ml	findings do not provide evidence that serum PFAS levels measured after diagnosis are related to breast cancer risk. The few inverse associations found may be due to chance or may be artifacts of study design. All adjusted ORs were close to 1.0 and not statistically significant – regardless of whether the PFAS was modelled continuously or categorically.
Mancini 2020 ³⁰	Case-control nested in E3N study of French women (teachers) 194 postmenopausal BC cases 194 controls matched with age, menopausal status at blood collection, BMI, year of blood collection	Background exposure Exposure via serum (drawn between 1994 and 1999) before diagnosis. Cases were identified up to 2013 (maximal followup of 20 years)	While PFASs concentrations were not associated with overall BC risk, they suggest a linear dose–response relationship between serum concentrations of PFOS and the risk of developing hormone receptor positive BC tumors in postmenopausal women

Author	Study Design	PFAS exposure	Conclusion
		Level of exposure: Median PFOS: 17.3ng/ml and fourth quartile of serum level PFOS: 22.5–85.3 ng/mL Median PFOA 6.8ng/ml and fourth quartile: 8.8–21.4 ng/mL	
Cohn et al 2020 ³⁶	Nested case control in cohort of 9300 daughters born 1959–1967 in the Child Health and Development Studies pregnancy cohort 102 breast cancer ≤ 52y 310 matched (on birth year and blood draw) controls	Background exposure In utero exposure via serum analysis of archived maternal perinatal serum 54-year follow-up Level of exposure: Median PFOS: 32.1 ng/ml in control group and 30.5ng/ml in breast cancer group.	Difficult to interpret: clear relationship between perinatal exposure to EtFOSAA (precursor to PFOS) and breast cancer risk in the presence of higher maternal total cholesterol, but protective effect of PFOS
Tsai et al 2020 ³⁹	Case-control in National Taiwan University Hospital 120 breast cancer patients consecutively recruited from July 2014 to November 2015 and 119 controls consecutively recruited from July 2014 to August 2016	Background exposure Exposure via plasma at diagnosis but before any treatment for BC	PFOS: For ≤50 years age group, continuous crude and adjusted OR was 2.37 (95% CI = 1.10, 5.10) and 2.34 (95% CI = 1.02, 5.38)
Itoh et al 2021 ⁴⁵	Case-control in Japanese women (recruited in four hospitals) 401 cases and 401 matched controls (on age and residential area)	Background exposure Exposure via blood after diagnosis but before treatment. Quartiles range for PFOS Q1: 0.64–7.72ng/ml Q2: 7.80–11.08ng/ml Q3: 11.15–14.81 ng/ml Q4: 14.85–156.76 ng/ml	overall no association between serum PFAS concentrations and increased risk of breast cancer (many inverse associations).

Author	Study Design	PFAS exposure	Conclusion
		Quartiles range for PFOA: Q1 0.68–3.88 ng/ml Q2: 3.89–5.46 ng/ml Q3: 5.48–7.52 ng/ml Q4: 7.54–36.72 ng/ml	
Li et al 2022 ²¹	Ronneby Register Cohort (n= 60 507) Comparison to - population of Blekinge County excluding Ronneby municipality - national reference population was the whole Swedish population	Contaminated Exposure via residency in the Ronneby area validity was confirmed by comparisons with serum levels in a subcohort Breast cancer via nationwide Swedish Cancer Register sex, age and calendar year standardized incidence ratios (SIR)	study reveals no evidence of an overall excess risk of cancer in the population, and no increased risks for the most common cancer types, such as prostate and breast EPA: concerns about exposure assessment and lack of data on important covariates
Li et al 2022 ⁴⁸	Chinese case–control study 380 cases 798 control randomly selected from the participants in the Chinese National Breast Cancer Screening Program (CNBCSP) cohort	Background exposure blood samples of the patients were collected within a week after breast cancer diagnosis and before treatment median serum concentrations 12.18 ng/mL for PFOS, 3.35 ng/mL for PFOA, 0.94 ng/mL for PFDA, and 0.38 ng/ml for PFTrDA	plasma concentrations of PFOA and PFDA were positively associated with breast cancer, and PFTrDA was negatively associated with breast cancer in Chinese women
Feng et al 2022 ⁵⁰	Case-cohort in the Chinese Dongfeng-Tongji cohort of retired workers 226 incident breast cancer Random subcohort of 990 women (of which 13 also developed BC)	Occupational? Enrolment and sampling between 2008 and 2013 Assessment in 2018 → 9.6-year follow-up PFOA Q1 <0.84 ng/ml Q2 (0.84–1.18 ng/ml)	each 1-unit increase in ln-transformed PFOA and PFHpA was associated with an elevated incident risk of breast cancer [HR(95%CI) = 1.35(1.03, 1.78) and 1.20(1.02, 1.40), respectively], which were also significant among postmenopausal females Quantile g computation analysis observed a 19% increased incident risk of breast cancer along with each simultaneous

Author	Study Design	PFAS exposure	Conclusion
		Q3 (1.19-1.79 ng/ml) Q4 ≥ 1.80 ng/ml PFOS Q1 <6.39 ng/ml Q2 (6.39 – 10.35 ng/ml) Q3 (10.36-15.66 ng/ml) Q4 ≥ 15.67 ng/ml	quartile increase in all In-transformed PFCA concentrations [HR(95%CI) = 1.19(1.01, 1.41)],
Velarde et al 2022 ⁴⁷	Case-Control in Pilipino women 75 Cases in hospital 75 control group comprised of randomly recruited healthy female subjects, also within the age range of 18–59 years old, without prior diagnosis of cancer and without family history of breast, ovarian, and endometrial cancer in first-degree relatives.	Background exposure Enrolment in 2018. Exposure measurement via blood after diagnosis (but before chemo) odds ratios were computed and adjusted for age and region of residence as potential confounders.	among the PFAS with detection frequencies ≥90%, PFDoA, PFDA, and PFHxA were the most significantly associated with breast cancer pilot study
Chang et al 2023 ⁴⁹	Nested Case-control in Prostate, Lung, Colorectal Ovarian Cancer Screening trial cohort 55–74 years 621 postmenopausal breast cancer cases 621 matched controls	Background exposure Median time from blood draw to case diagnosis: 5.6 year	In postmenopausal PFOS→ statistically significant increased risks of ER+and/or/PR+ tumors for the third vs. lowest quartile of serum (ORs [95% CIs]=1.59 [1.01–2.50], 2.34 [1.29–4.23], and 2.19 [1.21–3.98], respectively) and elevated but non-statistically significant ORs for the fourth quartile PFOA→ modest positive associations with ER–, PR–, ER+/PR–, and ER–/PR– tumors were generally seen in the upper quartiles.

2 DETECTING PFAS CONTAMINATION IN HUMAN BLOOD

KEY POINTS TABLE

- The measure of PFAS concentrations in the blood seems to be an appropriate measure of PFAS exposure.
- **Various organisations or institutions proposed PFAS cut-off values in blood, based on different methodologies and for different PFAS (HBM-I/HBM-II; NASEM; EFSA).**
- These cut-offs only apply at population level and are intended as an alarm bell for (European) policymakers to initiate exposure reduction actions. **There are not intended for testing individual measurement results.**
- **The positive predictive value of an individual PFAS blood concentration above current standards is unknown.** It is unknown whether or to what extent the risk of developing diseases is increased.
 - Current thresholds for defining an increased risk of health problems were established as benchmarks for population-based measures. These values cannot be used to quantify, with sufficient certainty, the risk that an individual will experience adverse health outcomes due to PFAS exposure.
 - Conversely, epidemiological studies examining health effects did not use these thresholds, but rather PFAS blood concentrations as a continuous variable or divided into terciles, quartiles, or quintiles (see Section 2). Furthermore, serum concentrations varied across studies, and duration of exposure was not considered.
 - Proposing a single threshold for a group of PFAS does not take into account the distinct physical, chemical, and toxicological properties of each type of PFAS. Not all PFAS have the same toxic potential. However, the toxic effects of PFAS other than PFOA and PFOS have been less studied.
- **The negative predictive value of an individual PFAS blood concentration below current thresholds is also unknown.**
 - The HBM-I/HBM-II, NASEM, and EFSA standards only cover a very limited number of PFAS, some of which have been banned in Europe for several years.
 - Although PFAS accumulate sustainably in the environment, they are gradually eliminated from the human body. Thus, the half-life would be 1.5 to 5.1 years for PFOA, 3.4 to 5.7 years for total PFOS, and 2.8 to 8.5 years for PFHxS. A low PFAS concentration therefore does not rule out a past exposure.
 - The potentiating effect of PFAS on each other is poorly understood. This adds uncertainty to the predictive value of a single blood test combining several PFAS.
- **There is no gold standard method to assess PFAS in blood nor is there a consensus on the list of PFASs that should be measured in blood.**
 - PFOS and PFOA are most often cited in health-related cutoff values, followed by PFNA and PFHxS. However these are part of the older PFASs, which have been banned in Europe. The EU-PARC project takes a pragmatic approach in their studies and recommends a PFAS panel consisting of 7 PFASs: PFOA, PFOS, PFNA, PFDA, PFBS, PFHxS, PFHpS, each to be reported as linear and total PFAS.

- PFAS with short chains and shorter half-lives have been introduced and these replacement molecules may need to be included in PFAS test panels.
- There is no good justification to use the sum of the specific PFAS molecules measured as an alternative for the use of specific PFAS levels.
- In addition to the avoidance of PFAS contamination during sample collection, processing and analysis, it is relevant for each laboratory to check the public database with compounds that may create PFAS analytical interference.
- There is evidence that certain PFASs can only be found using whole blood analyses.
- More recent methods for specific PFAS molecules approach a between-batch CV of 10%, opening the possibility of reliable longitudinal biomonitoring in individuals.

2.1 Cut-offs for defining PFAS blood contamination

Various organisations or institutions proposed PFAS cut-off values in blood, based on different methodologies and for different PFAS.

2.1.1 HBM-I/HBM-II cut-offs

In Germany, the German Human Biomonitoring Commission (HBM-C) focussed on the two most renowned PFAS, namely PFOS and PFOA which are actually already banned from production. The definition of cut-off values relied on a derivation procedure predominantly based on human studies, and experimental studies in animals were taken into account to augment results from investigations in exposed populations.⁵² The literature review included on human epidemiological studies showing relevant and statistically significant associations between PFOA and PFAS with various health effects, i.e. time to desired pregnancy, gestational toxicosis, birth weights of newborns, lipid metabolism, immunity after vaccination, hormonal development and age at puberty/menarche, thyroid metabolism and onset of menopause. Effects on cancer incidence or other pathologies were not part of the assessment. Here are the cut-offs defined by the HBM-C:

- **Healthy cut-offs** for PFOA (2 ng/mL blood plasma) and PFOS (5 ng/mL) under which no risk for health exists according to current knowledge (HBM-I) were defined in 2018.^z
- **Unhealthy cut-offs** for PFOA (10 ng/mL for the general population, 5 ng/mL for women of childbearing age) and PFOS (20 ng/mL in the general population, 10 ng/mL in women of childbearing age) above which, according to the knowledge and judgement of the HBM-C, there is an increased risk for adverse health effects (HBM-II) were defined in 2019. The HBM-II-value should thus be regarded as an intervention or action level, i.e. an acute need for exposure reduction measures and the provision of biomedical advice.
- **A Grey zone.** At a concentration level higher than the HBM-I- and lower than the HBM-II-value the result should be verified by further measurements.⁵² If these measurements confirm the initial result a search for potential sources of exposure should be undertaken. Exposure to such sources should be minimized or eliminated where necessary and achievable with an acceptable level of input.⁵² The HBM-I-value should thus be regarded as a verification or control value. It is recommended to identify and, if appropriate, consistently eliminate possible sources of PFOA/PFOS exposure of these exposed individuals. In addition to occupational sources of PFAS exposure, these may include, above all, the consumption of drinking water or food with elevated PFOA/PFOS levels (such as fish from contaminated waters), according to the current state of knowledge.

^z <https://www.umweltbundesamt.de/en/topics/health/commissions-working-groups/human-biomonitoring-commission/reference-hbm-values>

Both the HBM-I and the HBM-II value for PFOA and PFOS are based on the assessment of the population-related risks. The HBM-II values were chosen from the range of Point of Departure (POD) values by expert assessment, considering the uncertainties and the specifics of certain target groups. **However, this value cannot be used to quantify, with sufficient certainty, an individual's risk of suffering health impairment as a result of her/his internal exposure to PFOA or PFOS.**⁵³

2.1.2 NASEM cut-offs

In the USA in 2022, the National Academies of Sciences, Engineering, and Medicine (NASEM) used the HBM-I and HBM-II values to define cut-offs in human serum or plasma for 7 PFAS together: PFOA (n-PFOA linear and sb-PFOA branched isomer), PFOS (n-PFOS linear isomer and Sm-PFOS branched isomer), PFHxS, PFDA, PFUnDA, MeFOSAA, PFNA), applying an approach of weight-based dose additivity:¹

- **Healthy cut-off.** Under 2 nanograms per millilitres (ng/mL) (for the 7 PFAS together), adverse health effects related to PFAS exposure are not expected
- **Grey zone.** Between 2 and 20 ng/mL, there is a potential for adverse effects, especially in sensitive populations.
- **Unhealthy cut-offs.** Above 20 ng/mL, there is an increased risk of adverse effects.

It was acknowledged that other PFAS may also cause harm, though they do not all have the same biological persistence and toxicity.¹ Most people are exposed to mixtures of PFAS such that specific effects are difficult to disentangle. Considering these issues, and recognizing that some PFAS are infrequently measured, the NASEM committee provided one strength-of-evidence determination for all PFAS for each health effect, recognizing that **providing one conclusion across PFAS may not account for the distinct physical, chemical, and toxicological properties of each type of PFAS.**¹

To recommend PFAS levels that should inform clinical care, the committee conducted a literature review to determine health effects or conditions associated with PFAS. The Statement of Task limited this review to human studies of those PFAS included in the Centers for Disease Control and Prevention's (CDC's) National Report on Human Exposure to Environmental Chemicals (see above).¹

2.1.3 EFSA cut-offs

Based on the methodology used by the European Food Safety Authority (EFSA) to define cutoffs in food (see further) also a cutoff for the sum of PFOS, PFHxS, PFOA and PFNA in serum was derived for infants (Benchmark Dose Level^{aa} BMDL₁₀=17.5 ng/mL) and breastfeeding women (BMDL₁₀=6.9 ng/mL).⁵⁴ This value is based on extrapolation of an epidemiological study in German children at 1 year of age which had a value of 17.5 ng/ml for the four PFAS and had a lower antibody titer against diphtheria after vaccination.⁵⁵

2.1.4 Limitations of existing cut-offs

The cut-offs presented above have been endorsed by the Conseil Scientifique Indépendant (CSI) PFAS in Wallonia,^{bb} as well as by the Flemish communication and biomonitoring studies^{cc}. This is also the case at the level of the European Environment Agency.

However, it should be clear that these cut-offs only apply at population level and are intended as an alarm bell for (European) policymakers to initiate exposure reduction actions. There are **not intended for testing individual measurement results**.

Table 8 – Overview of cut-offs for PFAS blood concentration

	Population	PFAS *: linear and branched	NASEM ng/mL	HBM-I, HBM-II ng/mL	EFSA ng/mL
Healthy cut-offs	General	PFOA*, PFOS*, PFHxS, PFDA, PFUnDA, MeFOSAA, PFNA	<2		
	General	PFOA		<2	
	General	PFOS		<5	
Unhealthy cut-offs	General	PFOA*, PFOS*, PFHxS, PFDA, PFUnDA, MeFOSAA, PFNA	>20		
	General	PFOA		>10	
		PFOS		>20	
	Women of childbearing age	PFOA		>5	
		PFOS		>10	
	Breastfeeding women	PFOA, PFOS, PFHxS, PFNA			>6.9
	Infants				>17.5

The positive predictive value of a blood test result exceeding current standards is unknown. It is unclear whether or to what extent the risk of developing diseases is increased.

^{aa} The benchmark dose (BMD) is defined as the dose that corresponds to a specific change in an adverse response compared to the response in unexposed subjects, and the lower 95% confidence limit is termed the benchmark dose level (BMDL)

^{bb} https://www.issep.be/wp-content/uploads/Fiche-substance_PFAS_20240619.pdf

Les missions à réaliser en urgence par le Conseil scientifique sont les suivantes :

1. Remettre un avis sur le protocole scientifique qui sera proposé par l'ISSEP permettant le suivi médical des personnes concernées dans les zones où un dépassement de la future norme de 100 ng/l a été constaté dans l'eau de distribution. Ce protocole nécessitera également la validation du Comité d'éthique, conformément à la législation en vigueur.
2. Affiner, si nécessaire, les recommandations sanitaires générales, déjà annoncées, ou relatives à des publics spécifiques (ex : nourrissons, femmes enceintes, etc.) ;

^{cc} <https://www.vlaanderen.be/pfas-vervuiling/pfas-bloedonderzoeken-algemeen/informatie-voor-huisartsen-en-andere-medische-professionals>

- a. Current thresholds for defining an increased risk of health problems were established as benchmarks for population-based measures. These values cannot be used to quantify, with sufficient certainty, an individual's risk of experiencing adverse health outcomes due to PFAS exposure.³⁷
- b. Conversely, epidemiological studies examining health effects did not use these thresholds, but rather PFAS blood concentrations as a continuous variable or divided into terciles, quartiles, or quintiles (see section Section 1). Furthermore, serum concentrations varied across studies, and duration of exposure was not considered.
- c. Proposing a single threshold for a group of PFAS does not take into account the distinct physical, chemical, and toxicological properties of each type of PFAS. Not all PFAS have the same toxic potential. However, the toxic effects of PFAS other than PFOA and PFOS have been less studied.²

The negative predictive value of a PFAS concentration below current thresholds is also unknown.

- a. The HBM-I/HBM-II, NASEM, and EFSA standards only cover a very limited number of PFAS, some of which have been banned in Europe for several years.¹²
- b. Although PFAS accumulate sustainably in the environment, they are gradually eliminated from the human body. Thus, the half-life would be 1.5 to 5.1 years for PFOA, 3.4 to 5.7 years for total PFOS, and 2.8 to 8.5 years for PFHxS.^{4, 5, 6} A low PFAS concentration does not rule out past exposure.
- c. The potentiating effect of PFASs on each other is poorly understood. This adds uncertainty to the predictive value of a single blood test combining several PFASs.

Due to the many uncertainties surrounding the effects assessment (animal studies, human epidemiological studies, toxicokinetics, mode of action), it is still not possible to draw robust conclusions and determine a sound scientifically substantiated reliable guideline value for PFAS compounds in the blood.

It is often mentioned that these thresholds can be used to advise individuals on how to reduce their PFAS exposure. However, the precautionary principle requires that this advice be given to everyone, regardless of any given test.

2.2 Measuring PFAS blood concentration

2.2.1 *Is a blood sample an appropriate reflection of PFAS exposure?*

Observed PFAS distributions in liver, kidneys, lungs, spleen tissue from autopsy cases can largely be predicted using equilibrium models.⁵⁶ These models use predictions based on organ/blood and organ/liver concentration ratios based on the binding affinity of the PFASs to the individual components of the organ. Observed PFAS levels in brain are however lower than modelled. Overall, **the use of blood-PFAS concentrations seems to be an appropriate measure of PFAS exposure**, with the liver possibly acting as the main organ of retention.

2.2.2 *Should a whole blood sample be used instead of serum or plasma?*

The well documented PFAS compounds like perfluorooctanoic acid (PFOA) and perfluorooctane sulphonic acid (PFOS) tend to accumulate in the non-cellular blood fraction, the reason why **serum or plasma testing has traditionally been used**.

However, there is evidence that certain PFASs can only be found using whole blood analyses. An important example are perfluoroalkyl acid precursors (pre-PFAAs) including perfluoroalkyl sulfonamides, FOSA. These include perfluorooctanesulfonamide (PFOSA), which can be biotransformed into PFOS.⁵⁷ Depending on the sample matrices used for biomonitoring studies, pre-PFAAs might thus be overlooked or falsely assumed to be transformed. As described by Carignan et al, 2023⁵⁸ and others, FOSA including perfluorooctanesulfonamide (PFOSA) and perhaps other PFASs are missed when serum or plasma are analyzed instead of whole blood. FOSA may partition

to the white blood cells and/or platelets which are absent in serum and plasma. Not surprisingly, PFOSA has been detected in dried blood spots.⁵⁹

2.2.3 *Can non-invasive matrices be used for the human biomonitoring of PFAS?*

While most research has focused on PFAS analysis in total blood/plasma/serum or human milk, research reports based on other non-invasive matrices are less frequent. A recent review of the literature discusses urine, hair and nails as non-invasive matrices for PFAS detection.⁶⁰ While urine was reported as a valuable biomonitoring tool for short-chain PFAS, the method sensitivity for the detection of long-chain PFAS in urine samples was reported as insufficient, requiring further analytical advances. Studies using hair and nails are infrequent but these matrices may have more potential for use in biomonitoring, with higher detection frequencies and concentrations for PFOS and PFOA compared to urine. Nails were found particularly promising for the detection of PFAS with high molecular weights, while hair could be more sensitive to short-chain compounds.

2.2.4 *Elimination half-life of specific PFAS molecules*

Estimates of half-lives expressed as arithmetic means were reported in the range of 2.3 to 8.5 years (PFOA), of 3.1 to 7.4 years (PFOS), and of 4.7 to 8.5 years (PFHxS).⁵⁴ Shorter mean half-lives have been reported for short-chain PFAS.⁵⁴ A systematic review found a half-life of 1.48 to 5.1 years for PFOA, from 3.4 to 5.7 years for total PFOS, and from 2.84 to 8.5 years for PFHxS.²⁸ These estimates were confirmed in a controlled single volunteer experiment.⁶¹ However, for some PFAS the half-life can be higher, such as for CI-PFESAs (trade name F-53B) which displays a half-life of 15.3 years in humans.⁶²

2.2.5 *How to measure PFAS in blood and serum?*

2.2.5.1 *General considerations for PFAS testing in blood or serum*

There is no gold standard method to assess PFAS in blood nor is there a consensus on the list of PFASs that should be measured in blood. The EU PARC consortium (www.eu-parc.eu) has opted for serum as matrix and sampling tubes free of interferences for the human biomonitoring studies. The PFAS (aligned scope) panel is mainly driven by the PARC QA/QC programme, which is aligned with the German External Quality Assessment Scheme (G-EQUAS). The EU recommendations on the list of PFASs to be tested in food and water were also taken into account. Additional PFAS molecules can be detected under a discovery scope.

The resulting aligned scope PFAS panel consists of 7 PFASs: PFOA, PFOS, PFNA, PFDA, PFBS, PFHxS, PFHpS, each to be reported as linear and total PFAS. (PARC T4.1.2.: Selected biomarkers of exposure for PARC Aligned Studies, www.eu-parc.eu)

As discussed above, total PFAS methods are to be distinguished from the more commonly used methods to quantify specific PFASs. For example, when total PFAS is measured in serum using the extractable organic fluorine method, pharmaceuticals actually account for a major fraction. Such fluorinated pharmaceuticals represent an increasing proportion of newly marketed drugs, currently about 30%.⁶³

When targeted PFAS measured it needs to be specified whether the linear form and/or branched PFAS isomers are included, knowing that quantification of branched isomers is more of a challenge compared with the linear form, both for the liquid chromatography part as well as for the tandem mass spectrometry part of the system. In addition, there are many precursor molecules which may not be measured but which may, degrade to PFAS. This can result in an underestimation of human exposure because these precursors can be metabolized to terminal PFAS in the human body. Some precursors that can be biotransformed to PFOS such as perfluoroalkyl sulfonamides, FOSA, require a whole blood sample analysis and are missed in serum/plasma based tests.

In addition to PFAS contamination that may arise from the unintentional introduction of PFAS to samples during sample collection, preparation, or analysis, the possibility of PFAS analytical interference has emerged as a relevant “PFAS ghost” topic. PFAS analytical interference has been identified in several matrices including blood.⁶⁴ Known interfering compounds for example create closely or co-eluting chromatographic peaks, leading to an overestimation of the PFAS concerned.

Additional unidentified interferents are likely to be observed as PFAS research continues to expand. Identified PFAS test interferences can be accessed from the PFAS Interferents List database: [PDR: Per- and polyfluoroalkyl substances \(PFAS\) Interferents List](#) and laboratories can add any new identified interference. As industry has shifted production to alternative compounds, for example F-53B and PFECHS, these molecules may also be long lived and need to be included in the blood tests, e.g. as reported for a 30 PFAS panel.⁶⁵

Analytical methods for specific PFASs have generally improved in sensitivity and selectivity in the past few years, e.g., to meet lower regulatory limit values.⁶⁶ Such targeted methods that incorporate uses of isotopic-labeled internal standards cover about 50+ PFASs, mostly perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkyl sulfonates (PFASs) with four or more carbons.⁶⁶

Such methods have also been applied for the quantitation of specific PFAS molecules in whole blood, serum or plasma. In addition, detection of 22 PFASs is also possible using dried blood spots based on capillary blood samples.⁵⁹

2.2.5.2 Common test method

Standards for PFAS sampling, sample storage and transportation in the context of human biomonitoring studies have been published in the context of the EU-PARC project.⁶⁷

The common method for the measure of PFAS in serum or plasma is to first remove proteins using precipitation (e.g. using methanol or acetonitrile) and/or purification with solid-phase extraction. A specific quantity of isotope-labeled PFAS molecules (linear isomer) is added as internal standard for the quantification. Liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) has traditionally been used for detection after negative electrospray ionization.^{65, 68} For testing in serum of PFASs that are not strong acids, e.g. PFOSA, it is required to also collect and analyse the eluate derived from the weak anionic exchange cartridge washing step, if such solid phase extraction is not omitted from the purification step (an example of variation between assays)^{dd, 65} Every method, targeted or non-targeted, has a certain degree of subjectivity and selectivity, during sample collection, extraction, cleanup, chromatography (or direct infusion), mass separation and detection. For example, negative ionisation can exclude neutral PFAS and PFAS detectable in positive electrospray ionisation mode.⁶⁹

High throughput testing of 50 PFASs in serum or plasma can be achieved using 96-well plate technology and methanol precipitation directly followed by direct (Ultra High Performance) Liquid Chromatography-MS/MS analysis of the centrifuged supernatant, thus omitting the solid-phase extraction step.⁷⁰

PFAS measures can be presented as linear isomer only or as the sum of branched isomers and linear isomers. This detailed information is of course crucial when results are compared across methods. Branched isomers are more difficult to quantify due to the lack of reference standards and variations in methods. One thus often relies on the linear isomer calibration curve, for example to measure branched PFOS. In addition, the separation of the PFOS isomers by chromatography is problematic.⁷¹

Advances in high resolution mass spectrometry (HRMS) now allows for the annotation and identification of many unknown compounds added to the targeted ones.⁶⁸ In the context of a Spanish Environment and Childhood epidemiology project, the authors compared three plasma preparation methods to be used for LC-HRMS and selected the Captiva method which had a high average recovery, and above all a high precision.⁶⁸ This high-throughput method for 42 PFASs in plasma is fast and accurate at low levels ranging 0.001–0.6 ng mL⁻¹ and suitable for multi sample analysis (n = 96).

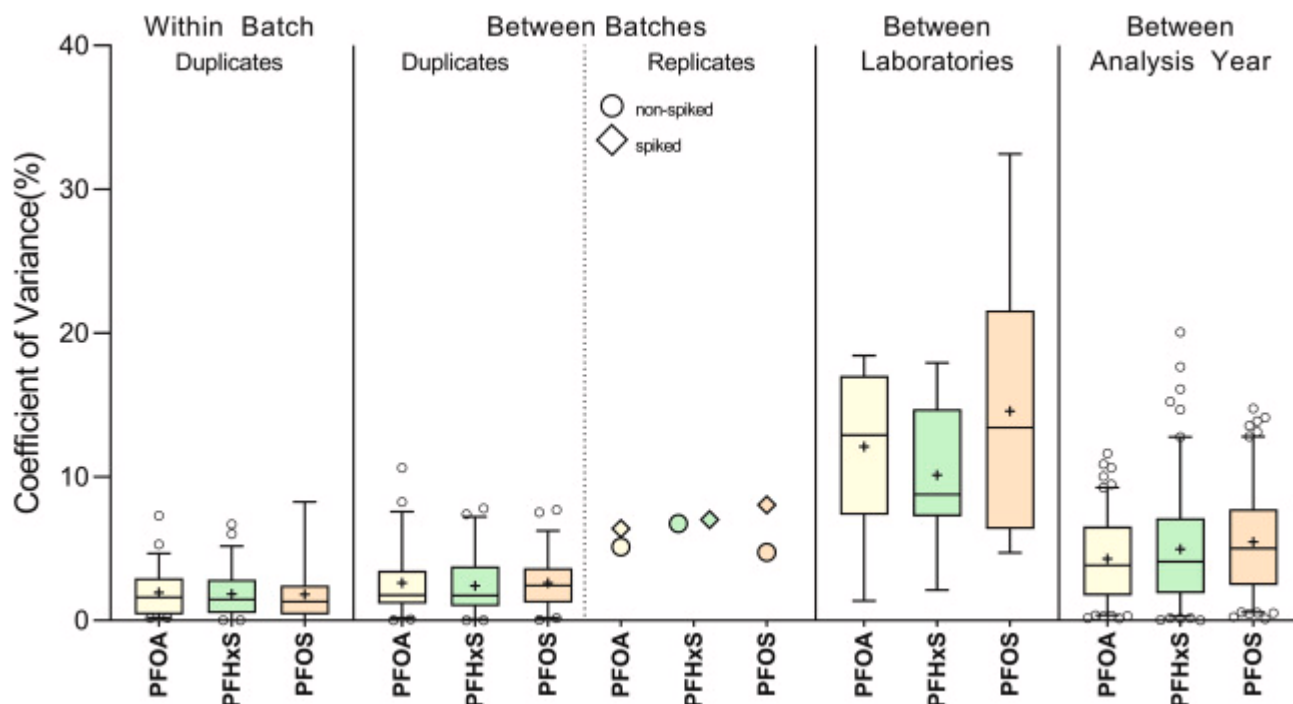
^{dd} Note that PFOSA was part of the 43 PFAS molecules selected based on production at 3M (eg PFOSA is an ingredient of 3M Scotchgard). PFOSA may not have been selected for further study in Flanders as it was probably not detectable in serum.

2.2.5.3 Can we measure blood PFAS with precision?

San Roman et al, 2023, reported for the Captiva extraction method followed by LC-HRMS an accuracy within $\pm 15\%$ of the nominal concentration and a coefficient of variation (CV) equal to or lower than 15%.⁶⁸

In a longitudinal follow-up PFAS study in serum multiple measures of variation were assessed.⁷² The CV values obtained for a limited number of PFAS are given in the figure 7 below.⁷²

Figure 7 – Coefficient of Variance reported by Nilson et al. 2021⁷²



Legend: The Coefficient of Variance (%) of PFOA (yellow), PFHxS (green) and PFOS (orange) for the measurements of variation in the current study; within batch variation (duplicates $n = 58$), between batch variation (duplicates $n = 57$ and replicates $n = 58 \times 2$), inter-laboratory variation ($n = 10$) and the variation of the re-analysis of archived samples ($n = 120$). Where several duplicate measurements are used to represent the variation, CV% of all pairs are presented as box and whiskers, where whiskers present the 5–95 percentiles and the + represents the mean. (copied from Nilson et al, 2021)⁷²

This compares to the PFAS tests performed at the laboratories of VITO in Flandres,⁷³ as a BELAC ISO 17025 accredited method. The reported within-sample variation based on duplicate testing of the same sample was 20-50%. More recently, Flanders contracted with Eurofins, accredited ISO/IEC 17025:2017, for analyses of 13 (+3) PFAS molecules in serum as well as using dried blood spots based on capillary blood.⁷⁴ The reported within-sample variation based on duplicate testing of the 13 PFAS molecules was 13-21%.

In conclusion, more recent methods measuring specific PFAS molecules are approaching a between-batch CV of 10% (<15%) which would allow for a reliable detection of a reasonably small PFAS level increase or decrease over time in a given subject.

3 RECOMMENDATIONS ON TESTING AND CLINICAL FOLLOW-UP

3.1 National and international recommendations

This chapter reviewed available national and international recommendations and programmes related to detection and management of PFAS exposure by health professionals.

3.1.1 *Methods*

The search for recommendations was a grey literature search. It was a combination of desk research searching for information on relevant governmental institutional websites (RIVM in the Netherlands, le Bundesinstitut für Risikobewertung and the Human Biomonitoring Commission of the German Environment Agency in Germany, the Agency for Toxic Substances and Disease Registry and the National Academies of Sciences, Engineering, and Medicine (NASEM) in the USA, the Australian Government Department of Health and Aged Care), and outreach to several country specific GP organisations (i.e. Royal College of General Practitioners (RCGP) in England, Nederlands huisartsen genootschap and ZonMw in the Netherlands, the German Society of General Practice/Family Medicine (DEGAM), the Collège National des Généralistes Enseignants (CNGE)-Collège Académique in France, on the existence of specific recommendations targeted to the health care professional. Also the available Belgian recommendations were examined (organisations such as SSMG, Domus Medica, Conseil Scientifique Indépendant in Wallonia, and the Flanders department of Care)

Of particular interest were the recommendations towards vulnerable populations such as pregnant women and lactating women.

Not all countries or institutions have clear recommendations targeted to their health care professionals. In some cases the recommendations are formulated in close link with a particular contamination, i.e. a high risk zone (RIVM report on PFOA contamination near Dupont factory, Flanders in the area around 3M factory)

An overview of the available recommendations can be found in Table 9.

Table 9 – Overview of available recommendations for health care professionals on opportunistic PFAS screening and post-testing management

Institution	Target population/situation	Recommendation/Advice
Agency for Toxic Substances and Disease Registry (ATSDR) Clinical Evaluation and Management: PFAS Information for Clinicians - 2024 ⁷⁵	Clinicians - When patients have concerns about PFAS	Actively listening and providing practical advice helping patients identify and reduce exposures - Exposure history - Exposure reduction and promote standard age-appropriate preventive care measures for physical health, mental health Blood testing? Clinicians need to decide with their patients weighing of benefits and risks →Benefits: - information that could guide exposure reduction - greater recognition of PFAS associated health effects - possible psychological relief from knowing one's PFAS blood level →Limitations: - PFAS blood test results do not identify sources of exposure - only certain PFAS can be tested in blood and these PFAS might not represent the PFAS to which a patient has been exposed - results do not indicate whether a current illness can be attributed to PFAS exposure - PFAS blood test results do not predict future health outcomes - comparison of PFAS results across laboratories can be difficult (e.g., due to differences in assays used and PFAS tested), - how long test results remain clinically meaningful is not known - neither the utility of repeat PFAS testing nor the optimum interval for testing is known
Agency for Toxic Substances and Disease Registry (ATSDR) Clinical Evaluation and Management: PFAS Information for Clinicians - 2024 ⁷⁵	Clinicians – when patient has PFAS blood results	ATSDR has not developed health-based screening based on PFAS blood levels and encourages clinicians to follow usual standards of care for health concerns Breastfeeding: Current science suggests the benefits of breastfeeding or providing human milk outweigh potential risks of PFAS. The Centers for Disease Control and Prevention and the American Academy of Pediatrics recommend that nursing mothers continue to breastfeed their babies despite the potential presence of environmental contaminants

Human Biomonitoring Commission of the German Environment Agency (2021) ⁵³	When the blood result is known	When PFOA > 10ng/ml (> 5ng /ml for women at child-bearing age) or PFOS > 20ng/ml (> 10ng/ml for women at child-bearing age): • If the HBM-II value is found to be exceeded in first-time measurements of PFOA or PFOS concentrations in the blood, a control measurement should be carried out at first • individuals should be offered environmental medical care or consultation, and, where appropriate, also long-term monitoring including follow-up measurements; no reason for recommending the determination of clinical-chemical parameters in cases where the HBM-II value is exceeded to a moderate extent, when other risk factors or pre-existing conditions are absent • Further exposure should be avoided immediately by eliminating specific sources of exposure, as far as these can be identified
German National Breastfeeding Commission (Stillcommission) PFAS and breastfeeding: Benefit-risk considerations (2021) ⁷⁶		The possible health risks are offset by numerous consistently observed positive effects of breastfeeding on the child and mother. The National Breastfeeding Commission therefore sees no reason to deviate from the existing breastfeeding recommendation in view of the current data situation, to deviate from the existing breastfeeding recommendation. This applies both to the general population and to people in regions particularly exposed to PFAS
Australian Government Department of Health and Aged Care PFAS Guidance Statement (2024) ⁷⁷	To patients and clinicians when there are concerns about PFAS	Individual blood tests are not recommended as they cannot determine whether any medical condition is attributable to exposure to PFAS and these tests have no current value in informing an individual's clinical management, including diagnosis, treatment, or prognosis in terms of increased risk of particular conditions over time. Breastfeeding: PFAS have been detected in human breast milk and breast feeding may contribute to an infant's exposure. Australian Health Protection Principal Committee does not recommend that mothers living in or around sites contaminated with PFAS cease breast feeding
USA National Academies Guidance on PFAS Exposure, Testing, and Clinical Follow-Up ¹	To patients and clinicians when there are concerns about PFAS	• Applying the principle of proportionality, the committee believes that the benefits of PFAS testing for those who request it, typically outweigh the harms. • Clinicians should describe the potential benefits and harms of the testing and the potential clinical consequences (such as additional followup) to make a shared informed decision. • Breastfeeding: Clinicians should explain that PFAS can pass through breast milk from a mother to her baby. PFAS may also be present in other foods, such as the water used to reconstitute formula and infant food, and potentially in packaged formula and baby food. It is not yet clear what types and levels of exposure to PFAS are of concern for child health and development.

USA National Academies Guidance on PFAS Exposure, Testing, and Clinical Follow-Up¹	To clinicians when the blood result is known	• When the sum of 7 PFAS is < 2ng/ml: no adverse health effects are expected • When the sum of 7 PFAS is >2 µg/l and < 20µg/l: ○ Clinicians should encourage PFAS exposure reduction if a source of exposure is identified, especially for pregnant persons. ○ <u>Within the usual standard</u> of care clinicians should: ▪ Prioritize screening for dyslipidemia with a lipid panel (once between 9 and 11 years of age, and once every 4 to 6 years over age 20) as recommended by the American Academy of Pediatrics (AAP) and the American Heart Association (AHA). ▪ Screen for hypertensive disorders of pregnancy at all prenatal visits per the American College of Obstetricians and Gynecologists (ACOG). ▪ Screen for breast cancer based on clinical practice guidelines based on age and other risk factors such as those recommended by the U.S. Preventive Services Task Force (USPSTF) • When the sum of 7 PFAS > 20 ng/mL: there is an increased risk of adverse effects: ○ Clinicians should encourage PFAS exposure reduction if a source of exposure is identified, especially for pregnant persons ○ In addition to the usual standard of care, clinicians should: ○ Prioritize screening for dyslipidemia with a lipid panel (for patients over age 2) following American Academy of Pediatrics (AAP) guidelines for high-risk children and American Heart Association (AHA) guidance for high-risk adults ○ At all visits: ▪ -conduct thyroid function testing (for patients over age 18) with serum thyroid stimulating hormone (TSH), ▪ -assess for signs and symptoms of kidney cancer (for patients over 45), including with urinalysis, and ▪ -for patients over 15, assess for signs and symptoms of testicular cancer and ulcerative colitis The benefits of breastfeeding are well known and are supported. Clinicians should explain that PFAS can pass through breast milk from a mother to her baby. PFAS may also be present in other foods, such as the water used to reconstitute formula and infant food, and potentially in packaged formula and baby food. It is not yet clear what types and levels of exposure to PFAS are of concern for child health and development.
USA PFAS Research, Education and Action for Community Health study (REACH)Medical screening	People living in contaminated areas	• Based on the NASEM recommendations: make blood test available for people likely with elevated PFAS exposure and offer additional medical screening for those with elevated levels. These recommendations are not targeted to those with average levels

guidance_clinicians 2022) ⁷⁸	(November	• Communication: acknowledge and address uncertainty • Lipid panels, liver function tests, serum creatinine and urinalysis, thyroid test • Screen regularly for testicular cancer, breast cancer • Screen for ulcerative colitis • Blood pressure monitoring during pregnancy Breastfeeding: There is insufficient evidence to broadly weigh the risks and benefits of breastfeeding in highly exposed mothers.
The Netherlands National Institute for Public Health and Environment: 2017 Report on blood values PFOA residents near DuPont factory ⁷⁹	People living in contaminated area, focus on PFOA	• Although PFOA exposure possibly alters cholesterol and liver enzyme (ALT), in the negative direction, these changes are relatively small compared to normal values. Changes in cholesterol and liver enzymes can be caused by many different factors. A small increase in these values also does not necessarily mean that someone is ill and/or needs treatment. Therefore, PFOA exposure is not a good reason to proceed to screening for these changes. • Exposure to PFOA possibly increases the risk of high blood pressure and pre-eclampsia in pregnant women, and possibly affects the growth of the baby. In the Netherlands, obstetricians routinely monitor pregnant women during pregnancy for the development of these complications. Additional research therefore does not seem necessary. However, obstetricians and gynaecologists in the area can be educated about the possible link between PFOA exposure and the above unwanted changes. • Exposure to PFOA possibly increases the risk of kidney cancer, testicular cancer, ulcerative colitis, thyroid disease and higher blood uric acid concentration. The relationship between these unwanted changes and PFOA exposure is uncertain. In addition, in general, the likelihood of these conditions is small. As a result, screening for these diseases is unlikely to detect new cases. It is advisable to educate general practitioners and medical specialists in the region about the possible link between PFOA exposure and these health effects in order to increase alertness for these conditions • The possible limited change in vaccine response could affect individual vaccine protection. Because more than sufficient antibodies are usually produced, this change is expected to have little impact. Due to high overall vaccination coverage, there are unlikely to be changes at the population level. In individual cases, the influenza vaccination might be less effective
Flanders Department Care – Nota on determination of PFAS in blood 2021 ⁸⁰	General public and clinicians	individual measurements of PFAS in blood that are not done as part of a medical environmental human biomonitoring (HBM) study are less meaningful.

Flanders Department Care PFAS information sheet for general practitioners (version June 2024)⁸¹	Clinicians of patients in the 3M region that participated to a biomonitoring study and have blood results	• communicate to patient ○ what can and cannot be expected of a blood test ○ the health-related guideline values for PFOS and PFOA are meant to be a signal. If the measured value exceeds one of the guideline values, there is no cause for concern. However, it can be a signal to take additional actions ○ there is no treatment to remove PFAS from the body. Reduce exposure. There are tips and a checklist available to limit exposure ○ the no regret measures³¹ • Is extra follow up needed after blood results? ○ A high PFAS exposure is one risk factor (of the many) that can contribute to some health effects. The general practitioner of the patient can best judge whether extra follow up is necessary, for example when there are also other risk factors such as obesity, smoking, diabetes, blood pressure, pregnancy,... Then the GP might consider screening cholesterol, liver enzymes, or thyroid hormones • Breastfeeding is still advised on current evidence because the benefits outweigh the risks • When patient has additional questions, referral to a prevention worker is available
The Walloon government Document d'information des médecins et professionnels de la santé sur les effets sanitaires des PFAS, les marqueurs utilisés pour les analyses sanguines et les modalités de prise en charge médicale. Le Conseil Scientifique Indépendant PFAS june 2024⁸²	To clinicians when the PFAS blood result is known	• The <i>Conseil Scientifique indépendant PFAS</i> proposes health cutoffs, based on the three existing sources (EFSA, HBM and National Academies)³² and advises following actions: ○ < 2µg/l – no risk ○ >2 µg/l and < 20µg/l : Reduce exposure, lipid profile (1 x children between 9-11y and then every 6 years), check pregnancy hypertension on every visit, mammography for breast cancer from 40y -74y (every 2y) ○ >20 µg/l: Reduce exposure, lipid profile, TSH (from 18y), check pregnancy hypertension on every visit. - Cancer screening: breast, renal (from 45y), testicular (from 15y) and colitis ulcerosis (from 15y) • Recommendations on reducing exposure (water, food, local eggs and vegetables, on cooking, on hygiene) • Pregnant women or women wishing to become pregnant: take folic acid 0.4mg/day minimum start 8 weeks before pregnancy. • Breastfeeding women: drink glass-bottled water, and don't alter (reduce) the length of the breastfeeding period

SSMG FAQ sur les PFAS à destination des médecins généralistes (june 2024) ⁸³	To clinicians	There is no clear recommendation on whether to test PFAS in blood. As almost everybody has PFAS detectable in the blood, a blood test is not necessary to know whether you have PFAS exposure or not. It can be useful to know whether the concentration is higher than the general population, for patients in contamination hotspots
SSMG FAQ sur les PFAS à destination des médecins généralistes (june 2024) ⁸³	To clinicians when the PFAS blood result is known	- The post-testing management is based on the Conseil Scientifique Indépendant PFAS >2 µg/l and < 20µg/l: - Biologie avec profil lipidique dès 11 ans, puis à partir de 20 ans 1x/6 ans (au lieu de 50 ans si facteurs de risques, sinon 65 ans) - Suivi médical habituel de la grossesse : risque d'hypertension, de dyslipidémie et de diabète de type II qui sont décrits en cas de surcharge corporelle en PFAS. - Démarrage des dépistages du cancer du sein par mammographie tous les deux ans à 40 ans (au lieu de 50 ans) >20µg/l : - Démarrage des dépistages du cancer du sein par mammographie tous les deux ans à 40 ans (au lieu de 50 ans) - Biologie avec profil lipidique dès 11 ans, puis à partir de 20 ans 1x/6 ans (au lieu de 50 ans si facteurs de risques, sinon 65 ans) - Biologie avec TSH dès 18 ans, à coupler avec le profil lipidique - Dépistage cancer du rein : à partir de 45 ans, anamnèse et tigelette urinaire. Plus tôt si facteurs de risques (tabagisme, surpoids, antécédents familiaux ou insuffisance rénale) - Dépistage cancer testiculaire : à partir de 15 ans, anamnèse, examen clinique, éducation à l'autopalpation - Dépistage colite ulcéreuse : à partir de 15 ans, anamnèse

3.1.2 Conclusion of international/national recommendations

There are no recommendations that PFAS should be tested in individuals in the general population. In case patients have concerns about high exposure, the available recommendations on performing PFAS blood testing are more nuanced, with some leaving it up to the clinicians based on a discussion/request of their patient (NASEM), and some others are not recommending individual blood testing, with the main arguments that it is not possible to determine whether any medical condition is attributable to exposure to PFAS, and that it cannot inform an individual's clinical management (Australia, Flanders). Importantly, a lot of countries do not have any recommendation on whether to test PFAS in the blood (France, UK, Sweden).

On the clinical follow-up based on individual PFAS blood levels, several recommendations suggest not taking any specific action but rather continuing with the usual standard of care, without additional health screenings **solely** based on PFAS levels (Agency for Toxic Substances and Disease Registry, Flanders, the RIVM report in the Netherlands). In contrast, the NASEM provides specific clinical follow-up recommendations based on PFAS blood levels. It states that when the combined concentration of seven PFAS exceeds the 20 ng/mL threshold, **additional** measures are advised—such as lipid profiling for individuals over the age of two, thyroid function testing at each visit, and urinalysis at each visit to screen for kidney cancer. While these recommendations have been a source of reference (e.g. the Walloon CSI), some organizations, such as the American College of Medical Toxicology, have expressed concerns about these additional measures:⁸⁴

- a. Lipid screening in children is controversial.
- b. Screening for thyroid disease is often performed in primary care settings but is not supported by evidence in asymptomatic adults outside of pregnancy.
- c. There are no evidence-based recommendations for primary care screening for testicular cancer or ulcerative colitis.
- d. There are no evidence-based recommendations for primary care screening for renal cancer. The positive predictive value of hematuria is very low, especially since renal cancer is generally a rare condition and it is unknown by how much the risk would be increased in individuals contaminated with PFAS. This test will therefore result in a high proportion of false-positive tests, resulting in unnecessary additional testing and patient anxiety.⁸⁴
- e. Furthermore, the additional testing recommended by NASEM for patients with intermediate blood PFAS concentrations between 2 and 20 ng/ml is presented as routine clinical monitoring. In reality, this so-called routine monitoring corresponds to American guidelines, such as mammography starting at age 40 for women, but does not necessarily correspond to current good medical practice recommendations in Belgium.

On whether or not to breastfeed in case there is risk of high PFAS exposure, none of the identified recommendations stated to stop breastfeeding. There is no evidence to indicate the possible harms might outweigh the benefits, therefore current recommendations support breastfeeding.

3.2 Stakeholders consultations

KEY POINTS

- Participants to the online survey agreed with all the recommendations but 3. The 3 recommendations with the most divergent agreement level were: no systematic screening - even in areas with high exposures; no opportunistic screening by GP; and no additional clinical follow-up for individuals with increased PFAS blood concentration.
- Participants to the stakeholder meeting highlighted the difficulty for GP of not “doing something” when facing patients (at risk of being) exposed to PFAS, particularly for vulnerable groups such as pregnant and breastfeeding women, young children and those with existing severe pathologies.

3.2.1 Aims and methods

This stakeholder consultation aimed at gathering the opinions of the key players and context setters on a set of policy and practice recommendations based on this research. This consultation did not aim at reaching a consensus but rather at collecting the elements supporting / not supporting the recommendations with a view to their dissemination.

3.2.1.1 Preparatory work – Stakeholder and expert mapping

The preparatory work consisted in a stakeholder mapping of key players and context setters, that is those with high interest and influence on the topic and those with high interest but less influence in the final decision-making process ^{85, 86}.

We approached scientific experts on an individual basis, and approached organisations and authorities concerned with the issue of PFAS on human health at regional and federal level as stakeholders. As these recommendations concern the practice of general practitioners, the general practitioners' federations were also involved in this consultation. Similarly, we also involved representatives of health professionals likely to be the first contact with patients (e.g. occupational medical doctors, child and maternal services...). As the focus was on human health, we did not include experts in water and food contamination, industrial contamination and chemicals.

Stakeholders were categorised according to the following dimensions:

- Individual versus organisation: this applied for individual experts with acknowledged expertise in the field of PFAS and human health by contrast with organisations participating on behalf of a larger group (e.g. representative organisation of GP). Individual experts were either members of the working group of the Superior Health Council, either experts from the Walloon Scientific Independent Council.
- Level of action: regional versus federal – this was also used to ensure a balance in the different regions as the focus and approach differs. Key domain of activity: research, administration, policy and (direct) health care
- Target groups: some stakeholders have a focus on a specific target group. Regarding PFAS, pregnant women and children and those with a professional exposure to PFAS were identified as particular target groups.

Stakeholder list was informed by the existing repository of stakeholders at KCE, previous projects concerning GP, and advice from KCE colleagues. Identified organisations and experts were contacted per mail to:

- Identify a referent person for the PFAS issue
- Identify additional stakeholders (snowballing strategy)
- Inform them about the upcoming stakeholder consultation

As some contact persons were cited by different sources, we could be confident that we somehow reached all the key players and context setters.

The final list of stakeholders included 77 persons, among which 14 experts involved on an individual basis and 63 contact persons for 41 organisations (a same organisation can have more than one contact person and some contact persons were identical for different organisations). The final list of stakeholders to be contacted was validated by the research team.

3.2.1.2 *Online consultation of key players and context setters*

Context setters and key players were invited to participate to an online consultation from April 15th to May 5th. An additional week was added to allow late participants to contribute. No reminder was sent. Organisations were asked to fill in only one questionnaire.

Based on the literature review, a first set of recommendations was drafted by the research team alongside a rationale to support the content of the recommendations (see Appendix 3.1, 3.2 for the surveys and 3.3 and 3.4 for the rationale).

Content of the questionnaire was elaborated based on the data collected in the literature review. It included a set of 7 provisional recommendations. For each recommendation, participants had to report their degree of agreement on a 4-point Likert scale. A 4-point Likert scale was chosen to force participants to choose. Participants also had to possibility to choose “I don’t know”. For each recommendation, participants were invited to share elements supporting / not supporting the recommendations (free text). If they had no comments, they had to mention “geen / aucun”. To help participants to understand the recommendations, a supporting document containing the rationale behind each recommendation. Questionnaires and supporting documents are presented in Appendix 3.1, 3.2, 3.3 and 3.4.

The online survey was first drafted in French then translated in Dutch. The survey was tested by KCE experts outside the research team to ensure the smoothness of the questionnaire, the clarity of the vocabulary and the length to fill it. Based on the test, language adaptations were made. Questionnaire was distributed via the LimeSurvey platform.

The survey was not anonymous to allow for additional follow-up with the participants – if needed – and to allow for checking that the participants cover the different categories of stakeholders, particularly those identified as key players. Results were therefore anonymised.

The questionnaire was accessed by 39 participants. There were 16 incomplete responses that were not included in the final sample. Additional questionnaires were received per email and registered manually. The final sample included 28 responses.

Results from the Likert scale were compiled in bar histograms. Results from the free text were synthesised per recommendation with a distinction between positive arguments that helped to support the recommendation versus negative argument. Arguments were discussed by the research team and served to adapt – when relevant – the content of the recommendations.

3.2.1.3 *Stakeholder meeting with key players*

Key players were invited to an online stakeholder meeting on May 20th 2025, from 16.00 to 18.00. The meeting was held via Zoom.

Key players invited to the meeting were categorised as follows:

- Administrations (n=5)
- Policymakers (n=4)
- Representatives of the GP practice (n=4)
- Representatives of the GP training (n=2)
- Scientific bodies (n=7)

Each organisation was invited to designate one representative to participate to the stakeholder meeting – at the exception of the 2 key organisations representing GP practice that were invited to designate two representatives to ensure a balance between the different stakeholder groups. Scientific

bodies were invited to ensure the coherence between the different recommendations that have been issued in Belgium so far. The full list of stakeholders is reported in the Colophon of the report. All organisations who participated to the meeting but 2 contributed to the online survey.

Before the meeting, participants received a preparatory document including a modified version of the recommendations and of the rationale, taking into account the comments and arguments shared during the online survey.

Participants to the meeting had to fill a declaration of conflict of interest before the meeting. They also were asked to give consent for the recording of the discussions.

Meeting was assisted by online interpreters, allowing participants to speak in their own language and ensuring a smooth discussion without interruptions because of language issues. The meeting was moderated by the PI (DOR – a French speaking KCE senior expert trained as medical doctor and epidemiologist), assisted by a KCE expert (MAD) for logistics and time keeping. Notes were taken by the other team members (DCA, JOB, FHK). The meeting was also attended by the project manager (NAS) and the responsible for scientific communication at KCE (EVC). In total, 17 stakeholders, 2 interpreters and 7 KCE members participated to the meeting. Two stakeholders did not show up.

Based on the results of the online survey, only the 3 recommendations with the highest dispersion of agreement were discussed.

After a short introduction on the context of the project, each recommendation – in its modified version – was presented to the participants by the PI. Participants had then the possibility to react before being invited to express their degree of agreement (4-point Likert scale + I don't know) via an anonymous vote (online poll generated through Zoom). At the end of the meeting, participants were invited to share their inputs about technical and scientific aspects per mail up to May 23. Notes taken during the meeting were synthesised and discussed by the research team.

3.2.1.4 *Limitations*

Despite our precautions, this stakeholder consultation had some limitations. We gathered a large group of stakeholders, reflecting the diverse opinions. PFAS is relatively “new” issue for public health and there are still a lot of uncertainties. As a consequence, attitudes and opinions highly vary and are particularly sensitive to public opinion, press coverage and political involvement. Similar to other health issues involving economic interests, PFAS generates lots of tension, questions and even conspiracy theories⁸⁷⁻⁸⁹. Mediatised precedents of environmental problems caused by industries also contribute to the sensitivity of this topic.^{ee}

We did not aim at reaching for a consensus, using a Delphi process or a nominal group, mainly for time constraints. The absence of consensus can be seen as a major limitation of this study as conflicting opinions were not resolved. However, as key players were invited to a stakeholder meeting, they had the possibility to explain their positioning to other key players. Recommendations on which opinions differed the most after the online survey were put to a new vote, leading to more distinct clearer positioning.

3.2.2 *First stakeholder consultation*

3.2.2.1 *Participants*

A total of 28 completed questionnaires was considered for analysis. The final participation rate was of 49.1% (n=28/57).

Participants belonged to the following sectors: academics (n=10 – individual experts), experts outside the academic sector (n=3), regional and federal administrations (n=9 – including perinatal public services), ministry cabinets (n=3), professional associations (n=4 – including pharmacists), scientific societies (n=6 – including GP practices, gynaecologists and occupational medicine).

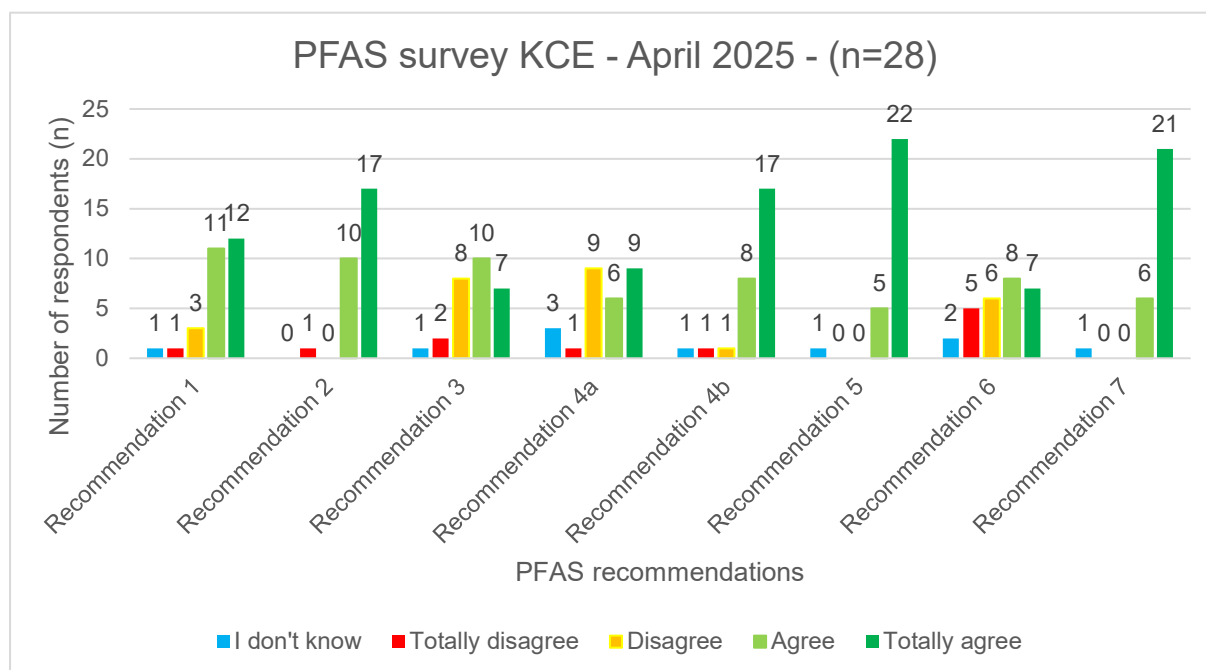
^{ee} For example, the notorious case of the Hinkley Groundwater Contamination was brought to the screen by Julia Roberts in the film Erin Brockovich https://en.wikipedia.org/wiki/Hinkley_groundwater_contamination

Non-respondents belonged to the following sectors: academics (n=9), experts outside academic sector (n=2), regional / federal administrations (n= 2), ministry cabinets (n=1), professional associations (n=5) and scientific societies (n=3).

3.2.2.2 Overview of the level of agreement

Figure 8 presents the level of agreement per recommendation according to the context setters and the key players. All recommendations but 3 were supported by the majority of the participants.

Figure 8 – Level of agreement per recommendation, April-May 2025 (n=28)



3.2.2.3 Inputs retrieved from the online survey per recommendation

Recommendation 1	a) We recommend that all scientific bodies concerned with the health impact of PFAS work together to produce an up-to-date and comprehensive information package for general practitioners b) This should involve collaboration with GP associations. c) The content of the package should be coordinated and harmonised across regions.
Survey result	23 out of 28 participants support the recommendation (agree or totally agree) 4 participants disagree
Inputs from participants on the recommendation	- This recommendation is very much targeted to the general practitioner, but it is also relevant for other health care practitioners, professionals in prevention and health promotion. Pharmacists were often cited, but also endocrinologists, gynaecologists, paediatricians, and professionals in contact with pregnant women and young children. - For recommendation b) limit to <i>scientific</i> associations

Inputs from participants on the rationale

- It was recommended not to make the information packet too long with a view to ensure a balance between comprehensive and communication and the readability. Some also suggested that this information should also be relevant and comprehensive for the patient.
- If the information packet contains information on PFAS water sampling, this should be completed with information on other regional environmental data (soil, water, air)
- It was also pointed to highlight the technical complexity of PFAS measurement in blood, and the inter-lab variability when conducting the tests
- Some also advised to put into context with other endocrine disrupter chemicals (pesticides, bisphenol A etc.)
- Some suggest to look at international guidance such as EFSA

Recommendation 2

We recommend that the federal and regional governments together with GP organisations ensure the successful dissemination of the information package.

Survey result

27 out of 28 participants support the recommendation

Inputs from participants on the recommendation

- Similar to recommendation 1, participants pointed that this recommendation is very much targeted to the general practitioner, but it is also relevant for other health care practitioners, professionals in prevention and health promotion. Again, pharmacists were often cited, but also endocrinologists, gynaecologists, paediatricians, and professionals in contact with pregnant women and young children.
- Some also mentioned it as relevant for students (in medicine)
- The dissemination requires a coordinated communication campaign by the various competent authorities, the KCE and the HGR were cited as facilitators of a wider dissemination
- The minimal expectation was to have a similar content of the advice is the same across regions (Brussels, Flanders and Wallonia). It was also suggest to have a bilingual (trilingual) inter-federal website.
- Some participants reminded to keep in mind the cultural diversity and the digital divide, implying that Internet-based communication only is not an efficient strategy

Recommendation 3

We advise regions not to organise a systematic screening programme through PFAS blood tests, even in areas where contamination of drinking water, food and/or soil has been demonstrated, unless organised in a research context.

Survey result

17 out of 28 participants support the recommendation

10 participants disagree

Input on the recommendations

- According to participants who disagreed with the recommendation, biomonitoring **in identified hotspots/contamination zones** must not

when participants were in disagreement

be excluded by default, and is sometimes necessary. There are other goals in addition to medical/healthcare goal to perform screening via blood sampling, for example, policy purpose, societal purpose, scientific purpose.

- Those against the recommendation also recalled that citizens have the right to know their exposure when there is an **identified and confirmed pollution**. Systematic measurements provide crucial data for targeted environmental policies. Blood tests can be both scientifically and socially relevant at the same time. Besides, they also stated that not offering tests damages trust in government and policy
- For them, it was important to be able to monitor patients in contaminated zones, and to offer dedicated medical follow-up.
- These participants also pointed that there should be a focus on pregnant women, children, and people in their fertile stage of life.

Input on the recommendations when participants were in agreement

- According to participants who agreed with the recommendation, individual screening is not relevant as there are no specific PFAS follow-up measures and no treatment.
- Those agreeing with the recommendation also pointed that PFAS measurements (technical as well as link with health values) are done in a research setting: this should be highlighted. It was recommended to start the recommendation with a sentence such as “Only in a scientific context,...
- These participants advised that PFAS data should be collected using harmonised analytical methods that have proven their performance for analysing PFAS in human blood (a specific audit of the laboratories involved would be welcome), to ensure comparability of results if not all analyses are carried out in the same laboratory.
- Screening and biomonitoring programs need to be linked to research, otherwise the results will be wasted. If extensive and ambitious biomonitoring is not carried out in accordance with the rules of the art, some municipalities or regions will do outside the framework of proper data exploitation, including with some sub-groups (children, breastfeeding women, etc.)..
- Further research is needed, for example measurement of PFAS in breast milk
- For these participants, a determination of PFAS in blood only has added value if it is done in the context of a well-considered and scientifically correctly designed medical environmental human biomonitoring study, in which markers of exposure (substance in humans) and effect (effect in humans) are linked to detailed environmental measurements and/or long-term follow-up of health effects.
- As pointed by a participant, given the costs of the setup and the lack of certainty about the results, it is important to set up a biobank to allow for carrying out analyses at a later date once there are more certainty, or to search for an association between a level in the blood at time X and a disease at time Z. This could be done on an individual or collective level.
- Some participants also found that it could relevant to have a decision tree to help deciding when a screening programme is opportune

Recommendation 4 a

We advise GPs not to promote opportunistic screening for PFAS contamination outside a research context, even in areas where contamination of drinking water, food and/or soil has been demonstrated

Survey result

15 out of 28 participants support the recommendation

10 participants disagree

Input on the recommendations when participants were in disagreement

- Similar to recommendation 3, those disagreeing with the recommendation 4a pointed that the population has the right to know its contamination level and adapt their habits.
- Access to testing was seen as a way to strengthen citizens' own control over their health.
- For some, a dismissive opinion may marginalise legitimate care requests from patients
- It was also pointed that uncertainties surrounding PFAS may not contribute to ignoring the problem. It was emphasised that there is a need to push to harmonise practices between laboratories and / or have a proper storing of blood samples until standards for analysis can be established.
- Some participants reported that one needs to adopt the precautionary principle, hereby supporting the opportunistic screening
- GPs need to be aware of the contamination of their region (contaminated eggs) and need to inform their patient correctly
- In the context of environmental medicine, opportunistic screening is seen as a way to reduce exposure.
- Some participants also recalled that opportunistic screening may not be as accurate as systematic and validated screening; nevertheless, it may serve as an initial indication for further investigation, especially if health threshold values are exceeded.
- For those agreeing with the recommendation, results not useful for an individual patient as there are too much uncertainties.
- It was also reported that, based on an individual PFAS result, one cannot make a statement about the patient's individual health. Thus, the result of a blood test will also not contribute to additional measures to mitigate potential health effects beyond reducing exposure as much as possible
- Some also pointed that a blood test can lead to patient anxiety and stress, additional follow-up tests, and a higher medical consumption without clear benefits.
- It was said that if screening is done *ad hoc* at the initiative of the GPs, the responses will be uncoordinated and uneven: the risk is to have some people tested, others not, without clear criteria. It is then of importance to define criteria when to test.
- A determination of PFAS in blood only has added value if it is done in the context of a well-considered and scientifically correctly designed medical environmental human biomonitoring study, in which markers of exposure (substance in humans) and effect (effect in humans) are linked to detailed environmental measurements and/or long-term follow-up of health effects

Input on the recommendations when participants were in agreement

- It was therefore pointed that a personalised approach for at risk-groups such young women of childbearing age, pregnant or breastfeeding women could be considered as part of a case-by-case basis for vulnerable groups, depending on the patient's medical situation.
- As pointed by some participants, individual opportunistic screening is not appropriate but one should be able to do it, e.g. for certain people who are very anxious despite the explanations given by the healthcare professionals.
- Instead of opportunistic screening, some suggested to have screening for target groups and specific geographical areas.

Recommendation 4b When patients request a PFAS blood test, we advise GPs to explain the current uncertainties about the benefits and risks of such a test, so that an informed discussion about the value of such a test is possible.

Survey result

25 out of 28 participants support the recommendation

Inputs on the recommendations

- Some participants advised to explicitly state the measurement uncertainty and the difficulties to interpret the test results.
- As recalled by some participants, informing patients is part of the obligations incumbent on all doctors / healthcare professionals as part of the Law on Quality of Care.
- It was also pointed the need to be transparent on costs of the tests, when it is paid by patients.
- Some reported that informed shared decision making is difficult as there is so much uncertainty (standardisation of tests, what to say to a patient that has a possible higher value...). However, this recommendation was seen as positive as it leaves the door open for testing.
- Similar to any medical approach, if a person requests a PFAS dosage, it cannot be refused, but clear information on is essential as the person needs to understand the costs and benefits of such dosage. Hence the importance for GPs of having a solid base of regularly updated information (the same goes for pharmacists and other healthcare professionals).
- As pointed in the recommendation 3, having a decision tree (e.g. PSA and prostate cancer) could facilitate the communication between the GP and their patients

Recommendation 5 In case a blood test was done, we recommend recording the PFAS concentration results in the patient's electronic medical record.

Survey result

27 out of 28 participants support the recommendation

Inputs on the recommendations

- For participants, these data should be shared for analysis and monitoring purposes, that is not only for individual follow-up but also more populational, i.e. for research purposes, to be able to link to

possible future diseases. Some participants recalled that **this should be checked whether patient needs to consent or not**.

- It was also mentioned that patient should be able to access the information.
- In addition to the results of the tests, the identity of the laboratory that carried out the analysis and the measurement uncertainty of the analytical method used should be recorded, as there is a difference between lab techniques.
- Recording in electronic patient file should be standardised. E.g. classified as a 'bad lifestyle habit'
- A practical issue was reported: at the moment, occupational health physicians are not able to transfer the results of the blood tests they carry out as part of their health monitoring of workers to the patient's electronic file. The transfer of results via the patient remains uncertain.

Recommendation 6

For clinical follow-up of patients with elevated PFAS blood levels, we recommend applying good clinical practice guidelines for the general population (e.g. current cancer screening guidelines) and not performing additional screening.

Survey result

15 out of 28 participants support the recommendation

11 participants disagree

Input on the recommendations when participants were in disagreement

- For those who did not agree with the recommendation, clinical follow-up of patients with elevated PFAS blood levels is a **personalised approach**. The total patient profile is very important: age, gender, frailty, mental attitude, etc. Consequently, they advised for no general guidelines but rather a personalised follow-up plan.
- For those participants, patient with elevated PFAS are a risk group, not a general population. According to them, there should be extra attention, with possibility for early detection of diseases, more specifically when the patients have other risk factors (e.g. high cholesterol, family history of thyroid problems)
- Monitoring does not necessarily mean serum measurement of PFAS, but also monitoring of clinical signs of pathologies potentially linked to PFAS.
- Clinical practice guidelines need to be adapted in light of scientific knowledge (PFAS rapid evolvement)
- If a health-based value is exceeded, further research should be carried out on the possible health effects determined when setting the health-based value
- According to the participants, it is not possible and unethical to explain to patients that they have a higher risk of kidney, testicular and/or breast cancer, but that the professionals will wait and see before taking any (preventive) actions. These participants pointed that this goes against the principles of prevention and increases the risk of morbidity and mortality for the patients.

Input on the recommendations

- Some agreed with the recommendation when it comes to the general population but questioned the actions to be taken for more vulnerable groups or those with very high PFAS values. Similarly, some

when participants were in agreement	wondered if an extra attention could be need for patients with high PFAS values and other risk factors such as obesity, smoking, diabetes... In these situations, it might be useful to conduct some follow-up for cholesterol, liver enzymes and thyroid hormones. • Some also pointed that giving advices on reduction of exposures could be envisioned as a clinical follow-up. • As the scientific knowledge on PFAS and human health is evolving very rapidly, this recommendation should be always up to date to the latest available evidence. • Despite agreeing, some also recalled that the GP needs to pay attention to clinical signs linked to high PFAS exposure. • A participant also reported that given the time lag between exposure and effect, in line with recommendation 5, it seems important to document exposure in the patient medical file, even in the absence of blood tests and asl for professional exposures.
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Recommendation 7	We recommend that governments and scientific institutions support and conduct PFAS research - to further elucidate and quantify potential health risks and limits - to identify efficient clinical follow-up of patients with increased PFAS exposure -to identify safe and effective therapeutic strategies to improve the elimination of PFAS in the human body
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Survey result	27 out of 28 participants support the recommendation
Input on the recommendation	• A participant pointed that “efficient clinical follow-up” is not clear • A participant suggested to add a recommendation on the need and availability of high-performance analysis methods. • It was also recommended to include the newer PFAS and precursors that are still being produced (and not only the EFSA 4), with a view to document the possible reference/cutoff values for these newer PFAS. • Research needs to be enlarged to other endocrine disruptor chemicals. • Research on PFAS should not undermine research on other pollutants • Research should be conducted in specialised university centres, projects selected by independent experts. • It is necessary to align any research agenda on PFAS with international research and debates (EFSA, WHO) • There should be research on the sources of contamination, for example also on (breast)milk. • It was also recommended to assess the impact on health of co-exposure to other chemical agents, including but not limited to tobacco addiction and alcohol. • The list of research topics is large, a lot is still unknown.

3.2.2.4 Suggested research axis

Participants were invited to suggest additional research axis. Table 10 presents the topics according to the research domains.

Table 10 – Additional research topics suggested by stakeholders

Research domain	Suggested topics
Related to exposure	- Impact of professional exposure to PFAS - Impact of information on health behaviours - Follow-up of in utero exposure and exposure through breastfeeding in regions with high exposures (additional) studies into the contribution of environmental pollution/PFAS relative to other factors (such as lifestyle factors) on human health to better scale the contribution of environmental pollution/PFAS - In-depth studies of relations between exposures and blood levels
Related to toxicology	- Toxicological studies on the different PFAS, action modes and their relative toxicity - Extension of analyses for short-chain PFAS - Checking relative toxicity of different PFAS in experimental model systems (cell cultures, lower organisms) - Development of robust toxicokinetic models for PFAS - Research into lesser known PFAS is much needed, for example, very high concentrations of Trifluoroacetic acid (TFA) are recovered in biomonitoring studies in the US and China, but very little is still known about their health effects
Related biomonitoring to	- Development of a surveillance methodology for those professionally exposed - Epidemiological research into cholesterol test deviations, liver tests, etc. in biology laboratories and georeferencing (based on blood samples taken in clinics and by doctors°)
Related to epidemiology	- Epidemiological PFAS studies - Cross-reference pfas rates from biomonitoring/systematic screening with clinical data from patients for comparison. - Measuring Pfas levels in patients suffering from these pathologies (a posteriori) for comparison - Increase studies on cross-referencing the exposome and clinical patient data - Audit of exposures through the life course (including for previous generations) based on confirmed pathologic diagnosed cases for which a PFAS causality has been established / is suspected - Registry of exposures of parents and grandparents based on malformations of children
Miscellaneous	- Impact on mental health of being informed of a high blood level rate of PFAS to develop adapted interventions - Development of efficient risk-related communication - Extend the information package for GPs to other chemical (pesticides, metals, POPs...) - Measuring the transfer pathways of PFAS molecules between the soil and plants - Creating a biobank of blood samples - Supporting experimental studies with animal subjects or environmental studies to provide clues for prevention and / or contribute to reassure population

3.2.2.5 Dissemination

Stakeholders were also invited to share their ideas for the dissemination of the recommendations.

Several attention points were mentioned. Information needs to be clear, coherent, repeated, available to all health care professionals and in low threshold places (e.g. pharmacies), disseminated via different channels. It was mentioned that information is better accepted by GP when shared first by their own channels (SSMG CMG) then by the authorities. GLEM/LOK can be a solution but time-consuming (70 GLEM for Brussels).

Multiple channels for dissemination among GP and other professionals were mentioned. scientific associations, publication in professional journals, Sciensano FAGG RIZIV (official institutions for more credibility), Domus Medical / SSMG, medicopharmaceutical concertation, LOK/GLEM (particularly in high risk zones). Some ideas were also shared for disseminating in the public via the regional administration but also via Gezinsbond / Ligue des Familles and the general press. Besides, multiple channels also imply multiple formats: information flyers or fiches, newsletters, checklists of possible exposures, podcasts, videos, webinars, (short) e-learning modules, website, phone line, tool for shared decision-making...

Regarding the content, it was suggested to have layered information with different levels of details and complexity, allowing the readers to decide to which extent they want to dig into the information. But, it was mentioned the need to have information for targeted groups easily recognisable by GP: elevated PFAS levels in children, PFAS in the blood of pregnant women, impact of PFAS in patients with cardio-metabolic risk factors, etc. A particular code in the electronic patient health record could also be of interest.

Some participants suggested to enforce accreditation of learning modules (e.g. double NIHDI accreditation similar to LOK/GLEM on antibiotics).

Finally, some participants suggested to add environmental health in the basic cursus of GP and to reinforce the specific services providing support for analysing environmental exposures on health.

3.2.2.6 Update of the recommendations

Elements shared by the participants were discussed by the team and integrated in an updated version of the recommendations (appendix 3.5 and 3.6). Some recommendations were split in order to make it more precise and to better identify the intended accountable subjects.

3.2.3 Second stakeholder consultation

3.2.3.1 Participants

A total of 17 stakeholders participated to the meeting. The different groups of stakeholders were represented during the meeting (policymakers, administrations, GP representatives and experts).

3.2.3.2 Synthesis of the inputs from the discussion

Based on the results of the online survey, three recommendations were discussed and submitted to the vote of the attending stakeholders. These three recommendations showed the most divergent opinions (recommendation 3 on regional systematic screening programme, recommendation 4a on opportunistic screening by GP and recommendation 6 on clinical follow-up).

From the discussion, it appeared that the recommendations will need to be accompanied with clear information for the GP, to help them to understand the rationale behind each recommendation. Participants stressed the need for easy-to-use information for the GP (in the 3 national languages). It also appeared from the discussion that the wording needs to be carefully appraised as some key concepts – as opportunistic screening – could be interpreted in different ways by GP. The added-value of a decisional tree/online tools – particularly for opportunistic screening – was also pointed by some participants.

A key element emerging was the “precautionary principle”: however, its translation into the GP practice varied according to the participants. One can consider that, as part of the precautionary principle is

based on the clinical judgement and a form of discretionary decision making, it can lead to heterogeneous practices, adding to the “cacophony” around PFAS. Some participants reported that they would not wait to have evidence of negative effects before taking actions for their patients as it is often too late. The need for extra follow-up for some at-risk groups was discussed: however, some participants also recalled that if the patients already have risk factors such as high blood cholesterol, an adapted follow-up needs to be already enforced (PFAS or not PFAS).

Some participants appeared to regret the focused nature of the research: as the current assessment of evidence on health impacts focused on breast and kidney cancer, no evidence was provided regarding the risks for pregnant and breastfeeding women as well as the risks for the thyroid function (particularly for newborns) the immune function and the cholesterol levels. As pointed by some participants, there are other important health effects that are relevant to check, and although they are more intermediate/surrogate, they are important in preventive medicine (when there is cancer it is already too late). In the absence of evidence, it could be of interest to organise expert meetings with specialists from endocrinology, nephrology, gynaecology or foetal medicine in order to establish guidelines for the screening and / or the clinical follow-up.

Several participants voiced their concerns regarding at risk groups such as pregnant women, lactating women and those with a pregnancy desire. From the discussion, it appears that this particular at-risk group requires additional research. There were concerns about the necessity of checking the PFAS levels, the impact of the combination of several contaminants (e.g. bisphenol), the concentration of PFAS in breast milk – including concerns about the need to monitor level, the thresholds, the balance between the benefits of breastfeeding versus the adverse outcomes of PFAS...These elements support the need for specific research.

During the meeting, participants also discussed the problems concerning the lab tests and communication on cutoff values. At the moment there is still uncertainty around cut-off values (e.g. HBM) as they were determined based on populations, and not meant as cutoff for individual health assessment. It was reported that the variation in individual tests was 30% in Flanders and problems are larger with branched PFAS. As reported by some participants, cutoffs values are indicative but there are no hard thresholds to state health problems. Nonetheless, participants seemed to agree that when a lab test indicates very high PFAS values, it indicates a high exposure (the available lab test can reliably identify very high values.).

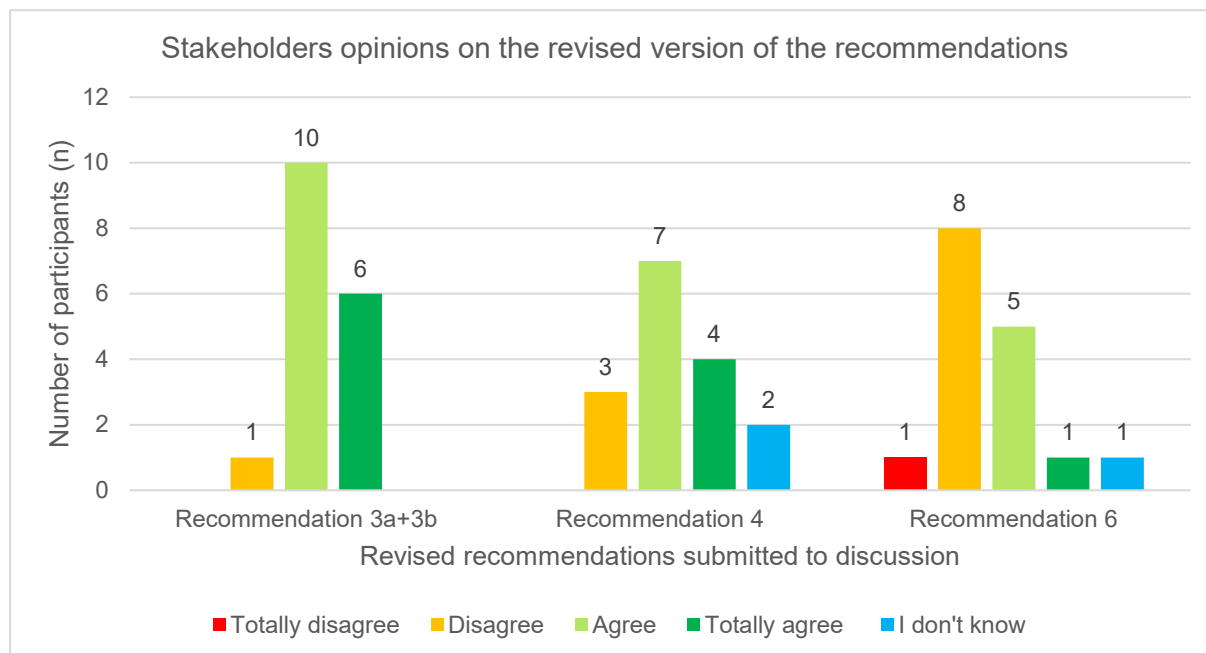
Not all these elements directly concerned the scope of this study. And – in the current state of knowledge – it is not yet possible to provide evidence-based responses for an appropriate clinical management (from early prevention to treatment) of all the problems related to PFAS. These elements are therefore important for further research, indicating priority areas.

3.2.3.3 *Level of agreement*

After discussing each recommendation, participants were invited to indicate their degree of agreement with the revised version of the recommendation. Results are presented in Figure 9. Recommendation 3 (presented in 3a and 3b) and recommendation 4 were supported by the majority of the participants attending the stakeholder meeting. A total of 16 participants agreed / totally agreed with the revised recommendation 3; 11 participants agreed / totally agreed with recommendation 4.

Recommendation 6 was supported by only 6 participants (agree / totally agree): 9 participants did not agree / totally not agree with its revised formulation, pointing to the difficulty of not offering extra clinical follow-up in case PFAS test results are known and indicate high exposure.

Figure 9 – Level of agreement per recommendation during stakeholder meeting, May 2025 (n=17*)



*Recommendations 3a+3b were presented to 17 participants. Recommendations 4 and 6 were presented to 16 participants as one had to leave the online stakeholder meeting early. **Recommendation 3a.** We advise the Regions not to organise a systematic screening programme for PFAS contamination based on blood tests, as the merits of such an approach have not been established in the current state of scientific knowledge. **Recommendation 3b.** If the Regions envisage organising systematic screening for PFAS contamination on the basis of blood tests, for example in areas where contamination of drinking water, food and/or soil is proven, this should be done within the framework of scientific research in order to assess the risk-benefit balance of such screening.

Recommendation 4: We advise GPs not to promote opportunistic screening via PFAS blood tests outside a research context.

Recommendation 6: For the medical follow-up of patients with elevated PFAS blood levels, we recommend applying only those good practice guidelines whose risk-benefit ratio has been scientifically demonstrated.

3.3 Clinical research to enhance PFAS elimination from blood

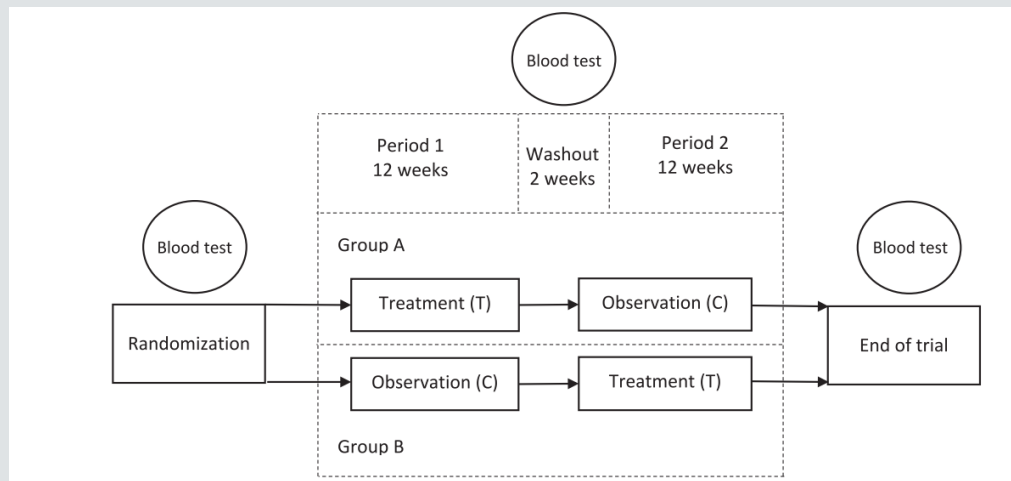
3.3.1 Anion exchange drugs

The promise of anion exchange drugs to enhance the elimination of certain PFASs was already reported in 2010 and was supported by studies in animals and observational data.^{90, 91} It took however over a decade before a first clinical trial was conducted. In 2021, Ducatman et al showed the potential for a large effect size of colestyramine to reduce PFOS in serum in a population study, the C8 Health Project in Ohio and West Virginia, USA, that enrolled individuals from six water districts with varying degrees of PFOA water contamination. Participants self-reported medication use. A more than tenfold lower PFOS serum level was found among those subjects using colestyramine (geometric mean 1.26 ng/mL, n=34) versus non-users of this drug (geometric mean 19.12 ng/mL, n=56139).⁹² Several reasons are cited in this paper why PFOA and PFAS reduction might in reality be greater than observed a.o. because colestyramine use is associated with the consumption of an extra volume of (possibly PFAS containing) drinking extra water to avoid constipation.

However, it took a long period before a first RCT was conducted. A first open-label cross-over RCT was conducted in 45 participants (mean age of 50y) in Denmark using colestyramine, a marketed anion exchange resin (AER) drug, in participants with a very high PFOS serum level (average baseline 191 ng/mL).⁹³

Box 4 – Outline of cross-over RCT on colestyramine by Moller et al. 202493*Methods*

A total of 45 participants were recruited. Each participant was randomly assigned into intervention group A or B using block-randomization in REDCap in blocks of 16.



Treatment (T) consisted of a fixed dose of the study medication and was compared to an observation period (C). The first four participants were treated with three tablets of colesevelam, at a dose of 625 mg twice daily with a total daily dose of 3,750 mg. The subsequent participants were treated three times daily with one pouch of colestyramine as powder to oral suspension, at a dose of 4 g with a total daily dose of 12 g. The protocol had to be amended because of a stock rupture of colesevelam.

The primary endpoint was the mean change in serum PFOS after 12 weeks of treatment with anion exchange resin (AER), compared to the 12 weeks of observation. The secondary endpoint was the percentage change in PFOS in the control period following treatment, as an indication of the level of post-treatment redistribution.

Serum from each point of measurement (blood test in figure) was stored at -80°C and analyzed for PFOS (sum of isomers), PFHxS, PFOA, PFNA and PFDA at the end of the study in one batch. The staff at the analyzing laboratory had no knowledge of the randomization sequence of the participants in the study.

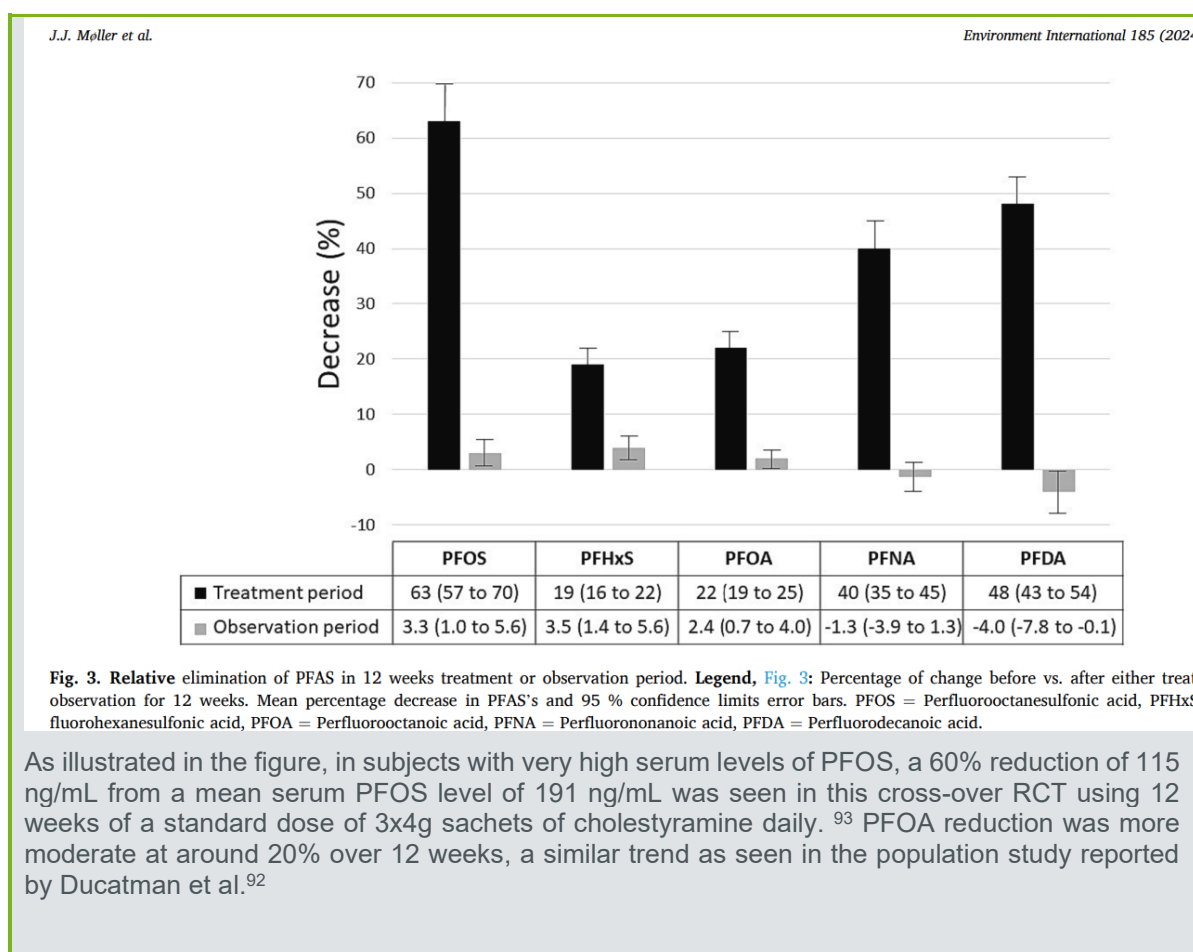
A statistician independent of the trial management and unaware of the group assignments performed the statistical analysis. An intent to treat analysis was conducted, no imputation for missing values was used.

According to the RoB 2 tool (2021 version) for cross-over trials⁹⁴ the risk-of-bias for this randomized crossover trials can be judged as low.

Results

Adverse effects of the study medication were registered for five participants, who reported mild gastrointestinal symptoms and headache. One participant did not complete the study due to gastrointestinal symptoms related to study drug. No serious adverse effects were recorded. In addition, eleven participants did not comply with protocol, with nine participants having a compliance of less than 80 % use of the study medication and two participants missing blood test for one of three measures of PFAS. No participants donated blood during the study period.

In the intervention group A, with the sequence treatment followed by observation, serum PFOS was further reduced by 2.5 ng/mL (95 % CI: -0.3 to 5.2) during the observational period indicating limited redistribution.



Colesevelam, another anion exchange resin treatment marketed as tablets, could possibly lead to a better treatment adherence. It was out of stock during the trial but it is again available and is currently being tested by the same team in a second clinical trial.(personal communication).

Accelerated elimination of specific molecules using anion exchange resin treatment is already being used in practice, e.g. 11 days of 3x8g colestyramine (thus double the dose used to eliminate PFAS in the trial) is recommended by the EMA to eliminate the (teratotoxic) drug leflunimide in women on this medication who want to become pregnant.⁹⁵ Interestingly, the leflunomide molecule contains one fully fluorinated methyl carbon and could thus be considered a PFAS according to the more broad PFAS definitions.

Further research seems justified to optimize the dose and duration of anion exchange resin treatment. A possible target group for such a clinical trial are women who want to become pregnant and who have elevated PFAS blood levels (PFOS in particular) as women pass on PFAS to their fetus and baby during pregnancy and through breast feeding. Dietary fiber interventions

Given that bile acids and PFAS are biochemically similar as amphiphilic compounds (possessing both hydrophilic and lipophilic properties), serum samples collected as part of a Canadian clinical trial in 2019–2020 testing the efficacy of an oat β -glucan intervention to reduce serum cholesterol, were also tested for changes in PFAS in serum. A one month administration of a moderate dose of dietary fiber (oat β -glucan) was associated with a small reduction in long-chain PFAS serum concentration (PFOA and PFOS).⁹⁶ The findings are also supported by results in mice fed with oat β -glucan. Longer administration studies are needed.⁹⁷

3.3.2 *Plasma donations*

In a RCT testing 6 weekly plasma donations in subjects with a mean PFOS level of 9.5 ng/mL an average change from baseline of -2.9 ng/mL was seen at 12 months.⁹⁸ This effect size is much smaller compared with anion exchange resin treatment.

■ APPENDIX

APPENDIX 1. EVIDENCE ON THE ASSOCIATION BETWEEN PFAS AND KIDNEY CANCER

Appendix 1.1. Complement to the study by Shearer *et al*

PFAS	aOR (95%CI) with adjustment for other PFAS
PFOA	Quartile 2 to quartile 4 (reference: quartile 1) : Q2: 1.41 (0.69-2.90) Q3: 1.12 (0.52-2.42) Q4: 2.19 (0.86-5.61) <i>Trend p-value 0.13</i> Continuous value of PFAS (log-2 transformed concentration): 1.68 (1.07-2.63)
PFOS	Quartile 2 to quartile 4 (reference: quartile 1) : Q2: 1.24 (0.59-2.57) Q3: 0.53 (0.22-1.24) Q4: 1.14 (0.45-2.88) <i>Trend p-value 0.64</i> Continuous value of PFAS (log-2 transformed concentration): 0.92 (0.60-1.42)
PFHxS	Quartile 2 to quartile 4 (reference: quartile 1) : Q2: 1.28 (0.66-2.51) Q3: 0.89 (0.43-1.85) Q4: 1.46 (0.67-3.18) <i>Trend p-value 0.40</i> Continuous value of PFAS (log-2 transformed concentration): 1.12 (0.88-1.43)
PFNA	Quartile 2 to quartile 4 (reference: quartile 1) : Q2: 1.08 (0.57-2.07) Q3: 2.00 (0.95-4.20) Q4: 1.29 (0.58-2.89) <i>Trend p-value 0.45</i> Continuous value of PFAS (log-2 transformed concentration): 1.00 (0.73-1.37)

Legend: aOR: adjusted odds ratio; 95%CI: 95% confidence interval; PFOA: Perfluorooctanoic acid; PFOS: Perfluorooctane sulfonic acid; PFHxs: Perfluorohexane sulfonate ; PFNA: Perfluorononanoic acid; Q: quartile

Appendix 1.2. Modified Newcastle-Ottawa quality Assessment scale used in the meta-analysis Seyyedsalehi et al, 2023

Case Control Studies

1. Selection of controls

- From study base (2)
- Not from study base (1)
- Other, incl. ecological, no description (0)

2. Adjustment of confounders

- Adjustment for most important potential confounders (2)
- Adjustment for some potential confounders (1)
- Adjustment for no confounders except age, gender, race/ethnicity, calendar period (0)

3. Ascertainment of exposure

- Objective record (eg employment records, biomarkers) (2)
- Structured interview blind to case/control status, GIS (1)
- Interview not blinded to case/control status, self-report, proxy (e.g., residence) (0.5)
- No description (0)

4. Response rate

- Both groups over 90% (2)
- One or both groups between 60- 90% (1)
- One group under 60%, no description (0)

5. Latency

- Adequate latency between exposure and outcome (>15 yrs) (2)
- Limited latency between exposure and outcome (5-15 yrs) (1)
- Inadequate latency between exposure and outcome (<5 yrs), no description (0)

6. Outcome

- Cancer registration (2)
- Death certificates, hospital records (1)
- Self report (0.5)
- No description (0)

Cohort Studies

1. Selection of unexposed cohort

- Derived from the same population as the exposed (2)
- Derived from a different source (1)
- Other, no description (0)

2. Adjustment of confounders

- Adjustment for most important potential confounders (2)
- Adjustment for some potential confounders (1)
- Adjustment for no confounders except age, gender, race/ethnicity, calendar period (0)

3. Ascertainment of exposure

- Objective record (e.g., employment records, biomarkers) (2)
- Structured interview blind to outcome status, GIS (1)
- Interview not blinded outcome status, self-report, proxy (e.g., residence) (0.5)
- No description (0)

4. Follow-up rate

- Follow-up of both groups over 90% (2)
- Follow-up of one or both groups between 60- 90% (1)
- Follow-up of one group under 60%, no description (0)

5. Latency

- Adequate latency between exposure and outcome (>15 yrs) (2)
- Limited latency between exposure and outcome (5-15 yrs) (1)
- Inadequate latency between exposure and outcome (<5 yrs), no description (0)

6. Outcome

- Cancer registration (2)
- Death certificates, hospital records (1)
- Self report (0.5)
- No description (0)

Appendix 1.3. Quality assessment of the included studies described in the meta-analysis Seyyedsalehi et al, 2023

Author, year	Quality score (adapted NOS tool score)
Leonard, 2008	6.5 (low)
Steenland, 2012	7 (low)
Vieira, 2013	7 (low)
Barry, 2013	8.5 (high)
Raleigh, 2014	10 (high)
Mastrantonio, 2018	6.5 (low)
Shearer, 2021	12 (high)
Li, 2022	7.5 (low)
Law, 2023	6.5 (low)

Appendix 1.4. Appraisal of the meta-analysis *Seyyedsalehi et al, 2023* with AMSTAR 2 criteria

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Partly: Population: individuals potentially exposed to PFAS (no other characteristics mentioned) Exposure: occupational and environmental exposure to PFAS (emphasizing PFOS and PFOA) Comparator: no comparator defined Outcomes: incidence or mortality from kidney cancer Timeframe: all English-language articles published up to February 2023 Studies: cohort, case-control, and ecological studies of occupational and environmental exposure to PFAS. Studies involving animals were excluded.
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No - Review question, search strategy, inclusion/exclusion criteria, risk of bias assessment present) - The review was not registered.
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No explanation is provided (cohort, case-control, ecological studies)
4. Did the review authors use a comprehensive literature search strategy?	Partial yes - Consulted databases (PubMed + reference lists of the IARC Monograph on PFOA and the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for perfluoroalkyls), search strategy and restrictions criteria are mentioned. Full-strategy with numbers is not available. - No consultation of registries, experts, grey literature. No list of excluded studies.
5. Did the review authors perform study selection in duplicate?	Yes for screening on titles and abstracts. Unclear for the second-level selection on full text. Strategy to decide on discrepancies between the 2 reviewers is not explained.
6. Did the review authors perform data extraction in duplicate?	Unclear (probably yes)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	Not enough details are provided in <i>Supl. table 3</i> , e.g. no patients' characteristics
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes (Newcastle-Ottawa scale- NOS)
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Partial yes (random-effect models, stratified analysis, meta-regression based on the quality score). No explanation is provided on how the RR per study is

	computed. Moreover, there is no explanation on how were defined low, medium or high exposure.
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes (meta-regression based on the quality score)
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes (it is mentioned that bias cannot be ruled out for the interpretation of the results, in the discussion and conclusion)
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partly (stratification analysis and meta-regressions were performed)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes (funnel plots)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	One author declared acting as an expert in litigation involving PFAS exposure unrelated to the present work.

Critical domains:

- items 2 and 4 are 'no' and 'partial yes'
- item 7 is answered 'no'
- 11 is answered 'partial yes'
- 9, 13 and 15 are answered 'yes'

Non-critical domains:

- Item 3 (justification for the types of studies)
- Item 8 (description of studies is lacking)
- Item 10 (source of funding of the studies)

Conclusion: Low

Appendix 1.5. Assessment of the study methodological quality using SIGN tool

Appendix 1.5.1. Quality assessment of case control studies (SIGN- checklist 4)

Item	Shearer (2021)	Rhee (2023)	Windquist (2023)
SECTION 1: INTERNAL VALIDITY			
1.1 The study addresses an appropriate and clearly focused question	Y	Y	Y
Selection of subjects			
1.2 The cases and controls are taken from comparable populations.	Y	Y	Y
1.3 The same exclusion criteria are used for both cases and controls.	Y	Y	Y
1.4 What percentage of each group (cases and controls) participated in the study?	**	**	control 3%; cases: 12%
1.5 Comparison is made between participants and non-participants to establish their similarities or differences.	CS	CS	
1.6 Cases are clearly defined and differentiated from controls.	Y	Y	Y
1.7 It is clearly established that controls are non-cases	Y	Y	Y
Assessment			
1.8 Measures will have been taken to prevent knowledge of primary exposure influencing cases ascertainment	NA	NA	NA
1.9 Exposure status is measured in a standard, valid and reliable way	Y	Y	Y
Confounders			
1.10 The main potential confounders are identified and taken into account in the design and analysis	Y	Y	Y
Statistical analysis			
1.11 Confidence intervals are provided.	Y	Y	Y
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1 How well was the study done to minimise the risk of bias or confounding.	High	High	Acceptable to high
2.2 Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Y ^{\$}	Y ^{\$}	Y
2.3 Are the results of this study directly applicable to the patient group targeted in this guideline?	Y	Y	Y

Legend: **: Authors selected cases and controls in the screening arm of the study. Although the denominator (number of patients included at the time of the study) is not mentioned, it is assumed that the denominator is the same for cases and controls; ^{\$}:if several were available for a same patient, how was the blood sample selected is not mentioned; Y: yes; N: no; NA: not applicable; CS: can't say

Appendix 1.5.2. Quality assessment of cohort studies (SIGN- checklist 3)

Item	Barry (2013)	Raleigh (2014)	Vieira (2013)
SECTION 1: INTERNAL VALIDITY			
1.1 The study addresses an appropriate and clearly focused question	Y	Y	Y
Selection of subjects			
1.2 The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	NA	CS	CS
1.3 The study indicates how many of the people asked to take part did so, in each of the groups being studied.	NA	NA	NA
1.4 The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis	NA	NA	NA
1.5 What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	NA	NA	NA
1.6 Comparison is made between full participants and those lost to follow up, by exposure status.	NA	NA	NA
Assessment			
1.7 The outcomes are clearly defined.	Y	Y	Y
1.8 The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable	NA	N	N
1.9 Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	CS	CS	CS
1.10 The method of assessment of exposure is reliable.	CS	CS	CS
1.11 Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Y	Y	Y
1.12 Exposure level or prognostic factor is assessed more than once.	NA	NA	NA
Confounding			
1.13 The main potential confounders are identified and taken into account in the design and analysis.	CS	N	CS
Statistical analysis			
1.14 Have confidence intervals been provided	Y	Y	Y
SECTION 2: OVERALL ASSESSMENT OF THE STUDY			
2.1 How well was the study done to minimise the risk of bias or confounding.	acceptable	acceptable	acceptable

2.2 Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	CS	CS	CS
2.3 Are the results of this study directly applicable to the patient group targeted in this guideline?	CS	CS	CS

Legend: **: Y: yes; N: no; NA: not applicable; CS: can't say

APPENDIX 2. EVIDENCE ON THE ASSOCIATION BETWEEN PFAS AND BREAST CANCER

Appendix 2.1. Quality assessment: systematic review via AMSTAR 2

Appendix 2.1.1. Appraisal of the meta-analysis Chang et al, 2024 with AMSTAR 2 criteria

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Population: Women at risk for breast cancer, without restriction based on life stage or age at exposure or outcome assessment Exposure: Exposure to PFAS or their salts based on concentrations quantified in biological samples (eg, serum, plasma), environmental measures, or indirect measures including self-reported information on occupation and residential area, without further restriction on life stage Comparator: Women who were exposed to lower levels of PFAS Outcomes: self-reported or medically confirmed breast cancer diagnosis, without restriction on life stage Timeframe: all English-language articles published up to February 2023
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	yes - Review question, search strategy, inclusion/exclusion criteria, risk of bias assessment present - No deviation of protocol mentioned - The review was registered with PROSPERO (CRD42022312825)
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes: epidemiologic studies with individual-level outcome information (cohort, case-studies)
4. Did the review authors use a comprehensive literature search strategy?	Partial yes - Databases consulted: PubMed, Web of Science, Scopus - Search strategy and publication restrictions are mentioned - Bibliographies of included studies were considered (1 additional study was identified via citation check) but no consultation of registries, experts, grey literature.
5. Did the review authors perform study selection in duplicate?	Yes: "Four reviewers, C.J.C., J.L.I., M.D., and V.C.C., worked on article screening, data extraction, risk-of-bias assessment, confidence rating, and evidence integration. Each task for the individual studies was independently performed by at least 2 reviewers. Any discrepancy was resolved by discussion with the involvement of A.J.W. when needed"
6. Did the review authors perform data extraction in duplicate?	Yes: "Four reviewers, C.J.C., J.L.I., M.D., and V.C.C., worked on article screening, data extraction, risk-of-bias assessment, confidence rating, and evidence integration. Each task for the individual studies was independently performed by at least 2 reviewers. Any

	discrepancy was resolved by discussion with the involvement of A.J.W. when needed"
7. Did the review authors provide a list of excluded studies and justify the exclusions?	The excluded studies were not referenced. in the flowchart, there was a general explanation of why studies were excluded
8. Did the review authors describe the included studies in adequate detail?	Yes (cf.: Table 2)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes: authors used the modified Risk of Bias Rating Tool for Human and Animal Studies from the National Toxicology Program Office of Health Assessment and Translation (NTP/OHAT) and the details are in supplement
10. Did the review authors report on the sources of funding for the studies included in the review?	No (in this area of research, conflict of interest is an important aspect)
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes (random-effects meta-analyses using DerSimonian-Laird's approach)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes (sensitivity analysis was performed based on the quality of studies: cf: Table S5).
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes, heterogeneity is discussed and explored: e.g. Table 3, discussion, limitations of the study.
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes (funnel plots and Egger's regression test)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	No author declared a conflict of interest. The work was supported by: Intramural Research Program of the National Institute of Environmental Health Science (project number Z1A ES103332) and National Cancer Institute (project number Z1A CP010125-28)

Summary and conclusion:

Critical domains:

- item 4 is 'partial yes' but only for the absence of consultation of experts and registries
- item 7 is answered 'no' (list of excluded studies)
- item 2, 9, 11 13 and 15 are answered 'yes'

Non-critical domains:

- Item 10 (funding of included studies is lacking)

➔ **Conclusion: Moderate to high**

Appendix 2.1.2. Appraisal of the meta-analysis Seyyedsalehi et al, 2024 with AMSTAR 2 criteria

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Partly: the article is publication of a part of wider study (no focus on BC in the methods 2.1) - Population: Women at risk for breast cancer, without restriction based on life stage or age at exposure or outcome assessment - Exposure: occupational or environmental exposure to PFAS or their salts based on concentrations quantified in biological samples (e.g., serum, plasma), environmental measures (drinking water, or workplace exposure) , or indirect measures including self-reported information on occupation and residential area, without further restriction on life stage - Comparator: Women who were exposed to lower levels of PFAS - Outcomes: incidence or mortality of BC (self-reported or medically confirmed breast cancer diagnosis) Timeframe all English-language articles published up to January 2024 Exclusion of studies where the full text was not available, in animals, or other non-human experimental systems
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes - Review question, search strategy, inclusion/exclusion criteria, risk of bias assessment present) - The review was registered in PROSPERO: CRD42024560837 <i>Per- and Poly-fluoroalkyl Substances (PFAS) Exposure and Risk of cancers other than liver, kidney and testicular: A Systematic Review and Meta-Analysis</i>
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes : cohort, case-control, cross-sectional, ecological studies of both occupational and environmental exposure
4. Did the review authors use a comprehensive literature search strategy?	Partial yes - Consulted databases (PubMed, scopus, reference lists of the IARC Monograph on PFOA and the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for perfluoroalkyls), search strategy and restrictions criteria are mentioned. Full-strategy with numbers is not available. - No consultation of registries, experts, grey literature. No list of excluded studies.
5. Did the review authors perform study selection in duplicate?	Yes, four independent researchers
6. Did the review authors perform data extraction in duplicate?	Unclear (probably yes)
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No

8. Did the review authors describe the included studies in adequate detail?	Partly yes, Table 1, but not enough details are provided e.g. no patients' characteristics
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes (Newcastle-Ottawa scale- NOS)
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Partly yes (random-effect models to account for heterogeneity, stratified analysis, meta-regression based on the quality score, But not sure how they identified a RR for each study
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes (meta-regression based on the quality score)
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes (it is mentioned that bias cannot be ruled out for the interpretation of the results, in the discussion and conclusion)
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Partly (stratification analysis and meta-regressions were performed)
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes (funnel plots)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	One author declared acting as an expert in litigation involving PFAS exposure unrelated to the present work.

Summary and conclusion:

Critical domains:

- item 4 is 'partial yes' but only for the absence of consultation of experts and registries
- item 7 is answered 'no' (list of excluded studies)

Item 11: partly yes on appropriate statistics to combine: the combination of several studies does not seem appropriate. Also not clear how all studies were transposed into RR. However sensitivity analyses available

- item 2, 9, 13 and 15 are answered 'yes'

Non-critical domains:

- Item 10 (funding of included studies is lacking)

□ Conclusion: Moderate to high

Appendix 2.2. Quality assessment of primary studies via modified NewCastle Ottawa Scale (NOS)

Appendix 2.2.1. Modified NOS scale as used in Seyyedsalehi et al 2023

Case Control Studies

1. Selection of controls

- From study base (2)
- Not from study base (1)
- Other, incl. ecological, no description (0)

2. Adjustment of confounders

- Adjustment for most important potential confounders (2)
- Adjustment for some potential confounders (1)
- Adjustment for no confounders except age, gender, race/ethnicity, calendar period (0)

3. Ascertainment of exposure

- Objective record (eg employment records, biomarkers) (2)
- Structured interview blind to case/control status, GIS (1)
- Interview not blinded to case/control status, self-report, proxy (e.g., residence) (0.5)
- No description (0)

4. Response rate

- Both groups over 90% (2)
- One or both groups between 60- 90% (1)
- One group under 60%, no description (0)

5. Latency

- Adequate latency between exposure and outcome (>15 yrs) (2)
- Limited latency between exposure and outcome (5-15 yrs) (1)
- Inadequate latency between exposure and outcome (<5 yrs), no description (0)

6. Outcome

- Cancer registration (2)
- Death certificates, hospital records (1)
- Self report (0.5)
- No description (0)

Cohort Studies

1. Selection of unexposed cohort

- Derived from the same population as the exposed (2)
- Derived from a different source (1)
- Other, no description (0)

2. Adjustment of confounders

- Adjustment for most important potential confounders (2)
- Adjustment for some potential confounders (1)
- Adjustment for no confounders except age, gender, race/ethnicity, calendar period (0)

3. Ascertainment of exposure

- Objective record (e.g., employment records, biomarkers) (2)
- Structured interview blind to outcome status, GIS (1)
- Interview not blinded outcome status, self-report, proxy (e.g., residence) (0.5)
- No description (0)

4. Follow-up rate

- Follow-up of both groups over 90% (2)
- Follow-up of one or both groups between 60- 90% (1)
- Follow-up of one group under 60%, no description (0)

5. Latency

- Adequate latency between exposure and outcome (>15 yrs) (2)
- Limited latency between exposure and outcome (5-15 yrs) (1)
- Inadequate latency between exposure and outcome (<5 yrs), no description (0)

6. Outcome

- Cancer registration (2)
- Death certificates, hospital records (1)
- Self report (0.5)
- No description (0)

Appendix 2.2.2. Quality assessment via modified NOS of primary studies in update literature

Primary study	Study design	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Total
Winqvist 2023	Case-cohort	Cases and comparison are taken from the same Cohort (USA Cancer prevention study) This design also includes a subcohort of people randomly selected from the entire eligible cohort. The subcohort serves as a comparison group è2	The selected confounders included well-established risk factors for each cancer type è2	Serum PFAS concentrations in CLIA certified lab (only linear PFAS) è2	Info for both cases and subcohort available è1	Mean follow up in the sub cohort of 499 women was 14.7y which is considered an adequate latency è2	Cancer diagnosis verified è1	10
Jia 2024	Cross-sectional	NHANES representative è2	Confounders taken into account è2	concentrations of PFASs were quantified in the serum (= validated measurement tool) 2	No description of the response rate or the characteristics of the responders and the non responders	No followup, no latency	Outcome self reported è0.5	6.5
Dou 2024	Nested case-control	Control are from the same cohort è2	Controls were matched and adjustment in the multivariate model è2	Exposure via blood sample in 2011-2013 è2	No info	The mean time between exposure and BC was 5.23 years è1	Medical record è1	8
Hammer strand 2024	Nested cohort study in a large cohort	Derived from the same population as the exposed (all the Ronneby area), but there is a level of exposure in the unexposed cohort è1	No adjustment of the HR. Sensitivity analysis for educational level, prepubertal exposure to PFAS, è0	Exposure via residency è1	There is no loss as it is the incidence . Not clear whether there were missings	Adequate latency between exposure and outcome 23/22 years è2	Swedish Cancer Registry for diagnosis , prescription for Hormone status => 2	6

Appendix 2.3. Search strategy

Search Strategy Systematic Review Chang et al 2024

((("Fluorocarbons/adverse effects"[Mesh] OR "perfluorooctanoic acid" [Supplementary Concept] OR "perfluorooctane sulfonic acid" [Supplementary Concept] OR "perfluorododecanoic acid"[Supplementary Concept] OR fluorocarbon*[tiab] OR fluorinated organic compound*[tiab] OR PFAS[tiab] OR PFASs[tiab] OR GenX[tiab] OR Gen-X[tiab] OR PFAA[tiab] OR perfluoroalkyl[tiab] OR polyfluoroalkyl[tiab] OR perfluorinated[tiab] OR PFCs[tiab] OR PFOS[tiab] OR perfluorobutanesulfonic[tiab] OR perfluorodecanoic[tiab] OR perfluoro-n-decanoic[tiab] OR nonadecafluoro-n-decanoic[tiab] OR perfluorododecanoic[tiab] OR PFDa[tiab] OR perfluoroheptanoic[tiab] OR PFHpA[tiab] OR perfluorohexanesulfonic[tiab] OR PFHS[tiab] OR perfluorohexanesulfonate[tiab] OR Perfluorohexane sulfonate[tiab] OR PFHxS[tiab] OR perfluorononanoic acid[tiab] OR perfluorooctanoic acid[tiab] OR pentadecafluorooctanoic[tiab] OR perfluorooctanoyl-chloride[tiab] OR PFOA[tiab] OR sodium-perfluorooctanoate[tiab] OR perfluorooctanoate[tiab] OR ammonium-perfluorooctanoate[tiab] OR "APFO"[tiab] OR perfluorooctane-sulfonic acid[tiab] OR perfluorooctanesulfonic acid[tiab] OR PFOSA[tiab] OR perfluorooctanyl-sulfonate[tiab] OR Perfluorooctanesulfonate[tiab] OR perfluorooctane-sulfonate[tiab] OR perfluorooctanesulfonamide[tiab] OR perfluoroundecanoic[tiab] OR Perfluorohexanoic acid[tiab] OR PFHxA[tiab] OR perfluorobutanoic acid[tiab] OR PFBA[tiab] OR PFBS[tiab] OR perfluorinated alkylate*[tiab] OR perfluorinated alkylated[tiab] OR perfluorinated alkyl[tiab] OR perfluorinated compound*[tiab] OR perfluorinated chemical*[tiab] OR perfluorinated acid*[tiab] OR perfluorinated substance*[tiab] OR PFPeA[tiab] OR PFPeS[tiab] OR PFHpS[tiab] OR PFUnA[tiab] OR PFUnDA[tiab] OR PFTrDA[tiab] OR PFTeDA[tiab] OR FOSAA[tiab])) AND ((cancer*[tiab] OR neoplasm*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR malignan*[tiab] OR carcinoma*[tiab] OR "Neoplasms"[Mesh]) AND (breast*[tiab] OR mammar*[tiab]))

Filters: from 2023 - 2025

APPENDIX 3. STAKEHOLDER CONSULTATIONS

Appendix 3.1. Online questionnaire in French

CONSULTATION DES PARTIES PRENANTES ET EXPERTS SUR LES RECOMMANDATIONS PFAS À DESTINATION DES MÉDECINS GÉNÉRALISTES

Ceci est une consultation des parties prenantes et experts concernant un ensemble de recommandations à destination des médecins généralistes en vue de leur permettre d'accompagner au mieux leurs patients sur la question de la contamination aux PFAS (projet KCE 2024-53-HSR).

Vous participez à cette enquête en tant qu'expert(e) ou représentant(e) d'une organisation impliquée dans les processus décisionnels en matière de santé. Si vous participez au nom d'une organisation, nous vous demandons de remplir **un seul questionnaire pour votre organisation.**

Ce questionnaire contient 7 recommandations. Les champs signalés par une * sont obligatoires. Répondre à l'entièreté du questionnaire vous prendra environ 30 minutes. Il est possible de le compléter en plusieurs fois : les réponses que vous avez données seront automatiquement enregistrées.

Les réponses seront anonymisées dans le rapport final. Nous vous demandons cependant les coordonnées d'une personne de contact qui puisse répondre à nos éventuelles demandes de précision.

L'enquête sera clôturée le 04 mai 2025 à minuit.

En cas de questions, n'hésitez pas à contacter notre équipe.

Il y a 29 questions dans ce questionnaire.

INFORMATIONS GÉNÉRALES

*A quel(s) titre(s) participez-vous à cette enquête ?

Veuillez choisir toutes les réponses qui conviennent :

- Expert(e) académique
- Expert(e) scientifique hors milieu académique
- Représentant(e) d'une administration publique (régionale ou fédérale)
- Représentant(e) d'un cabinet ministériel (régional ou fédéral)
- Représentant(e) d'une association professionnelle
- Représentant(e) d'une société scientifique
- Autre
- **Si vous avez choisi "Autre", merci de préciser ci-après**

*Nom et prénom d'une personne de contact

Veuillez écrire votre réponse ici :

*Adresse électronique de la personne de contact

Veuillez écrire votre réponse ici :

*Nom de l'organisation / affiliation

Veuillez écrire votre réponse ici :

Si vous souhaitez nous communiquer d'autres informations concernant votre organisation, votre affiliation professionnelle ou votre participation (passée ou présente) à d'autres groupes de travail en lien avec la thématique des PFAS, merci de le faire dans l'espace ci-après :

Veuillez écrire votre réponse ici :

Si vous souhaitez ajouter d'autres éléments, merci de le faire dans l'espace ci-après :

Veuillez écrire votre réponse ici :

RECOMMANDATION 1

a. Nous recommandons que toutes les instances scientifiques concernées par la question de l'impact des PFAS sur la santé travaillent ensemble à l'élaboration d'un kit d'information actualisé et complet destiné aux médecins généralistes.

b. Ce travail doit se faire en collaboration avec les associations de médecine générale.

c. Le contenu du kit doit être coordonné et harmonisé entre les différentes régions.

Il est indispensable que les médecins généralistes aient accès à un document de référence fiable et pratique sur les PFAS, rassemblant toutes les sources d'information pertinentes pour une prise en charge de qualité des patients concernés par la question des PFAS.

Il est essentiel d'harmoniser les informations et les recommandations destinées aux médecins généralistes dans toutes les régions du pays afin d'éviter les incertitudes et les inquiétudes dues à des informations contradictoires. Il existe déjà des documents d'information destinés aux médecins généralistes au niveau régional ([SSMG](#), [Domus Medica-Zorg Vlaanderen](#)), mais ils diffèrent sur des points importants, notamment en ce qui concerne les recommandations relatives au suivi clinique des personnes présentant des taux sanguins élevés de PFAS.

Le kit d'information doit contenir :

- des informations générales sur les PFAS ;

- des conseils scientifiquement fondés pour réduire l'exposition individuelle aux PFAS. Des checklists d'actions préventives adaptées au contexte belge peuvent servir de base ([SSMG](#), [Zorg Vlaanderen](#)), mais leur validité scientifique doit être démontrée ;
- les limites du dosage sanguin des PFAS pour évaluer la contamination aux PFAS au niveau populationnel et individuel (voir les explications de la recommandation 3 dans le document annexé à cette enquête) ;
- des informations sur les valeurs sanguines de référence dans la population et dans les zones à risque, sur la base des sources d'informations-clés (par exemple, les résultats des études de biomonitoring en Wallonie ([BMH-Wal](#)) et en Flandre ([FLEHS](#)), la géolocalisation des quartiers de Bruxelles à risque effectuée par [Bruxelles Environnement](#), les échantillonnages d'eau par la Société Wallonne des Eaux ([SWDE](#)), etc.) ;
- des informations sur les incertitudes actuelles sur le plan scientifique concernant l'association entre les PFAS et certains problèmes de santé graves comme, par exemple, le cancer du sein (voir l'argumentaire de la recommandation 6 dans le document annexé à cette enquête) ;
- des informations sur les incertitudes actuelles sur le plan scientifique concernant une prise en charge médicale adéquate des patients présentant un taux sanguin élevé de PFAS (voir l'argumentaire de la recommandation 6) ;
- des informations sur les recherches en cours en Belgique, qu'il s'agisse d'activités de biomonitoring, d'études épidémiologiques ou d'études cliniques portant sur de nouveaux traitements pour diminuer le taux sanguin de PFAS (voir la recommandation 7).

*Choisissez la réponse appropriée pour chaque élément :

	Pas du tout d'accord	Pas d'accord	D'accord	Tout à fait d'accord	Je ne sais pas
--	----------------------	--------------	----------	----------------------	----------------

Etes-vous d'accord avec cette recommandation ?

***Si vous voulez nous communiquer des arguments et/ou des éléments d'information complémentaires, veuillez les résumer dans l'espace ci-après :**

Si vous n'avez pas de commentaires, indiquez "aucun"

Veuillez écrire votre réponse ici :

Selon vous, quelle(s) institution(s) ou organisation(s) devrai(en)t coordonner la mise à jour continue des informations contenues dans le kit d'information ?

Veuillez écrire votre réponse ici :

RECOMMANDATION 2

Nous recommandons aux autorités fédérales et fédérées, en collaboration avec les associations de médecine générale, de veiller à ce que le kit d'information décrit ci-dessus soit diffusé avec succès.

*Choisissez la réponse appropriée pour chaque élément :

Pas du tout d'accord	Pas d'accord	D'accord	Tout à fait d'accord	Je ne sais pas
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Etes-vous d'accord avec cette recommandation ?

*Si vous voulez nous communiquer des arguments et/ou des éléments d'information complémentaires, veuillez les résumer dans l'espace ci-après :

Si vous n'avez pas de commentaires, indiquez "aucun"

Veuillez écrire votre réponse ici :

RECOMMANDATION 3

Nous conseillons aux régions de ne pas organiser de programme de dépistage systématique de la contamination par les PFAS basé sur des analyses sanguines, même dans les zones où la contamination de l'eau potable, des aliments et/ou des sols est avérée, à moins que cela ne soit organisé dans un contexte de recherche. *

*Choisissez la réponse appropriée pour chaque élément :

Pas du tout d'accord	Pas d'accord	D'accord	Tout à fait d'accord	Je ne sais pas
-------------------------	--------------	----------	-------------------------	----------------------

Etes-vous d'accord avec cette recommandation ?

*Si vous n'êtes pas d'accord avec cette recommandation - par exemple si vous estimez qu'un dépistage systématique est nécessaire -, merci de résumer vos arguments et/ou de nous communiquer les éventuels éléments d'information complémentaires dans l'espace ci-après (

Par exemple : comment le dépistage devrait-il être organisé, à quelle fréquence, sur la base de quels seuils sanguins, dans quelle(s) population(s)...

Veuillez écrire votre réponse ici :

*Si vous voulez nous communiquer des arguments et/ou des éléments d'information complémentaires, veuillez les résumer dans l'espace ci-après :

Si vous n'avez pas de commentaires, indiquez "aucun"

Veuillez écrire votre réponse ici :

RECOMMANDATION 4

a. Nous conseillons aux médecins généralistes de ne pas promouvoir le dépistage opportuniste de la contamination par les PFAS en dehors d'un contexte de recherche, même dans les zones où une contamination de l'eau potable, des aliments et/ou des sols a été démontrée.

*Choisissez la réponse appropriée pour chaque élément :

Pas du tout d'accord	Pas d'accord	D'accord	Tout à fait d'accord	Je ne sais pas
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Etes-vous d'accord avec cette recommandation ?

*Si vous voulez nous communiquer des arguments et/ou des éléments d'information complémentaires, veuillez les résumer dans l'espace ci-après :

Si vous n'avez pas de commentaires, indiquez "aucun"

Veuillez écrire votre réponse ici :

b. Lorsque les patients demandent un dosage de PFAS sanguin, nous conseillons aux médecins généralistes d'expliquer les incertitudes actuelles sur les bénéfices et les risques pour permettre une discussion éclairée sur l'intérêt d'un tel dosage.

*Choisissez la réponse appropriée pour chaque élément :

Pas du tout d'accord	Pas d'accord	D'accord	Tout à fait d'accord	Je ne sais pas
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Etes-vous d'accord avec cette recommandation ?

*Si vous voulez nous communiquer des arguments et/ou des éléments d'information complémentaires, veuillez les résumer dans l'espace ci-après :

Si vous n'avez pas de commentaires, indiquez "aucun"

Veuillez écrire votre réponse ici :

RECOMMANDATION 5

En cas de dosage sanguin des PFAS, nous recommandons d'enregistrer systématiquement les résultats dans le dossier médical électronique du patient. *

*Choisissez la réponse appropriée pour chaque élément :

Pas du tout d'accord	Pas d'accord	D'accord	Tout à fait d'accord	Je ne sais pas
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Etes-vous d'accord avec cette recommandation ?

***Si vous voulez nous communiquer des arguments et/ou des éléments d'information complémentaires, veuillez les résumer dans l'espace ci-après :**

Si vous n'avez pas de commentaires, indiquez "aucun"

Veuillez écrire votre réponse ici :

RECOMMANDATION 6

En ce qui concerne le suivi clinique des personnes avec un taux sanguin élevé de PFAS, nous recommandons de suivre les recommandations de bonne pratique clinique qui s'appliquent pour la population générale (par exemple, suivre les directives actuelles sur le dépistage du cancer) et ne pas procéder à des dépistages supplémentaires, à moins que cela ne soit organisé dans un contexte de recherche.

*Choisissez la réponse appropriée pour chaque élément :

Pas du tout d'accord Pas d'accord D'accord Tout à fait d'accord Je ne sais pas

Etes-vous d'accord avec cette recommandation ?

***Si vous voulez nous communiquer des arguments et/ou des éléments d'information complémentaires, veuillez les résumer dans l'espace ci-après :**

Si vous n'avez pas de commentaires, indiquez "aucun"

Veuillez écrire votre réponse ici :

RECOMMANDATION 7

Nous recommandons aux autorités et aux instances scientifiques de soutenir et de mener des recherches sur les PFAS pour :

- clarifier et quantifier davantage les risques sanitaires possibles en fonction des seuils sanguins de PFAS,
- définir un suivi clinique efficace des patients présentant une exposition accrue aux PFAS,
- identifier des stratégies thérapeutiques sûres et efficaces pour améliorer l'élimination des PFAS du corps humain.

*Choisissez la réponse appropriée pour chaque élément :

Pas du tout d'accord Pas d'accord D'accord Tout à fait d'accord Je ne sais pas

Etes-vous d'accord avec cette recommandation ?

***Si vous voulez nous communiquer des arguments et/ou des éléments d'information complémentaires, veuillez les résumer dans l'espace ci-après :**

Si vous n'avez pas de commentaires, indiquez "aucun"

Veuillez écrire votre réponse ici :

Si vous avez connaissance de projets ou d'études en lien avec la thématique des PFAS et la santé humaine en Belgique, merci de nous en faire part ci-après :

Veuillez écrire votre réponse ici :

Avez-vous d'autres axes de recherche en lien avec les PFAS et la santé humaine à proposer (autre que ceux proposés ci-dessus) ?

Veuillez écrire votre réponse ici :

CLÔTURE

Selon vous, quels sont les éléments qui favoriseraient l'adoption de ces recommandations par les médecins généralistes ?

Par exemple : l'envoi de directives via les autorités compétentes, la mise à disposition de données scientifiques actualisées, une session spécifique dans chaque GLEM, une fiche d'information simplifiée à destination des patients....

Veuillez écrire votre réponse ici :

Si vous souhaitez ajouter un dernier commentaire, merci d'utiliser l'espace ci-après :

Veuillez écrire votre réponse ici :

Merci pour votre participation.

Les résultats de cette enquête et de l'étude KCE vous parviendront via l'adresse électronique à laquelle a été envoyée l'invitation à participer.

Si vous souhaitez contacter notre équipe, vous pouvez nous joindre par courrier électronique aux adresses suivantes :

Dr. Dominique Roberfroid (FR) dominique.roberfroid@kce.fgov.be

Dr. Frank Hulstaert (NL) frank.hulstaert@kce.fgov.be

Merci d'avoir complété ce questionnaire.

Appendix 3.2. Online questionnaire in Dutch

Bevraging van stakeholders en experts over PFAS-aanbevelingen voor huisartsen

U vindt hier een bevraging van stakeholders en experts over een voorstel van aanbevelingen voor huisartsen, voor een optimale aanpak van patiënten met een PFAS-verontreiniging (KCE-project 2024-53-HSR).

U neemt deel als expert of als vertegenwoordiger van een organisatie die betrokken is bij de besluitvorming in de gezondheidszorg. Als u deelneemt als organisatie, vragen wij u **om één enkele vragenlijst voor uw organisatie in te vullen.**

Deze vragenlijst bevat 7 aanbevelingen. Vragen met een * zijn verplicht. Het invullen van de vragenlijst duurt ongeveer 30 minuten. U kan het invullen ervan onderbreken en later verderzetten.

De antwoorden worden geanonimiseerd in het eindrapport. We zullen u vragen om ons de gegevens van een contactpersoon te bezorgen, dit voor het geval dat we nood hebben aan verduidelijking.

U kan de vragenlijst invullen tot 04 mei 2025 om 00:00 uur.

Als u nog vragen hebt, aarzel dan niet om contact met ons op te nemen.

Er zijn 29 vragen in deze enquête.

ALGEMENE INFORMATIE

*In welke hoedanigheid / hoedanigheden neemt u deel aan dit onderzoek?

Kies alle voor u geldende mogelijkheden:

- Academisch expert
- Wetenschappelijk expert buiten de academische wereld
- Vertegenwoordiger van een overheidsinstantie (regionaal of federaal)
- Vertegenwoordiger van een ministerieel kabinet (regionaal of federaal)
- Vertegenwoordiger van een beroepsvereniging
- Vertegenwoordiger van een wetenschappelijke vereniging
- Andere
- **Bij "Andere", gelieve hieronder te specificeren:**

*Naam en voornaam van een contactpersoon

Vul uw antwoord hier in:

*E-mailadres van de contactpersoon

Vul uw antwoord hier in:

*Naam van uw organisatie

Vul uw antwoord hier in:

Als u meer informatie wenst te geven over uw organisatie of uw (huidige of eerdere) deelname aan andere werkgroepen over PFAS, kunt u dat doen in de ruimte hieronder:

Vul uw antwoord hier in:

Wenst u nog bijkomende informatie te geven ? Vul dan de ruimte hieronder in:

Vul uw antwoord hier in:

AANBEVELING 1

a. We bevelen aan dat alle wetenschappelijke instanties die zich bezighouden met de impact van PFAS op de gezondheid, samenwerken om een actueel en volledig informatiepakket voor huisartsen samen te stellen.

b. Hiervoor moet worden samengewerkt met huisartsenverenigingen.

c. De inhoud van het pakket moet worden gecoördineerd en geharmoniseerd tussen de verschillende regio's.

Huisartsen moeten kunnen beschikken over een betrouwbaar en gebruiksvriendelijk referentiedocument over PFAS. Het moet alle relevante informatie over kwaliteitsvolle zorg voor patiënten met een PFAS-probleem bevatten.

Het is cruciaal belang dat de informatie en aanbevelingen voor huisartsen in alle regio's van het land op elkaar worden afgestemd, om onzekerheid en ongerustheid door tegenstrijdige informatie te vermijden.

Informatiedocumenten voor huisartsen bestaan al op regionaal niveau, maar verschillen op belangrijke punten ([SSMG](#), [Domus Medica - Zorg Vlaanderen](#)), met name wat betreft de aanbevelingen voor klinische follow-up van personen met een verhoogde PFAS-bloedwaarde.

Het informatiepakket moet het volgende bevatten:

- *Algemene informatie over PFAS;*
- *Wetenschappelijk onderbouwd advies om de individuele blootstelling aan PFAS te verminderen. Bestaande checklists met preventieve acties in de Belgische context kunnen als basis dienen maar hun wetenschappelijke validiteit moet wel aangetoond worden ([SSMG](#), [Department Zorg Vlaanderen](#));*
- *De beperkingen van PFAS-bloedtesten om PFAS-verontreiniging op populatie- en individueel niveau vast te stellen (zie uitleg bij aanbeveling 3 in het begeleidende document);*
- *Informatie over bloedreferentiewaarden in de algemene bevolking en risicozones, op basis van belangrijke informatiebronnen (resultaten van biomonitoringstudies in Wallonie ([BMH-Wal](#)) en in Vlaanderen ([FLEHS](#)), [geodata van risicogebieden in Brussel \(Brussel Leefmilieu\)](#), waterbemonstering door Société Wallonne des eaux ([SWDE](#)), etc.);*
- *Huidige wetenschappelijke onzekerheden over het verband tussen blootstelling aan PFAS en ernstige gezondheidsproblemen bij mensen, zoals bijvoorbeeld borstkanker (zie ook de onderbouwing van de aanbeveling 6);*
- *Huidige wetenschappelijke onzekerheden met betrekking tot een adequate medische behandeling van patiënten met hoge bloedspiegels van PFAS (zie de onderbouwing van de aanbeveling 6);*
- *Lopend onderzoek in België, of het nu gaat om biomonitoringactiviteiten, epidemiologische studies of klinische studies naar nieuwe behandelingen om de bloedspiegels van PFAS te verlagen (zie aanbeveling 7).*

*Kies het toepasselijke antwoord voor elk onderdeel:

	Helemaal niet akkoord	Niet akkoord	Akkoord	Helemaal akkoord	Ik weet het niet
Bent u het eens met deze aanbeveling?					

***Geef hieronder een samenvatting van uw argumenten en/of aanvullende informatie:**

Als u geen opmerkingen hebt, vul dan “geen” in.

Vul uw antwoord hier in:

Welke instelling(en) of organisatie(s) zou(den) volgens u het voortdurende bijwerking van de informatie in het informatiepakket moeten coördineren?

Vul uw antwoord hier in:

AANBEVELING 2

We bevelen aan dat de federale en regionale overheden samen met de huisartsenorganisaties instaan voor de succesvolle verspreiding van het informatiepakket.

***Kies het toepasselijke antwoord voor elk onderdeel:**

	Helemaal niet akkoord	Niet akkoord	Akkoord	Helemaal akkoord	Ik weet het niet
Bent u het eens met deze aanbeveling?					

Geef hieronder een samenvatting van uw argumenten en/of aanvullende informatie:

Als u geen opmerkingen hebt, vul dan “geen” in.

Vul uw antwoord hier in:

AANBEVELING 3

We adviseren de regio's om geen systematisch screeningsprogramma via PFAS bloedtesten te organiseren, zelfs niet in gebieden waar verontreiniging van drinkwater, voedsel en/of bodem is aangetoond, tenzij dit wordt georganiseerd in een onderzoekscontext.

***Kies het toepasselijke antwoord voor elk onderdeel:**

	Helemaal niet akkoord	Niet akkoord	Akkoord	Helemaal akkoord	Ik weet het niet
Bent u het eens met deze aanbeveling?					

***Als u het niet eens bent met de aanbeveling - bijvoorbeeld als u van vindt dat systematische screening noodzakelijk is - geef dan hieronder een samenvatting van uw argumenten en/of eventuele bijkomende informatie. Bijvoorbeeld, hoe moet de screening worden georganiseerd, hoe vaak, op basis van welke bloeddrempels, in welke populatie(s), enz.**

Vul uw antwoord hier in:

Geef hieronder een samenvatting van uw argumenten en/of aanvullende informatie:

Als u geen opmerkingen hebt, vul dan “geen” in.

Vul uw antwoord hier in:

AANBEVELING 4

a. We adviseren huisartsen om opportunistische screening op PFAS-verontreiniging buiten een onderzoekscontext niet te promoten, zelfs niet in gebieden waar verontreiniging van drinkwater, voedsel en/of bodem is aangetoond.

*Kies het toepasselijke antwoord voor elk onderdeel:

	Helemaal niet akkoord	Niet akkoord	Akkoord	Helemaal akkoord	Ik weet het niet
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Bent u het eens met deze
aanbeveling?

*Geef hieronder een samenvatting van uw argumenten en/of aanvullende informatie:

Als u geen opmerkingen hebt, vul dan "geen" in.

Vul uw antwoord hier in:

b. Wanneer patiënten vragen om een PFAS-bloedtest, adviseren wij huisartsen om de huidige onzekerheden over de voordelen en de risico's van een dergelijke test uit te leggen, zodat een geïnformeerde discussie over de waarde van een dergelijke test mogelijk is.

*Kies het toepasselijke antwoord voor elk onderdeel:

	Helemaal niet akkoord	Niet akkoord	Akkoord	Helemaal akkoord	Ik weet het niet
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Bent u het eens met deze
aanbeveling?

*Geef hieronder een samenvatting van uw argumenten en/of aanvullende informatie:

Als u geen opmerkingen hebt, vul dan "geen" in.

Vul uw antwoord hier in:

AANBEVELING 5

In het geval een bloedtest is gedaan, raden we aan om de resultaten van de PFAS-concentratie te registreren in het elektronisch medisch dossier van de patiënt.

*Kies het toepasselijke antwoord voor elk onderdeel:

	Helemaal niet akkoord	Niet akkoord	Akkoord	Helemaal akkoord	Ik weet het niet
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Bent u het eens met deze
aanbeveling?

*Geef hieronder een samenvatting van uw argumenten en/of aanvullende informatie:

Als u geen opmerkingen hebt, vul dan "geen" in.

Vul uw antwoord hier in:

AANBEVELING 6

Voor de klinische follow-up van patiënten met verhoogde PFAS-bloedwaarden, raden we aan de richtlijnen voor goede klinische praktijk voor de algemene bevolking toe te passen (bijvoorbeeld de huidige richtlijnen voor kankerscreening) en geen bijkomende screening uit te voeren, tenzij binnen het kader van onderzoek.

*Kies het toepasselijke antwoord voor elk onderdeel:

Helemaal niet akkoord	Niet akkoord	Akkoord	Helemaal akkoord	Ik weet het niet
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Bent u het eens met deze
aanbeveling?

*Geef hieronder een samenvatting van uw argumenten en/of aanvullende informatie:

Als u geen opmerkingen hebt, vul dan “geen” in.

Vul uw antwoord hier in:

AANBEVELING 7

We raden overheden en wetenschappelijke instellingen aan om PFAS-onderzoek te ondersteunen en uit te voeren:

- om de mogelijke gezondheidsrisico's en grenswaarden verder op te helderen en te kwantificeren,
- om een efficiënte klinische follow-up te identificeren van patiënten met een verhoogde PFAS-blootstelling,
- om veilige en effectieve therapeutische strategieën te identificeren om de eliminatie van PFAS in het menselijk lichaam te verbeteren.

*Kies het toepasselijke antwoord voor elk onderdeel:

Helemaal niet akkoord	Niet akkoord	Akkoord	Helemaal akkoord	Ik weet het niet
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Bent u het eens met deze
aanbeveling?

*Geef hieronder een samenvatting van uw argumenten en/of aanvullende informatie:

Als u geen opmerkingen hebt, vul dan “geen” in.

Vul uw antwoord hier in:

Als u op de hoogte bent van Belgische projecten of onderzoeken met betrekking tot PFAS en de menselijke gezondheid, gelieve het ons dan hieronder te melden:

Vul uw antwoord hier in:

Hebt u nog andere suggesties voor onderzoek naar PFAS en de menselijke gezondheid?

Vul uw antwoord hier in:

EINDE

Wat zou de huisartsen ertoe kunnen aanzetten om de aanbevelingen toe te passen?

Bijvoorbeeld: het versturen van richtlijnen via de bevoegde instanties, het beschikbaar stellen van actuele wetenschappelijke gegevens, een presentatie in elke LOK, een vereenvoudigde informatiefiche voor patiënten

Vul uw antwoord hier in:

Hebt u nog een laatste opmerking? Gebruik dan de ruimte hieronder:

Vul uw antwoord hier in:

Bedankt voor uw deelname

We zullen de resultaten van deze enquête en van het KCE-project versturen naar hetzelfde e-mailadres als dat voor uw uitnodiging tot deelname aan de enquête.

U kunt u ons per e-mail bereiken op het volgende adres:

Dr. Frank Hulstaert (NL) frank.hulstaert@kce.fgov.be

Dr. Dominique Roberfroid (FR) dominique.roberfroid@kce.fgov.be

Bedankt voor uw deelname aan deze enquête.

Appendix 3.3. Supporting document in French (online survey)

CONSULTATION DES PARTIES PRENANTES ET EXPERTS À PROPOS DES RECOMMANDATIONS À DESTINATION DES MÉDECINS GÉNÉRALISTES SUR LA QUESTION DE LA CONTAMINATION HUMAINE AUX PFAS

Document de travail confidentiel

Introduction

A la demande de la Conférence Interministérielle Santé Publique (fin 2024), le Centre fédéral d'Expertise des Soins de Santé (KCE) a été chargé d'élaborer des recommandations nationales pour permettre aux professionnels de la santé d'accompagner au mieux leurs patients sur la question de la contamination aux PFAS.

Cette première partie du projet se concentre sur un ensemble de 7 recommandations essentiellement à destination des médecins généralistes. Par extension, ces recommandations sont susceptibles d'être d'application pour d'autres prestataires de soins de santé de première ligne, tels que les médecins du travail et les médecins des consultations périnatales (ONE). Cette première version des recommandations a été élaborée sur la base d'une revue rapide des données probantes disponibles actuellement (avril 2025). Les recommandations finales seront publiées à la fin du mois de juin 2025.

Nous insistons sur le fait que ce document de travail est préliminaire et CONFIDENTIEL.

Recommandations provisoires

Recommandations	Argumentaire et commentaires
1.a. Nous recommandons que toutes les instances scientifiques concernées par la question de l'impact des PFAS sur la santé travaillent ensemble à l'élaboration d'un kit d'information actualisé et complet destiné aux médecins généralistes 1.b. Ce travail doit se faire en collaboration avec les associations de médecine générale 1.c. Le contenu du kit doit être coordonné et harmonisé entre les différentes régions	• Il est indispensable que les médecins généralistes aient accès à un document de référence fiable et pratique sur les PFAS, rassemblant toutes les sources d'information pertinentes pour une prise en charge de qualité des patients concernés par la question des PFAS • Il est essentiel d'harmoniser les informations et les recommandations destinées aux médecins généralistes dans toutes les régions du pays afin d'éviter les incertitudes et les inquiétudes dues à des informations contradictoires • Il existe déjà des documents d'information destinés aux médecins généralistes au niveau régional, mais ils diffèrent sur des points importants (SSMG, Domus Medica & Zorg Vlaanderen) notamment en ce qui concerne les recommandations relatives au suivi clinique des personnes présentant des taux sanguins élevés de PFAS • Le kit d'information doit contenir : ○ des informations générales sur les PFAS ○ des conseils scientifiquement fondés pour réduire l'exposition individuelle aux PFAS. Des checklists d'actions préventives adaptées au contexte belge peuvent servir de base (SSMG, Zorg Vlaanderen), mais leur validité scientifique doit être démontrée ○ les limites du dosage sanguin des PFAS pour évaluer la contamination aux PFAS au niveau populationnel et individuel (voir l'argumentaire de la recommandation 3) ○ des informations sur les valeurs sanguines de référence dans la population et dans les zones à risque, sur la base des sources d'informations-clés (par exemple, les résultats des études de biomonitoring en Wallonie (BMH-Wal) et en Flandre (FLEHS), la géolocalisation des quartiers de Bruxelles à risque effectuée par Brussels environnement, les échantillonnages d'eau par la Société Wallonne des Eaux (SWDE), etc.)

	○ des informations sur les incertitudes actuelles sur le plan scientifique concernant l'association entre les PFAS et certains problèmes de santé graves, comme par exemple le cancer du sein (voir l'argumentaire de la recommandation 6) ○ des informations sur les incertitudes actuelles sur le plan scientifique concernant une prise en charge médicale adéquate des patients présentant un taux sanguin élevé de PFAS (voir l'argumentaire de la recommandation 6) ○ des informations sur les recherches en cours en Belgique, qu'il s'agisse d'activités de biomonitoring, d'études épidémiologiques, ou d'études cliniques portant sur de nouveaux traitements pour diminuer le taux sanguin de PFAS (voir la recommandation 7)
2. Nous recommandons aux autorités fédérales et fédérées, en collaboration avec les associations de médecine générale, de veiller à ce que le kit d'information décrit ci-dessus soit diffusé avec succès	• Les médecins généralistes doivent être bien informés concernant les PFAS, d'une part pour pouvoir informer correctement leurs patients, d'autre part pour leur assurer une prise en charge médicale adéquate • La diffusion peut se faire par la distribution d'une brochure scientifique mise à jour régulièrement, d'un site internet de référence avec des FAQs, et des sessions de formation dans le cadre de la formation continue des professionnels de la santé • Des sites internet de référence existants peuvent servir de base (Environnement Santé en Wallonie, PFAS vervuiling en Flandre) mais il faut s'assurer qu'ils donnent accès à l'entièreté du kit d'information décrit plus haut
3. Nous conseillons aux régions de ne pas organiser de programme de dépistage systématique de la contamination par les PFAS basé sur des analyses sanguines, même dans les zones où la contamination de l'eau potable, des aliments et/ou des sols est avérée, à moins que cela ne soit organisé dans un contexte de recherche	En application des guidelines internationales pour évaluer le bien-fondé d'un programme de dépistage systématique d'une maladie, il ressort que plusieurs critères clés ne sont pas remplis : Il n'existe pas à l'heure actuelle de données robustes pour établir un risque pathologique en lien avec un niveau défini de PFAS dans le sang Les seuils actuels du taux de PFAS sanguins pour définir un risque augmenté de problèmes de santé tels que définis par la Commission allemande HBM-I/HBM-II pour les PFOA (>10 ng/mL) et PFOS (>20 ng/mL),^{52, 53} la National Academies of Sciences (NASEM) pour 7 PFAS : PFOA, PFOS, PFHxS, PFDA, PFUnDA, MeFOSAA, PFNA (>20 ng/mL),¹ ou l'Autorité Européenne pour la Sécurité Alimentaire (EFSA) pour les PFOA, PFOS, PFHxS et PFNA chez les femmes allaitantes et les enfants de moins d'un an,⁵⁴ ne sont pas couplés à

des études épidémiologiques. Par conséquent, la valeur prédictive positive d'un test dont le résultat serait supérieur aux normes actuelles est inconnue, avec le risque d'inquiéter la personne testée

Les normes HBM-I/HBM-II, NASEM et EFSA ne couvrent qu'un nombre très limité de PFAS, dont certains sont interdits depuis plusieurs années en Europe (PFOS depuis 2009, PFOA depuis 2020, PFHxS et PCFA depuis 2023, et PFHxA prévu en 2026). Par ailleurs, bien que les PFAS soient appelés « polluants éternels », la demi-vie des PFAS les plus étudiés dans le corps humain est limitée (1,48 à 5,1 ans pour le PFOA, 3,4 à 5,7 ans pour le PFOS, et 2,84 à 8,5 ans pour le PFHxS)²⁸. La valeur prédictive négative d'un test est donc susceptible d'être réduite, notamment pour une exposition ancienne, ce qui peut donner un faux sentiment de sécurité

La plupart des études épidémiologiques ne font référence à aucune de ces valeurs limites. Elles analysent l'association entre les effets sur la santé et la concentration sanguine en PFAS en tant que variable continue ou divisée en terciles, quartiles, ou quintiles. En outre, les concentrations sériques varient d'une étude à l'autre.

Il n'existe actuellement pas de données suffisamment robustes pour déterminer le traitement médical le plus approprié lorsqu'une concentration élevée de PFAS dans le sang est détectée chez un individu. Premièrement, les seuils sanguins pour définir un risque augmenté de problèmes de santé ont été proposés par le comité HBM-I/HBM-II comme points de référence pour des mesures basées sur la population. Deuxièmement, le suivi clinique recommandé par le NASEM en fonction du niveau de concentration sanguine en PFAS,¹ et parfois relayé en [Belgique](#), n'est pas étayé par des preuves scientifiques consolidées.⁸⁴ Certaines actions de suivi recommandées sont controversées, comme le dépistage de la dyslipidémie dès l'âge de 2 ans,⁸⁴ ou le dépistage du cancer des testicules et du cancer du rein.⁸⁴

4.a. Nous conseillons aux médecins généralistes de ne pas promouvoir le dépistage opportuniste de la contamination par les PFAS en-dehors d'un contexte de recherche, même dans les

- La prise de décision partagée sur l'opportunité de tester les PFAS dans le sang nécessite une information éclairée et transparente des patients (voir recommandation 1).

zones où une contamination de l'eau potable, des aliments et/ou des sols a été démontrée

4.b. Lorsque les patients demandent un dosage de PFAS sanguin, nous conseillons aux médecins généralistes d'expliquer les incertitudes actuelles sur les bénéfices et les risques pour permettre une discussion éclairée sur l'intérêt d'un tel dosage

5. En cas de dosage sanguin de PFAS, nous recommandons d'enregistrer systématiquement les résultats dans le dossier médical électronique des patients

6. En ce qui concerne le suivi clinique des personnes avec un taux sanguin élevé de PFAS, nous recommandons de suivre les recommandations de bonnes pratiques cliniques qui s'appliquent pour la population générale (par exemple, suivre les directives actuelles sur le dépistage du cancer) et ne pas procéder à des dépistages supplémentaires, à moins que cela ne soit organisé dans un contexte de recherche

- Les arguments soutenant la recommandation 3 s'appliquent également à cette recommandation, c'est-à-dire en bref l'incapacité de prédire un résultat de santé spécifique ; l'impossibilité de distinguer la ou les sources spécifiques d'exposition (passées ou présentes) ; l'absence d'interventions/traitements clairs, et l'anxiété que cela peut induire ; les différences entre les laboratoires dans les techniques/modalités de test ; et enfin le coût du test en raison de l'absence de couverture des frais par l'assurance maladie obligatoire

- Étant donné que les recherches se poursuivent pour comprendre les mécanismes de la toxicité des PFAS et leur impact sur la santé, il est important de maximiser l'utilisation des résultats des tests sanguins, où qu'ils soient collectés (médecine du travail, études de biosurveillance, dépistage opportuniste par le médecin généraliste, autres types d'études), à des fins épidémiologiques
- Par conséquent, les résultats des tests sanguins devraient être systématiquement communiqués au médecin généraliste des patients concernés pour que ces résultats soient enregistrés dans le dossier médical électronique. Idéalement, cela devrait se faire dans le cadre d'une étude longitudinale (une étude de cohorte ou un essai clinique)

- Bien que le PFOA ait été classé comme «cancérigène pour l'homme» par le Centre international de recherche sur le cancer (CIRC) sur la base de preuves expérimentales «suffisantes» chez l'animal et de preuves mécanistiques «fortes», il existe des preuves « limitées » pour le carcinome rénal et le cancer testiculaire, et des preuves «insuffisantes» pour tous les autres cancers⁹⁹
- Bien que le PFOS ait été classé comme «cancérigène possible pour l'homme » sur la base de preuves mécanistiques «fortes», il existe des preuves « limitées » provenant d'études animales et des preuves «insuffisantes» provenant d'études humaines pour une association avec le cancer⁹⁹
- Le suivi clinique recommandé par la NASEM en fonction du niveau de concentration sanguine en PFAS,¹ auquel il est également parfois fait référence en [Belgique](#), n'est pas soutenu par des données probantes.⁸⁴ Les recommandations font principalement référence à des actions de dépistages supplémentaires, et pour la plupart d'entre elles des preuves solides sur les risques et les avantages manquent, par exemple dans le cas du dépistage du cancer du rein ou des testicules.

7. Nous recommandons aux autorités et aux instances scientifiques de soutenir et de mener des recherches sur les PFAS pour :

- clarifier et quantifier davantage les risques sanitaires possibles en fonction des seuils sanguins de PFAS ;
- définir un suivi clinique efficace des patients présentant une exposition accrue aux PFAS ;
- identifier des stratégies thérapeutiques sûres et efficaces pour améliorer l'élimination des PFAS dans le corps humain ;

- Compte tenu des incertitudes, des recherches plus approfondies sont justifiées et indispensables
- Des données préliminaires suggèrent que les résines échangeuses d'anions telles que la colestyramine et le colesevelam peuvent réduire de manière significative les PFAS dans le sang.
- Un essai randomisé contrôlé cross-over de 12 semaines portant sur une dose modérée de 3x4 g de colestyramine par jour chez 45 sujets présentant des niveaux sériques de SPFO très élevés a fait état d'une réduction de 60 % (de 115 ng/mL par rapport à un niveau sérique moyen de SPFO de 191 ng/mL).⁹³ Ces résultats prometteurs doivent être confirmés par d'autres essais randomisés contrôlés de haute qualité
- Par ailleurs, l'élimination accélérée d'un médicament spécifique (également un PFAS car il contient un carbone méthylique entièrement fluoré) à l'aide d'un traitement par résine échangeuse d'anions est déjà utilisée dans la pratique, par exemple 11 jours de 3x8g de colestyramine (donc le double de la dose utilisée pour éliminer les PFAS dans l'essai) est recommandé par l'EMA pour éliminer le médicament (tératotoxique) léflunimide chez les femmes prenant ce médicament qui souhaitent devenir enceintes⁹⁵

Appendix 3.4. Supporting document in Dutch (online survey)

CONSULTATIE VAN STAKEHOLDERS EN EXPERTEN OMTRENT HUISARTS-AANBEVELINGEN OVER PFAS VERONTREINIGING BIJ DE MENS

Vertrouwelijk werkdocument

Introductie

De Interministeriële Conferentie Volksgezondheid heeft het Federaal Kenniscentrum voor de Gezondheidszorg gevraagd om nationale aanbevelingen voor zorgverleners in staat stellen hun patiënten zo goed mogelijk te ondersteunen bij het probleem van PFAS-verontreiniging.

In het eerste deel van dit project ontwikkelen we een reeks van 7 aanbevelingen voor de huisartsen. Bij uitbreiding zijn deze aanbevelingen waarschijnlijk ook van toepassing op andere eerstelijns zorgverleners, zoals arbeidsartsen en perinatale consultatieartsen (Kind en Gezin). Deze eerste versie is opgesteld op basis van een rapid review van het wetenschappelijke bewijs dat momenteel beschikbaar is (april 2025). We zullen de definitieve aanbevelingen eind juni 2025 publiceren.

We benadrukken dat dit werkdocument voorlopig en vertrouwelijk is.

Voorlopige aanbevelingen

Aanbevelingen	Argumentatie en opmerkingen
1.a. We bevelen aan dat alle wetenschappelijke instanties die zich bezighouden met de impact van PFAS op de gezondheid, samenwerken om een actueel en volledig informatiepakket voor huisartsen samen te stellen. 1.b. Hiervoor moet worden samengewerkt met huisartsenverenigingen. 1.c. De inhoud van het pakket moet worden gecoördineerd en geharmoniseerd tussen de verschillende regio's.	- Huisartsen moeten kunnen beschikken over een betrouwbaar en gebruiksvriendelijk referentiedocument over PFAS. Het moet alle relevante informatie over kwaliteitsvolle zorg voor patiënten met een PFAS-probleem bevatten. - Het is cruciaal dat de informatie en aanbevelingen voor huisartsen in alle regio's van het land op elkaar worden afgestemd om onzekerheid en ongerustheid door tegenstrijdige informatie te vermijden. - Informatiedocumenten voor huisartsen bestaan al op regionaal niveau, maar verschillen op belangrijke punten (SSMG, Domus Medica -Zorg Vlaanderen), met name wat betreft de aanbevelingen voor klinische follow-up van personen met een verhoogde PFAS-bloedwaarde. - Het informatiepakket moet het volgende bevatten: - Algemene informatie over PFAS ; - Wetenschappelijk onderbouwd advies om de individuele blootstelling aan PFAS te verminderen. Bestaande checklists met preventieve acties in de Belgische context kunnen als basis dienen maar hun wetenschappelijke validiteit moet wel aangetoond worden (SSMG, Zorg Vlaanderen); - De beperkingen van PFAS-bloedtesten om PFAS-verontreiniging op populatie- en individueel niveau vast te stellen (zie uitleg bij aanbeveling 3); - Informatie over referentiebloedwaarden in de bevolking en in risicogebieden, op basis van belangrijke informatiebronnen (resultaten van biomonitoringstudies in Wallonië (BMH-Wal) en in Vlaanderen (FLEHS), geodata van risicowijken in Brussel (Brussel Leefmilieu), waterbemonstering door Société Wallonne des eaux (SWDE), etc.) - Huidige wetenschappelijke onzekerheden over het verband tussen blootstelling aan PFAS en ernstige gezondheidsproblemen bij mensen, zoals bijvoorbeeld borstkanker (zie ook aanbeveling 6) - Huidige wetenschappelijke onzekerheden met betrekking tot een adequate medische behandeling van patiënten met hoge bloedspiegels van PFAS (zie de onderbouwing van de aanbeveling 6).

	○ Lopend onderzoek in België, of het nu gaat om biomonitoringactiviteiten, epidemiologische studies of klinische studies naar nieuwe behandelingen om de bloedspiegels van PFAS te verlagen (zie aanbeveling 7).
2. We bevelen aan dat de federale en regionale overheden samen met de huisartsenorganisaties instaan voor de succesvolle verspreiding van het informatiepakket.	• Huisartsen moeten goed geïnformeerd zijn over PFAS, in de eerste plaats om hun patiënten correct te informeren, in de tweede plaats om ervoor te zorgen dat zij de juiste zorg krijgen. • De disseminatie kan gebeuren door de verspreiding van een up-to-date scientific folder, een referentiewebsite met FAQ's en trainingssessies als onderdeel van de bijscholing van gezondheidsprofessionals • Bestaande referentiewebsites kunnen als basis dienen (Environnement Santé in Wallonië, PFAS vervuiling in Vlaanderen) maar het is noodzakelijk om ervoor te zorgen dat ze toegang bieden tot alle hierboven beschreven informatie.
3. We adviseren de regio's om geen systematisch screening programma via PFAS bloedtesten te organiseren, zelfs niet in gebieden waar verontreiniging van drinkwater, voedsel en/of bodem is aangetoond, tenzij dit wordt georganiseerd in een onderzoekscontext.	Bij toepassing van de internationale richtlijnen voor het beoordelen van systematische screeningprogramma's, is het zo dat aan verschillende belangrijke criteria niet wordt voldaan: Er zijn momenteel geen voldoende robuuste gegevens om het pathologische risico te bepalen dat is verbonden aan een bepaalde bloedspiegel van PFAS. De huidige normen om een verhoogd gezondheidsrisico aan te tonen zoals deze gedefinieerd door de Duitse HBM-I/HBM-II Commissie voor PFOA ($\geq 10\text{ng/ml}$) en PFOS ($\geq 20\text{ng/ml}$),^{52, 53} de Amerikaanse National Academies -aanbeveling voor 7 PFAS: PFOA (n-PFOA lineair en sb-PFOA vertakt isomeer), PFOS (n-PFOS lineair isomeer en Sm-PFOS vertakt isomeer), PFHxS, PFDA, PFUnDA, MeFOSAA, PFNA) ($\geq 20\text{ng/ml}$),¹ of de Europese Autoriteit voor Voedselveiligheid (EFSA) voor PFOA, PFOS, PFHxS en PFNA,⁵⁴ zijn niet gekoppeld aan epidemiologische studies. De positief voorspellende waarde van een test boven de huidige normen is daarom onbekend, met het risico dat de geteste persoon ongerust wordt. De HBM-I/HBM-II, NASEM- en EFSA-normen hebben slechts betrekking op een zeer beperkt aantal PFAS, waarvan sommige al enkele jaren in Europese landen verboden zijn (PFOS sinds 2009, PFOA sinds 2020, PFHxS en PCFA sinds 2023, en PFHxA in 2026). Bovendien, hoewel PFAS 'forever chemicals' worden genoemd, is de halfwaardetijd van de meest bestudeerde PFAS in het menselijk lichaam beperkt (1,48 tot 5,1 jaar voor PFOA, 3,4 tot 5,7 jaar voor PFOS en 2,84 tot 8,5 jaar voor PFHxS).²⁸ De negatieve voorspellende waarde van een test zal daarom waarschijnlijk laag zijn, vooral bij eerdere blootstelling, wat een vals gevoel van veiligheid kan geven.

De meeste epidemiologische studies verwijzen niet naar een van deze afkapwaarden. Ze analyseren de associatie tussen gezondheidsuitkomsten en de PFAS-bloedconcentratie als een continue variabele of verdeeld in tertielen/kwartielen/kwintielen. Bovendien verschillen de serumniveaus per studie.

Er zijn momenteel geen voldoende robuuste gegevens om de meest geschikte medische behandeling te bepalen wanneer bij een persoon een hoge PFAS-concentratie in het bloed wordt gedetecteerd. Ten eerste werden de grenswaarden voor bloedconcentraties gelinkt aan een verhoogd gezondheidsrisico door de Commissie HBM-I/HBM-II voorgesteld als referentiepunten voor populatiegerelateerde maatregelen. Ten tweede wordt de klinische opvolging die door de NASEM wordt aanbevolen volgens het niveau van de PFAS-bloedconcentratie,¹ en die soms in [België](#) wordt onderschreven, niet ondersteund door geconsolideerd wetenschappelijk bewijsmateriaal.⁸⁴ Sommige aanbevolen vervolgacties zijn controversieel, zoals screening op dyslipidemie vanaf de leeftijd van 2 jaar, of screening op zaadbal- en nierkanker.⁸⁴

4.a. We adviseren huisartsen om opportunistische screening op PFAS-verontreiniging buiten een onderzoekscontext niet te promoten, zelfs niet in gebieden waar verontreiniging van drinkwater, voedsel en/of bodem is aangetoond.

4.b. Wanneer patiënten vragen om een PFAS-bloedtest, adviseren wij huisartsen om de huidige onzekerheden over de voordelen en de risico's van een dergelijke test uit te leggen, zodat een geïnformeerde discussie over de waarde van een dergelijke test mogelijk is.

- De gedeelde besluitvorming over het al dan niet testen op PFAS in het bloed vereist een valide en transparante voorlichting van de patiënt (zie aanbeveling 1).
- De beweegredenen voor aanbeveling 3 zijn ook hier van toepassing, in het kort, het onvermogen om een specifieke gezondheidsuitkomst te voorspellen ; het onvermogen om specifieke bron(nen) van blootstelling (vroeger of nu) te onderscheiden; het ontbreken van duidelijke interventies/behandelingen, en de angst die dit kan opwekken; de verschillen tussen laboratoria in testtechnieken/modaliteiten; de kosten van het testen door een gebrek aan verzekeringsdekking door de verplichte ziekteverzekering.

5. In het geval een bloedtest is gedaan, raden we aan om de resultaten van de PFAS-concentratie te registreren in het elektronisch medisch dossier van de patiënt.

- Naarmate er meer onderzoek wordt gedaan naar de mechanismen van PFAS-toxiciteit en de impact ervan op de gezondheid, is het belangrijk om de resultaten van bloedonderzoek, ongeacht waar ze zijn verzameld (arbeidsgeneeskunde, biomonitoringonderzoeken, opportunistische screening door de huisarts, andere soorten onderzoeken), maximaal te gebruiken voor epidemiologische doeleinden.
- Daarom moeten de uitslagen van bloedonderzoeken routinematig naar de huisarts van de patiënt worden gecommuniceerd, zodat deze in het elektronisch medisch dossier kunnen worden vastgelegd. Idealiter zou dit moeten gebeuren als onderdeel van een longitudinaal onderzoek (een cohortonderzoek of een klinische proef).

6. Voor de klinische follow-up van patiënten met verhoogde PFAS-bloedwaarden, raden we aan de richtlijnen voor goede klinische praktijk voor de algemene bevolking toe te passen (bijvoorbeeld de huidige richtlijnen voor kankerscreening) en geen bijkomende screening uit te voeren,

- Hoewel PFOA door het Internationaal Instituut voor Kankeronderzoek (IARC) werd geclassificeerd als “kankerverwekkend voor de mens” op basis van voldoende onderzoek bij dieren en sterk mechanistisch bewijs, is er ‘beperkt’ bewijs voor niercelcarcinoom en teelbalkanker bij de mens, en “onvoldoende” bewijs voor alle andere vormen van kanker.⁹⁹ Hoewel PFOS werd geclassificeerd als “mogelijk kankerverwekkend voor de mens” op basis van sterk mechanistisch bewijs, is er ‘beperkt’ bewijs bij proefdieren en “onvoldoende” bewijs van onderzoeken bij de mens voor een verband met kanker.⁹⁹
- De klinische opvolging aanbevolen door de NASEM volgens het niveau van de PFAS-bloedconcentratie,¹ waar ook soms in [België](#) wordt naar gerefereerd, wordt niet ondersteund door geconsolideerd bewijs.⁸⁴ De aanbevelingen hebben voornamelijk betrekking op extra screeningsacties, en voor de meeste daarvan ontbreekt sterk bewijs over de risico's en voordelen, bijv. screening op nier- of teelbalkanker

7. We raden overheden en wetenschappelijke instellingen aan om PFAS onderzoek te ondersteunen en uit te voeren:

- om de mogelijke gezondheidsrisico's en grenswaarden verder op te helderen en te kwantificeren
- om een efficiënte klinische follow-up te identificeren van patiënten met een verhoogde PFAS-blootstelling
- om veilige en effectieve therapeutische strategieën te identificeren om de eliminatie van PFAS in het menselijk lichaam te verbeteren

- Gezien de onzekerheden is meer onderzoek gerechtvaardigd en noodzakelijk
- Voorlopige gegevens wijzen erop dat anionenwisselende harsen zoals colestyramine en colesevelam PFAS in het bloed aanzienlijk kunnen verminderen:
 - Een cross-over RCT met 12 weken van een matige dosis van 3x4 g colestyramine per dag bij 45 proefpersonen met zeer hoge PFOS-serumniveaus (≥ 20 ng/mL) meldde een afname van 60% van 115 ng/mL van een gemiddeld PFOS-serumniveau van 191 ng/mL.⁹³ Zulke veelbelovende resultaten moeten worden bevestigd door verdere RCT's van hoge kwaliteit.
 - Bovendien wordt in de praktijk al gebruik gemaakt van versnelde eliminatie van een specifiek geneesmiddel (ook een soort PFAS omdat het een volledig gefluoreerde methyloolstof bevat) met behulp van een anionenwisselingsharsbehandeling: Het EMA adviseert om 11 dagen lang 3x8 g colestyramine te nemen (dus het dubbele van de dosis die in het onderzoek werd gebruikt om PFAS te elimineren) om het (teratotoxische) medicijn leflunimide te elimineren bij vrouwen die dit medicijn gebruiken en zwanger willen worden ⁹⁵

Referenties

Appendix 3.5. Supporting document in French (stakeholder meeting)

CONSULTATION DES PARTIES PRENANTES ET EXPERTS À PROPOS DES RECOMMANDATIONS À DESTINATION DES MÉDECINS GÉNÉRALISTES SUR LA QUESTION DE LA CONTAMINATION HUMAINE AUX PFAS

Document confidentiel pour la préparation de la réunion du 20 mai 2025

INTRODUCTION

Objectifs

A la demande de la Conférence Interministérielle Santé Publique (fin 2024), le Centre fédéral d'Expertise des Soins de Santé (KCE) a été chargé d'élaborer des recommandations nationales pour permettre aux professionnels de la santé d'accompagner au mieux leurs patients sur la question de la contamination aux PFAS.^{ff}

Cette première partie du projet se concentre sur un ensemble de 7 recommandations essentiellement à destination des médecins généralistes. Par extension, ces recommandations sont susceptibles de s'adresser à d'autres prestataires de soins de santé de première ligne, tels que les médecins du travail et les médecins des consultations périnatales (ONE). Les recommandations finales seront publiées à la fin du mois de juin 2025.

Méthodologie

Une première version des recommandations a été élaborée sur la base d'une revue rapide des données probantes disponibles actuellement (avril 2025). Cette étude se concentre sur les aspects humains de la contamination aux PFAS et des études épidémiologiques, en dehors des études environnementales ou animales. De plus, en ce qui concerne les effets sur la santé, nous avons choisi de nous concentrer sur deux maladies graves, à savoir le cancer du rein et du sein. Ce choix a été posé compte tenu du délai court imparti à cette étude, mais aussi en raison de la charge de morbidité élevée de ces deux maladies.

Un large panel de stakeholders a ensuite été invité à commenter ces recommandations préliminaires fin avril 2025 via une enquête en ligne. Suite à cette enquête, les recommandations et/ou leurs justifications ont été revues et amendées. Ce document présente la seconde version des recommandations.

Les avis des stakeholders étaient contrastés surtout sur les recommandations 3, 4.b et 6. L'objectif de cette réunion est de revenir sur ces 3 recommandations et de travailler si possible à un plus grand consensus concernant leur nouvelle formulation. Une discussion de 20 minutes sera consacrée à chacune de ces recommandations, à la suite de quoi un vote semblable à celui de l'enquête sera réalisé.

A la suite des discussions avec les stakeholders durant la réunion du 20 mai, les recommandations seront à nouveau revues, et le cas échéant amendées. Nous rappelons toutefois que les recommandations formulées à l'issue des projets de recherche du KCE relèvent de sa seule responsabilité. La formulation finale des recommandations pourra donc différer de la formulation actuelle, mais les grandes orientations seront respectées.

Avec l'accord des participants, la discussion sera enregistrée, essentiellement à des fins d'archivage. Les éléments d'information issus de la discussion et consignés dans le rapport scientifique du KCE ne seront pas reliés au nom des intervenants (anonymisation). Toutefois, le nom des participants sera mentionné dans le colophon du rapport KCE.

Terminologie

Biomonitoring versus dépistage systématique ou opportuniste

^{ff} Les personnes qui ne sont pas familières avec le fonctionnement du KCE pourront trouver [ici](#) une petite vidéo de présentation

En lien avec la détection de la contamination aux PFAS dans le sang, ce document fait référence aux notions de biomonitoring (ou biosurveillance) et de dépistage systématique ou opportuniste. Ces programmes diffèrent par leur objectif, leur méthodologie, et leur public cible.

Le biomonitoring vise à surveiller l'exposition d'une population aux PFAS en procédant à des mesures au sein d'un échantillon d'individus représentatifs soit de la population générale, soit de groupes spécifiques (par exemple la population habitant une zone contaminée). C'est un outil de santé publique utile à la fois pour documenter une exposition environnementale ou professionnelle et mettre en place des actions correctives.

Par analogie avec le dépistage des maladies, le dépistage des PFAS vise à identifier les individus ayant une concentration sanguine augmentée en PFAS afin de leur proposer une prise en charge médicale permettant d'améliorer leur santé. Le dépistage peut être systématique dans le cadre d'un programme coordonné concernant tous les individus répondant à certains critères (par exemple un certain âge) et incluant des lignes directrices claires sur son organisation, sur la prise en charge des patients, et sur la balance risque-bénéfice (comme par exemple les programmes de dépistage du cancer du sein, du côlon, du col de l'utérus). Le dépistage est parfois opportuniste, c'est-à-dire mis en œuvre à l'initiative d'un professionnel de santé dans un contexte particulier pour un individu ou un groupe restreint, en dehors de tout programme coordonné.

Aspects pratiques de la réunion

- Au moment de la connexion, merci d'indiquer votre nom et votre institution pour qu'ils apparaissent à l'écran durant la réunion.
- Une traduction simultanée dans les deux langues sera disponible.
- Merci de lever la main (dans Zoom) lorsque vous souhaitez intervenir.
- Merci de ne pas utiliser le chat (sauf pour signaler un problème technique), afin de ne pas entamer des discussions parallèles.

Confidentialité

Nous insistons sur le fait que ce document de travail est préliminaire et CONFIDENTIEL.

RECOMMANDATIONS PROVISOIRES

Recommandations	Argumentaire et commentaires
1.a. Nous recommandons que toutes les instances scientifiques concernées par la question de l'impact des PFAS sur la santé travaillent ensemble à l'élaboration d'un kit d'information actualisé et complet destiné aux médecins généralistes 1.b. Ce travail doit se faire en collaboration avec les associations de médecine générale 1.c. Le contenu du kit doit être coordonné et harmonisé entre les différentes régions	• Il est indispensable que les médecins généralistes aient accès à un document de référence fiable et pratique sur les PFAS, rassemblant toutes les sources d'information pertinentes pour une prise en charge de qualité de leurs patients • Il est essentiel d'harmoniser les informations et les recommandations destinées aux médecins généralistes dans toutes les régions du pays afin d'éviter les incertitudes et les inquiétudes dues à des informations contradictoires • Il existe déjà des documents d'information destinés aux médecins généralistes au niveau régional, mais ils diffèrent sur des points importants (SSMG, Domus Medica & Zorg Vlaanderen) notamment en ce qui concerne les recommandations relatives au suivi clinique des personnes présentant des taux sanguins élevés de PFAS • Le kit d'information doit contenir : ○ des informations générales sur les PFAS ○ des conseils scientifiquement fondés pour réduire l'exposition individuelle aux PFAS. Des checklists d'actions préventives adaptées au contexte belge peuvent servir de base (SSMG, Zorg Vlaanderen), mais leur validité scientifique doit être démontrée ○ l'état actuel des connaissances scientifiques sur la validité du dosage sanguin pour évaluer la contamination aux PFAS au niveau populationnel et individuel (voir l'argumentaire de la recommandation 3) ○ des informations sur les valeurs sanguines de référence dans la population générale et dans les zones à risque, sur la base des sources d'informations-clés (par exemple, les résultats des études de biomonitoring en Wallonie (BMH-Wal) et en Flandre (FLEHS), les recommandations internationales, la géolocalisation des quartiers à risque à Bruxelles à risque par Brussels environnement, les échantillonnages d'eau par la Société Wallonne des Eaux (SWDE), les échantillonnages de terre ou d'air, etc.) ○ l'état actuel des connaissances scientifiques sur l'association entre une concentration sanguine élevée en PFAS et l'incidence de problèmes de santé graves, comme le cancer du rein (voir l'argumentaire de la recommandation 6) ○ l'état actuel des connaissances scientifiques concernant une prise en charge médicale adéquate des patients présentant une concentration sanguine élevée en PFAS (voir l'argumentaire de la recommandation 6) ○ des informations sur les recherches en cours en Belgique, qu'il s'agisse d'activités de biomonitoring, d'études épidémiologiques, ou d'études cliniques

	portant sur de nouveaux traitements pour diminuer le taux sanguin de PFAS (voir la recommandation 7)
2.a. Nous recommandons aux autorités fédérales et fédérées, en collaboration avec les associations de médecine générale, de veiller à ce que le kit d'information décrit ci-dessus soit diffusé avec succès 2.b. Cette diffusion devrait être étendue à d'autres professionnels de la santé 2.c. Une version simplifiée du kit devrait être mise à la disposition du public	• Les médecins généralistes doivent être bien informés concernant les PFAS, d'une part pour pouvoir informer correctement leurs patients, d'autre part pour leur assurer une prise en charge médicale adéquate. • Le kit d'information peut être utile à d'autres professionnels de la santé, particulièrement pour les professionnels qui sont un premier point / unique point de contact avec le système de santé comme les pharmaciens, les médecins du travail ou médecins scolaires, les professionnels des consultations ONE... • Des professionnels de la communication devraient être impliqués dans la formulation et la présentation générale du kit d'information • La diffusion peut se faire par la distribution d'une brochure scientifique mise à jour régulièrement, d'un site internet de référence avec des FAQs, et des sessions de formation dans le cadre de la formation continue des professionnels de la santé. • Il est aussi important que le public soit correctement informé sur la problématique des PFAS et sur les avantages et désavantages des dosages sanguins. Des sites internet de référence existants pourraient servir de base (Environnement Santé en Wallonie, PFAS vervuiling en Flandre) mais il faut s'assurer qu'ils donnent accès à l'entièreté du kit d'information décrit plus haut. Afin d'harmoniser les informations et les recommandations dans toutes les régions du pays, un site internet fédéral en trois langues serait une option à privilégier. • Il faut identifier l'institution qui sera responsable de la mise à jour régulière du kit d'information et de sa diffusion.
3.a. Nous conseillons aux Régions de ne pas organiser de programme de dépistage systématique de la contamination par les PFAS basé sur des analyses sanguines, car le bien-fondé d'une telle approche n'est pas établi dans l'état actuel des connaissances scientifiques. 3.b. Si les Régions envisagent d'organiser un dépistage systématique de la contamination par les PFAS sur la base des analyses sanguines, par exemple dans des zones où la contamination de l'eau potable, des aliments et/ou des sols est avérée, cela devrait se faire dans le cadre d'une recherche scientifique afin d'évaluer la balance risque-bénéfice d'un tel dépistage	Remarques préliminaires : Cette recommandation ne concerne pas le biomonitoring. Réduire l'exposition aux sources de PFAS relève du principe de précaution. Celui-ci s'applique même en l'absence de dosage sanguin individuel. Il est aussi du ressort des pouvoirs publics, particulièrement dans les zones où la contamination de l'eau potable, des aliments et/ou des sols est avérée. • En application des guidelines internationaux pour évaluer le bien-fondé d'un programme de dépistage systématique d'une maladie, il ressort que plusieurs critères-clés ne sont pas remplis : • Il n'existe pas encore de méthode de référence pour mesurer la concentration de PFAS dans le sang, ni de consensus sur la liste des PFAS qui devraient être recherchées.

- Il n'existe pas à l'heure actuelle de données robustes pour établir une gradation du risque pathologique en lien avec un niveau défini de PFAS dans le sang.
 - Les seuils actuels^{gg} pour définir un risque augmenté de problèmes de santé ont été définis comme points de référence pour des mesures basées sur la population, et non sur la base d'études épidémiologiques d'occurrence de pathologies.
 - Inversement, les études épidémiologiques examinant les effets sur la santé n'ont pas utilisé ces seuils, mais la concentration sanguine en PFAS en tant que variable continue ou divisée en terciles, quartiles, ou quintiles. En outre, les concentrations sériques variaient d'une étude à l'autre.
 - Par conséquent, la valeur prédictive positive d'un dosage sanguin dont le résultat serait supérieur aux normes actuelles est inconnue.
 - Annoncer au patient que son risque de pathologies graves est augmenté pourrait générer de l'anxiété, particulièrement si une prise en charge appropriée ne peut pas être proposée.
- Il n'existe pas, actuellement, de données robustes sur la valeur prédictive négative d'un dosage sanguin des PFAS selon les normes actuelles.
 - Les normes HBM-I/HBM-II, NASEM et EFSA ne couvrent qu'un nombre très limité de PFAS, dont certains sont interdits depuis plusieurs années en Europe.^{hh}
 - Bien que les PFAS soient appelés « polluants éternels », la demi-vie des PFAS les plus étudiés dans le corps humain est limitée (1,48 à 5,1 ans pour le PFOA, 3,4 à 5,7 ans pour le PFOS, et 2,84 à 8,5 ans pour le PFHxS).²⁸
- Il n'existe actuellement pas de données robustes pour déterminer la prise en charge la plus appropriée lorsqu'une concentration élevée de PFAS dans le sang est détectée chez un individu. Le suivi clinique recommandé par la NASEM en fonction du niveau de concentration sanguine en PFAS,¹ et parfois relayé en Belgique, n'est pas étayé par des preuves scientifiques consolidées.⁸⁴ Certaines actions de suivi recommandées sont controversées, comme le dépistage de la dyslipidémie dès l'âge de 2 ans,⁸⁴ ou le dépistage du cancer des testicules et du cancer du rein.⁸⁴ La balance risque-bénéfice de ces approches n'est pas établie, et pourrait

^{gg} Ces seuils ont été définis par la Commission allemande HBM-I/HBM-II pour les PFOA (>10 ng/mL) et PFOS (>20 ng/mL),⁵² la National Academies of Sciences (NAS) pour 7 PFAS : PFOA, PFOS, PFHxS, PFDA, PFUnDA, MeFOSAA, PFNA (>20 ng/mL),¹ ou l'Autorité Européenne pour la Sécurité Alimentaire (EFSA) pour les PFOA, PFOS, PFHxS et PFNA chez les femmes allaitantes et les enfants de moins d'un an.⁵⁴

^{hh} PFOS depuis 2009, PFOA depuis 2020, PFHxS et PCFA depuis 2023, et PFHxA prévu en 2026

	potentiellement être négative (anxiété, morbidité liée aux examens complémentaires). Un dosage sanguin des PFAS n'a de sens que s'il est couplé avec un suivi médical bien organisé des individus, dans le cadre d'une recherche scientifique, afin d'évaluer l'impact d'une contamination en PFAS sur l'état de santé et la balance risque-bénéfice du dépistage.
4.a. Nous conseillons aux médecins généralistes de ne pas promouvoir le dépistage opportuniste de la contamination sanguine par les PFAS, si ce n'est pas dans le cadre d'une recherche scientifique 4.b. Lorsque les patients demandent un dosage de PFAS sanguin, nous conseillons aux médecins généralistes d'expliquer les incertitudes actuelles sur les bénéfices et les risques, afin de permettre une discussion éclairée sur l'intérêt d'un tel dosage et parvenir à un choix qui soit le plus bénéfique pour le patient	- La prise de décision partagée sur l'opportunité de tester les PFAS dans le sang nécessite une information éclairée et transparente des patients (voir recommandation 1). - Les arguments soutenant la recommandation 3 s'appliquent également à cette recommandation, c'est-à-dire en bref : l'absence de technique de laboratoire de référence ; l'impossibilité de distinguer la ou les sources spécifiques d'exposition (passées ou présentes) ; l'incapacité de prédire un résultat de santé spécifique ; l'absence d'interventions/traitements clairs, et l'anxiété que cela peut induire ; et, enfin, le coût du test en raison de l'absence de couverture des frais par l'assurance maladie obligatoire. - La décision finale doit tenir compte de la situation particulière de chaque patient et du bénéfice escompté (par exemple, réduire une anxiété morbide pour les personnes vivant dans une zone de contamination avérée). Les femmes envisageant une grossesse, enceintes ou allaitantes, nécessitent une attention particulière, même s'il n'est pas clair à ce stade quelles recommandations spécifiques peuvent être formulées pour ce groupe.
5. a. En cas de dosage sanguin de PFAS, nous recommandons d'enregistrer systématiquement et de façon structurée les résultats dans le dossier médical électronique des patients afin qu'ils puissent être identifiés facilement lors d'études scientifiques à des fins épidémiologiques (études de cohorte) 5.b. Une procédure efficace devrait être mise en place pour que les résultats (positifs ou négatifs) d'un dépistage opportuniste éventuellement effectué par le médecin soit transmis à l'institution en charge du biomonitoring	- Étant donné que les recherches se poursuivent pour comprendre les mécanismes de la toxicité des PFAS et leur impact sur la santé, il est important de maximiser l'utilisation des résultats des tests sanguins, où qu'ils soient collectés (médecine du travail, biomonitoring, dépistage opportuniste par le médecin généraliste, autres types d'études), à des fins épidémiologiques - Par conséquent, les résultats des tests sanguins devraient être systématiquement communiqués au médecin généraliste des patients concernés pour que ces résultats soient enregistrés dans le dossier médical électronique, avec le consentement du patient, et qu'ils puissent être identifiés et collectés facilement par la suite. Le laboratoire qui a effectué le dosage, ainsi que la technique utilisée, devraient aussi être répertoriés. Idéalement, cela devrait se faire dans le cadre d'une étude longitudinale (une étude de cohorte ou un essai clinique)

	• Quand le patient a été exposé aux PFAS (par exemple, exposition professionnelle), cela devrait aussi être consigné dans son dossier médical, même en l'absence de résultats sanguins.
6.a. En ce qui concerne le suivi médical des personnes avec une concentration sanguine élevée en PFAS, nous recommandons de ne mettre en œuvre que les recommandations de bonnes pratiques dont la balance risque-bénéfice a été scientifiquement démontrée 6.b. Si un suivi médical spécifique est proposé aux personnes avec une concentration sanguine élevée en PFAS (par exemple un dépistage opportuniste du cancer rénal), cela devrait se faire dans le cadre d'une recherche scientifique qui permettra d'établir la balance risque-bénéfice d'une telle approche	• La recommandation de réduire son exposition aux sources de PFAS relève du principe de précaution. Elle s'applique donc même en l'absence de dosage sanguin, même si l'association entre PFAS et problèmes de santé graves n'est pas encore établie. • Les examens médicaux supplémentaires recommandés par la NASEM,¹ auxquels il est également parfois fait référence en Belgique, tels qu'un dépistage du cancer du rein ou du testicule, donne des problèmes à deux niveauxⁱⁱ : ○ Le lien entre PFAS et cancer est encore mal établi. Un avis de 2024 par le Centre international de recherche sur le cancer (CIRC) stipule pour les deux PFAS les plus étudiés que : ▪ Bien que le PFOA ait été classé comme «cancérogène pour l'homme» par le CIRC sur la base de preuves expérimentales «suffisantes» chez l'animal et de preuves mécanistiques «fortes», il existe des preuves « limitées » pour le carcinome rénal et le cancer testiculaire, et des preuves «insuffisantes» pour tous les autres cancers.⁹⁹ ▪ Bien que le PFOS ait été classé comme «cancérogène possible pour l'homme » sur la base de preuves mécanistiques «fortes», il existe des preuves « limitées » provenant d'études animales et des preuves «insuffisantes» provenant d'études humaines pour une association avec le cancer.⁹⁹ ○ des preuves solides sur les risques et les avantages de ces examens complémentaires font actuellement défaut.
7. Nous recommandons aux autorités et aux instances scientifiques de soutenir et de mener des recherches sur les PFAS pour : - établir les techniques de laboratoire de référence pour mesurer les PFAS dans le sang, y compris pour les PFAS peu reconnus aujourd'hui ou difficiles à doser (par exemple, les PFAS à chaîne courte) - clarifier et quantifier davantage les risques sanitaires possibles en fonction des seuils sanguins de PFAS	• Compte tenu des incertitudes dans de nombreux domaines (à la fois techniques et cliniques), des recherches plus approfondies sont justifiées et indispensables. • Des données préliminaires suggèrent que les résines échangeuses d'anions telles que la colestyramine et le colesevelam peuvent réduire de manière significative les

ⁱⁱ Dans le cadre de premier projet, le KCE s'est concentré sur le cancer du rein et du sein, et n'a pas revu la littérature scientifique sur les autres problèmes de santé reconnus comme étant liés à la contamination de PFAS (par exemple, une réponse immunitaire diminuée lors de vaccination chez le nourrisson)

- clarifier les bases scientifiques de certaines recommandations pour diminuer l'exposition aux PFAS (par exemple, l'efficacité des filtres pour l'eau potable à domicile)
- évaluer la balance risque-bénéfice d'un suivi médical (tel que ceux recommandés actuellement par la NASEM) des patients présentant une exposition accrue aux PFAS
- identifier des stratégies thérapeutiques sûres et efficaces pour améliorer l'élimination des PFAS dans le corps humain

PFAS dans le sang.^{jj} Ces résultats prometteurs doivent être confirmés par d'autres essais randomisés contrôlés de haute qualité.

^{jj} Un essai randomisé contrôlé cross-over de 12 semaines portant sur une dose modérée de 3x4 g de colestyramine par jour chez 45 sujets présentant des niveaux sériques de SPFO très élevés a fait état d'une réduction de 60 % (de 115 ng/mL par rapport à un niveau sérique moyen de SPFO de 191 ng/mL).⁹³ Par ailleurs, l'élimination accélérée d'un médicament spécifique (également un PFAS car il contient un carbone méthylique entièrement fluoré) à l'aide d'un traitement par résine échangeuse d'anions est déjà utilisée dans la pratique, par exemple 11 jours de 3x8g de colestyramine (donc le double de la dose utilisée pour éliminer les PFAS dans l'essai) est recommandé par l'EMA pour éliminer le médicament (tératotoxique) léflunimide chez les femmes prenant ce médicament qui souhaitent devenir enceintes.⁹⁵

Appendix 3.6. Supporting document in Dutch (stakeholder meeting)

CONSULTATIE VAN STAKEHOLDERS EN EXPERTEN OMTRENT HUISARTS-AANBEVELINGEN OVER PFAS VERONTREINIGING BIJ DE MENS

Vertrouwelijk document ter voorbereiding van meeting 20 mei 2025

INTRODUCTIE

Doelstelling

De Interministeriële Conferentie Volksgezondheid heeft het Federaal Kenniscentrum voor de Gezondheidszorg (KCE) gevraagd om nationale aanbevelingen voor zorgverleners in staat stellen hun patiënten zo goed mogelijk te ondersteunen bij het probleem van PFAS-verontreiniging.

In het eerste deel van dit project ontwikkelen we een reeks van 7 aanbevelingen voor de huisartsen. Bij uitbreiding zijn deze aanbevelingen waarschijnlijk ook van toepassing op andere eerstelijns zorgverleners, zoals arbeidsartsen en perinatale consultatieartsen (Kind en Gezin). De definitieve aanbevelingen worden eind juni 2025 gepubliceerd.

Methodologie

Een eerste versie van de aanbevelingen is opgesteld op basis van een rapid review van het wetenschappelijke bewijs dat momenteel beschikbaar is (april 2025). Dit KCE onderzoek richt zich op de menselijke aspecten van PFAS-verontreiniging en epidemiologische studies, en dus niet op milieu- of dierstudies. Bovendien hebben we ervoor gekozen om ons wat gezondheidseffecten betreft te richten op twee ernstige pathologieën, namelijk nier- en borstkanker. Deze keuze is gemaakt vanwege de korte tijd die beschikbaar was voor dit onderzoek, maar ook vanwege de hoge morbiditeit van deze twee pathologieën.

Een breed panel van belanghebbenden werd eind april 2025 via een online-enquête om input gevraagd. Naar aanleiding van deze enquête werden de aanbevelingen en/of hun motivering aangepast. Dit document presenteert de tweede versie van de aanbevelingen.

De meningen van belanghebbenden waren verdeeld, vooral over aanbevelingen 3, 4.b en 6. Het doel van de vergadering is om deze 3 aanbevelingen opnieuw te bekijken en, indien mogelijk, te werken aan een grotere consensus over de nieuwe formulering ervan. Er wordt 20 minuten gediscussieerd over elk van deze aanbevelingen, waarna er gestemd wordt zoals in de enquête.

Na discussies met belanghebbenden tijdens de bijeenkomst op 20 mei zullen de aanbevelingen opnieuw worden bekeken en indien nodig worden aangepast. We herinneren u er echter aan dat de aanbevelingen die aan het einde van de KCE-onderzoeksprojecten worden geformuleerd uitsluitend onder de verantwoordelijkheid van het KCE vallen. De finale formulering van de aanbevelingen kan verschillen van de huidige formulering, maar de algemene richting van de aanbevelingen zal worden gerespecteerd.

Met instemming van de deelnemers wordt de discussie opgenomen, voornamelijk voor archiveringsdoeleinden. De informatie die uit de discussie voortvloeit en in het wetenschappelijk rapport van het KCE wordt opgenomen, zal echter niet worden gekoppeld aan de namen van de sprekers (anonimisering). De namen van de deelnemers worden wel vermeld in het colofon van het KCE-rapport.

Terminologie

Biomonitoring versus systematische screeningprogramma's en opportunistische screening

Met betrekking tot de opsporing van PFAS-verontreiniging in het bloed verwijst dit document naar de concepten *biomonitoring* en systematische of opportunistische *screening*. Deze programma's verschillen qua doelstelling, methodologie en doelgroep.

Biomonitoring heeft tot doel de blootstelling van een bevolking aan PFAS te monitoren door metingen uit te voeren bij een steekproef van individuen die representatief zijn voor de algemene bevolking of voor specifieke groepen (bijv. de bevolking die in een verontreinigd gebied woont). Het is een nuttig instrument voor de volksgezondheid, zowel om blootstelling in het milieu of op het werk te documenteren en om corrigerende maatregelen te nemen.

Naar analogie van het screenen op ziekten is het doel van PFAS-screening het identificeren van personen met verhoogde PFAS-concentraties in hun bloed, zodat hen een medische behandeling kan worden aangeboden om hun gezondheid te verbeteren. Een screening kan systematische zijn in het kader van een gecoördineerd programma bijvoorbeeld alle personen die aan bepaalde criteria (bv. een bepaalde leeftijd) voldoen en met duidelijke richtlijnen voor de organisatie, het patiëntenbeheer en de risico-batenbalans (denk aan de screeningprogramma's rond borstkanker, colonkanker, baarmoederhalskanker). Screening kan ook opportunistisch zijn, d.w.z. geïmplementeerd op initiatief van een zorgverlener in een bepaalde context voor een individu of een beperkte groep, buiten een gecoördineerd programma om.

Praktische aspecten

- Geef bij het inloggen uw naam en instelling op, zodat deze tijdens de bijeenkomst worden weergegeven.
- Simultane vertaling in beide talen is beschikbaar.
- Steek je hand op (in Zoom) als je wilt spreken.
- Maak geen gebruik van de chat (behalve om een technisch probleem te melden), zodat er geen parallelle discussies ontstaan.

Vertrouwelijkheid

We benadrukken dat dit werkdokument voorlopig en vertrouwelijk is.

VOORLOPIGE AANBEVELINGEN

Aanbevelingen	Argumentatie en opmerkingen
1.a. We bevelen aan dat alle wetenschappelijke instanties die zich bezighouden met de impact van PFAS op de gezondheid, samenwerken om een actueel en volledig informatiepakket voor huisartsen samen te stellen. 1.b. Hiervoor moet worden samengewerkt met huisartsenverenigingen. 1.c. De inhoud van het pakket moet worden gecoördineerd en geharmoniseerd tussen de verschillende regio's.	- Huisartsen moeten kunnen beschikken over een betrouwbaar en gebruiksvriendelijk referentiedocument over PFAS. Het moet alle relevante informatie over kwaliteitsvolle zorg voor hun patiënten bevatten. - Het is cruciaal dat de informatie en aanbevelingen voor huisartsen in alle regio's van het land op elkaar worden afgestemd om onzekerheid en ongerustheid door tegenstrijdige informatie te vermijden. - Informatiedocumenten voor huisartsen bestaan al op regionaal niveau, maar verschillen op belangrijke punten (SSMG, Domus Medica -Zorg Vlaanderen), met name wat betreft de aanbevelingen voor klinische follow-up van personen met een verhoogde PFAS-bloedwaarde. - Het informatiepakket moet het volgende bevatten: - Algemene informatie over PFAS ; - Wetenschappelijk onderbouwd advies om de individuele blootstelling aan PFAS te verminderen. Bestaande checklists met preventieve acties in de Belgische context kunnen als basis dienen maar hun wetenschappelijke validiteit moet wel aangetoond worden (SSMG, Zorg Vlaanderen); - de huidige stand van de wetenschappelijke kennis over de validiteit van PFAS-bloedtesten om PFAS-verontreiniging op populatie- en individueel niveau vast te stellen (zie uitleg bij aanbeveling 3); - Informatie over referentiebloedwaarden in de algemene bevolking en in risicogebieden, op basis van belangrijke informatiebronnen (resultaten van biomonitoringstudies in Wallonië (BMH-Wal) en in Vlaanderen (FLEHS), internationale aanbevelingen, geodata van risicowijken in Brussel (Brussel Leefmilieu), waterbemonstering door Société Wallonne des eaux (SWDE), bodem of lucht bemonstering, etc.) - Huidige wetenschappelijke kennis over het verband tussen een verhoogde PFAS-concentratie in het bloed en ernstige gezondheidsproblemen bij mensen, zoals bijvoorbeeld nierkanker (zie ook aanbeveling 6) - Huidige wetenschappelijke kennis met betrekking tot een adequate medische behandeling van patiënten met hoge bloedspiegels van PFAS (zie de onderbouwing van de aanbeveling 6).

	○ Lopend onderzoek in België, of het nu gaat om biomonitoringactiviteiten, epidemiologische studies of klinische studies naar nieuwe behandelingen om de bloedspiegels van PFAS te verlagen (zie aanbeveling 7).
2. a) We bevelen aan dat de federale en regionale overheden samen met de huisartsenorganisaties instaan voor de succesvolle verspreiding van het informatiepakket. 2. b) Deze verspreiding moet worden uitgebreid naar andere zorgverleners 2. c) Een vereenvoudigde versie van het informatiepakket moet beschikbaar worden gesteld aan het publiek	• Huisartsen moeten goed geïnformeerd zijn over PFAS, in de eerste plaats om hun patiënten correct te informeren, in de tweede plaats om ervoor te zorgen dat zij de juiste zorg krijgen. • Het informatiepakket kan ook nuttig zijn voor andere gezondheidszorg professionals, voornamelijk diegene in eerste lijn, of een uniek contact hebben met de patiënt, zoals apothekers, arbeidsartsen, schoolartsen, medewerkers Kind en gezin, etc. • Communicatieprofessionals moeten worden betrokken bij de formulering en algemene presentatie van het informatiepakket. • De disseminatie kan gebeuren door de verspreiding van een up-to-date scientific folder, een referentiewebsite met FAQ's en trainingssessies als onderdeel van de bijscholing van gezondheidsprofessionals • Het is ook belangrijk dat het publiek correct geïnformeerd wordt rond de PFAS problematiek, omtrent voor en nadelen van bloed-testen. • Bestaande referentiewebsites kunnen als basis dienen (Environnement Santé in Wallonië, PFAS vervuiling in Vlaanderen) maar het is noodzakelijk om ervoor te zorgen dat ze toegang bieden tot alle hierboven beschreven informatie. Om de informatie en aanbevelingen in alle regio's van het land te harmoniseren, zou een federale website in drie talen de voorkeur genieten. • Er moet een instelling worden aangewezen die verantwoordelijk is voor het regelmatig updaten en verspreiden van het informatiepakket
3. a) We adviseren de Regio's om geen systematisch screening programma via PFAS bloedtesten te organiseren, aangezien er op basis van huidige wetenschappelijke kennis niet voldoende fundamenteen zijn voor zo een programma b) Indien de Regio's een systematisch screeningprogramma voor PFAS bloedtesten opzetten, bijvoorbeeld in gebieden waar verontreiniging van drinkwater, voedsel en/of bodem is aangetoond, dan moet dit in de context van wetenschappelijk onderzoek gebeuren om de risico-batenverhouding van een dergelijke screening te beoordelen	Inleidende opmerkingen Deze aanbeveling heeft geen betrekking op biomonitoring. Het verminderen van de blootstelling aan PFAS-bronnen maakt deel uit van het voorzorgsprincipe. Dit geldt zelfs zonder individuele bloedtests. Het is ook de verantwoordelijkheid van de overheden, vooral in gebieden waar de verontreiniging van drinkwater, voedsel en/of bodem is bevestigd. • Bij toepassing van de internationale richtlijnen voor het beoordelen van systematische screeningprogramma's, is het zo dat aan verschillende belangrijke criteria niet wordt voldaan:

- Er bestaat nog geen referentiemethode om de PFAS bloed-concentratie te meten, noch een consensus omtrent de lijst van welke PFAS moeten getest worden
- Er zijn momenteel geen voldoende robuuste gegevens om een gradatie van pathologische risico te bepalen dat is verbonden aan een bepaalde bloedspiegel van PFAS.

De huidige normen/drempelwaarden om een verhoogd gezondheidsrisico aan te tonen,^{52, 53 1 54} zijn gedefinieerd als referentiepunten voor metingen op basis van de populatie, en niet op basis van epidemiologische studies rond incidentie van bepaalde pathologieën.

Daarnaast maakten de epidemiologische studies die gezondheidseffecten onderzochten geen gebruik van deze drempelwaarden, maar maakten ze gebruik van de PFAS-bloedconcentratie als continue variabele of onderverdeeld in tertielen, kwartielen of kwintielen. Bovendien verschilden de serumconcentraties van studie tot studie.

De positief voorspellende waarde van een test boven de huidige normen is daarom onbekend. Patiënten vertellen dat hun risico op ernstige pathologieën verhoogd is, kan angst opwekken, vooral als er geen geschikte behandeling kan worden aangeboden..

Op dit moment zijn er geen robuuste gegevens omtrent de negatieve voorspellende waarde van een PFAS bloedconcentratie ten aanzien van normen/drempelwaarden.

De HBM-I/HBM-II, NASEM- en EFSA-normen hebben slechts betrekking op een zeer beperkt aantal PFAS, waarvan sommige al enkele jaren in Europese landen verboden zijn .

hoewel PFAS 'forever chemicals' worden genoemd, is de halfwaardetijd van de meest bestudeerde PFAS in het menselijk lichaam beperkt (1,48 tot 5,1 jaar voor PFOA, 3,4 tot 5,7 jaar voor PFOS en 2,84 tot 8,5 jaar voor PFHxS).²⁸

Er zijn momenteel geen robuuste gegevens om de meest geschikte behandeling te bepalen wanneer bij een persoon een hoge PFAS-concentratie in het bloed wordt gedetecteerd. De klinische opvolging die door de NASEM wordt aanbevolen volgens het niveau van de PFAS-bloedconcentratie,¹ en die soms in [België](#) wordt onderschreven, niet ondersteund door geconsolideerd wetenschappelijk bewijsmateriaal.⁸⁴ Sommige aanbevolen vervolgacties zijn controversieel, zoals screening op dyslipidemie vanaf de leeftijd van 2 jaar, of screening op zaadbal- en nierkanker.⁸⁴ De risico-batenverhouding van deze benaderingen is niet vastgesteld en zou negatief kunnen zijn (angst, morbiditeit in verband met extra onderzoeken).

4.a. We adviseren huisartsen om opportunistische screening via PFAS bloedtesten buiten een onderzoekscontext niet te promoten.

4.b. Wanneer patiënten vragen om een PFAS-bloedtest, adviseren wij huisartsen om de huidige onzekerheden over de voordelen en de risico's van

- De gedeelde besluitvorming over het al dan niet testen op PFAS in het bloed vereist een valide en transparante voorlichting van de patiënt (zie aanbeveling 1).
- De beweegredenen voor aanbeveling 3 zijn ook hier van toepassing, in het kort, het ontbreken van een referentielaboratoriumtechniek, het onvermogen om specifieke bron(nen) van blootstelling (vroeger of nu) te onderscheiden, het onvermogen om een

een dergelijke test uit te leggen, zodat een geïnformeerde discussie over de waarde van een dergelijke test mogelijk is, en tot een keuze komen die het meest gunstig is voor de patiënt.

specifieke gezondheidsuitkomst te voorspellen ; het ontbreken van duidelijke interventies/behandelingen, en de angst die dit kan opwekken; de kosten van het testen door een gebrek aan verzekeringsdekking door de verplichte ziekteverzekering.

- De uiteindelijke beslissing moet rekening houden met de specifieke situatie van elke patiënt en het verwachte voordeel (bijvoorbeeld het verminderen van morbide angst voor mensen die in een gebied wonen waarvan bekend is dat ze besmet zijn). Vrouwen die een zwangerschap overwegen, of ze nu zwanger zijn of borstvoeding geven, verdienen speciale aandacht, hoewel het in dit stadium niet duidelijk is welke specifieke aanbevelingen voor deze groep kunnen worden gedaan.

5. a) In het geval een PFAS- bloedtest is gedaan, raden we aan om de resultaten te registreren op een systematische en gestructureerde manier in het elektronisch medisch dossier van de patiënt., zodat ze gemakkelijk kunnen worden geïdentificeerd voor wetenschappelijke studies en epidemiologische doeleinden (cohort studies)

- Naarmate er meer onderzoek wordt gedaan naar de mechanismen van PFAS-toxiciteit en de impact ervan op de gezondheid, is het belangrijk om de resultaten van bloedonderzoek, ongeacht waar ze zijn verzameld (arbeidsgeneeskunde, biomonitoring, opportunistische screening door de huisarts, andere soorten onderzoeken), maximaal te gebruiken voor epidemiologische doeleinden.

5. b) Er moet een effectieve procedure worden ingesteld om ervoor te zorgen dat de resultaten (positief of negatief) van elke opportunistische screening die door de arts wordt uitgevoerd, worden doorgegeven aan de instelling die verantwoordelijk is voor biomonitoring.

- Daarom moeten de uitslagen van bloedonderzoeken systematisch naar de huisarts van de patiënt worden gecommuniceerd, zodat deze in het elektronisch medisch dossier kunnen worden vastgelegd, en met toestemming van de patiënt, zodat latere identificatie en data verzameling mogelijk is. Zowel informatie over het uitvoerend labo als de gebruikte techniek moet gespecificeerd worden. Idealiter zou dit moeten gebeuren als onderdeel van een longitudinaal onderzoek (een cohortonderzoek of een klinische proef).
- Als de patiënt is blootgesteld aan PFAS (bijv. beroepsmatige blootstelling), moet dit ook worden vastgelegd in het medisch dossier, zelfs als er geen bloedresultaten zijn.

6. a) Voor de medische follow-up van patiënten met verhoogde PFAS-bloedwaarden, bevelen we aan om alleen de goede praktijkrichtlijnen toe te passen waarvan de risico-batenverhouding wetenschappelijk is aangetoond.

- De aanbeveling om de blootstelling aan PFAS-bronnen te verminderen is gebaseerd op het voorzorgsprincipe. Het is daarom zelfs van toepassing als er geen bloedtesten zijn uitgevoerd, zelfs als het verband tussen PFAS en ernstige gezondheidsproblemen nog niet is vastgesteld.

6. b) Als specifiek medisch toezicht wordt voorgesteld voor mensen met verhoogde PFAS-niveaus in het bloed (bijvoorbeeld opportunistische screening op nierkanker), moet dit gebeuren in de context van wetenschappelijk onderzoek dat het mogelijk maakt de risico-batenverhouding van een dergelijke aanpak vast te stellen.

- De supplementaire medische screenings aanbevolen door de NASEM volgens het niveau van de PFAS-bloedconcentratie,¹ waar ook soms in [België](#) wordt naar gerefereerd, zoals een screening op nierkanker of teelbalkanker geeft problemen op twee niveaus:
 - De link tussen PFAS en kanker is nog niet volledig helder. Een advies in 2024 van het Internationaal Instituut voor Kankeronderzoek (IARC) geeft advies voor de twee meest onderzochte PFAS:
 - Hoewel PFOA door het Internationaal Instituut voor Kankeronderzoek (IARC) werd geclassificeerd als “kankerverwekkend voor de mens” op basis van voldoende onderzoek bij dieren en sterk mechanistisch bewijs, is er ‘beperkt’

bewijs voor niercelcarcinoom en teelbalkanker bij de mens, en “onvoldoende” bewijs voor alle andere vormen van kanker.⁹⁹

- Hoewel PFOS werd geclassificeerd als “mogelijk kankerverwekkend voor de mens” op basis van sterk mechanistisch bewijs, is er ‘beperkt’ bewijs bij proefdieren en “onvoldoende” bewijs van onderzoeken bij de mens voor een verband met kanker.⁹⁹
- Er is momenteel een gebrek aan solide bewijs over de risico's en voordelen van deze aanvullende tests/screenings.⁸⁴

7. We raden overheden en wetenschappelijke instellingen aan om PFAS onderzoek te ondersteunen en uit te voeren:

- referentielaboratoriumtechnieken vaststellen voor het meten van PFAS in bloed, ook voor PFAS die momenteel niet algemeen erkend worden of moeilijk te meten zijn (bv. PFAS met een korte keten)
- om de mogelijke gezondheidsrisico's en grenswaarden verder op te helderen en te kwantificeren
- de wetenschappelijke basis verduidelijken voor bepaalde aanbevelingen om de blootstelling aan PFAS te verminderen (bijvoorbeeld de effectiviteit van filters voor drinkwater thuis)
- de risico-batenbalans van medische follow-up (zoals momenteel aanbevolen door de NASEM) voor patiënten met verhoogde blootstelling aan PFAS beoordelen
- om veilige en effectieve therapeutische strategieën te identificeren om de eliminatie van PFAS in het menselijk lichaam te verbeteren

- Gezien de onzekerheden op de vele verschillende vlakken (zowel labo-technisch, klinisch) is meer onderzoek gerechtvaardigd en noodzakelijk.

- Voorlopige gegevens wijzen erop dat anionenuitwisselende harsen zoals colestyramine en colesevelam PFAS in het bloed aanzienlijk kunnen verminderen.⁹³
⁹⁵ Veelbelovende resultaten moeten bevestigd worden in hoge kwaliteit gerandomiseerde studies.

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Colophon



The Rapid Response Reports aim to answer urgent questions from decision-makers. They apply expedited methods to produce timely evidence-based recommendations.

Title:	Screening for PFAS exposure in humans
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Acknowledgements:	We would like to thank all experts and organisations that have participated to our online survey and gave us input
Reported Interest:	All experts and stakeholders consulted within this report were selected because of their involvement in the topic of antivirals. Therefore, by definition, each of them might have a certain degree of conflict of interest to the main topic of this report

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Publication date:	02 July 2025
Project number:	2024-53-1-HSR
Domain:	Health Services Research (HSR)
MeSH:	Fluorocarbons; Hematologic tests; General Practitioners; Breast neoplasms; Kidney neoplasms
NLM Classification:	WA 670 Environmental pollution (General)
Language:	English
Format:	Adobe® PDF™ (A4)
Legal depot:	D/2025/10.273/15
ISSN:	2644-6459

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How to refer to this document? Roberfroid D, Bourgeois J, Castaneres-Zapatero D, Dauvrin M, Hulstaert F. Screening for PFAS exposure in humans. Brussels: Belgian Health Care Knowledge Centre (KCE). 2025. KCE Rapid Response Reports 403S. D/2025/10.273/15.

<https://doi.org/10.57598/R403S>

This document is available on the website of the Belgian Health Care Knowledge Centre.