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WHAT IS THE CLINICAL UTILITY OF PFAS TESTS? FOCUS ON PREGNANT AND BREASTFEEDING WOMEN, AND OCCUPATIONALLY EXPOSED INDIVIDUALS



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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ACGIH	American Conference of Governmental Industrial Hygienists
ADHD	Attention-Deficit/Hyperactivity Disorder
APFO	Ammonium perfluorooctanoate
ALL	Acute Lymphoblastic Leukaemia
AMSTAR-2	A Measurement Tool to Assess Systematic Reviews.
ATSDR	US Agency for Toxic Substances and Disease Registry
BEI	Biological Exposure Index
BKMR	Bayesian Kernal Machine Regression
BGV	Biological Guidance Values
BLV	Biological Limit Values
BMI	Body Mass Index
CHD	Congenital Heart Disease
DOHAD	Developmental Origins of Health and Disease framework
ECHA	European Chemicals Agency
ECHA-RAC	European Chemicals Agency – Committee for Risk Assessment
ECHA-SEAC	European Chemicals Agency - Committee for Socio-Economic Analysis
EFSA	European Food Safety Authority
EU CLP	EU regulation on Classification, Labelling and Packaging
EU OSHA	European Agency for Safety and Health at Work
EWAS	Environment-wide association study
FEDRIS	Federal Agency for Occupational Disease
FOSA	Perfluorooctane sulfonamidoethanol (precursor)
GDM	Gestational diabetes mellitus
Ggcomp	Quantile g-Computation model
GRADE	Grading of Recommendations Assessment, Development and Evaluation - framework
HBM	German Human Biomonitoring
HBM-I	Human biomonitoring guidance value where no risk for health is expected
HBM-II	Human biomonitoring guidance value where some risk for health is expected
HBM4EU	Human Biomonitoring for Europe (EU-funded initiative 2017-2022)
HFPO-DA	hexafluoropropylene oxide dimer acid (GenX)
HR	Hazard's Ratio
IARC	International Agency for Research on Cancer

IMC	Interministerial conference
IQR	Interquartile range
KCE	Belgian Health Care Knowledge Centre
LBW	Low birth weight
MA	Meta-Analysis
MeFOSAA	N-methyl perfluorooctane sulfonamidoacetic acid (precursor)
NASEM	US National Academies of Sciences, Engineering, and Medicine
NIOSH	US National Institute for Occupational Safety and Health
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational exposure limits
OGTT	Oral blood Glucose Tolerance Test
OHAT	U.S. National Toxicology Program's Office of Health Assessment and Translation
OR	Odds ratio
PARC	Partnership for the Assessment of Risk from Chemicals
PECO	Population, Exposure, Comparator, Outcome
PFAS	Per- and polyfluoroalkyl substances (a group)
PFBA	Perfluorobutanoic acid
PFCA	perfluoroalkyl carboxylic acids (a group)
PFDA	Perfluorodecanoic acid
PFDoDA	perfluorododecanoic acid
PFHpA	Perfluoroheptanoic acid
PFHxA	Perfluorohexanoic acid
PFHxS	Perfluorohexane sulfonic acid
PFNA	Perfluorononanoic acid
PFUnDA/PDUdA	Perfluoroundecanoic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid
PFPeA	Perfluoropentanoic acid
PFPeS	Perfluoropentane sulfonic acid
PTB	Preterm birth
RIVM	Dutch Rijksinstituut voor Volksgezondheid en Milieu
RR	Relative Risk
SD	Standard deviation
SMD	Standardised Mean Difference
SR	Systematic Review

TFA	Trifluoroacetic acid
UK	United Kingdom
WHO	World Health Organisation
WQS	Weighted Quantile Sum Regression

SCIENTIFIC REPORT

1 BACKGROUND

Perfluoroalkyl and polyfluoroalkyl substances (PFAS) are a class of chemicals that includes more than 12,000 different compounds which are commonly used in thousands of products, from nonstick cookware to firefighting foams and protective gear, because they have desirable chemical properties that impart oil and water repellence, friction reduction, and temperature resistance.[1] Exposure to PFAS have been linked to various health problems (see KCE report 403 for the list of suspected diseases and uncertainties),[1-3] though causality and clinical impact are not clear.[4]

The toxicological classifications[a] of PFAS warrant the application of the precautionary principle and the recommendation that exposure to these substances should be limited as much as possible.[5, 6] This primarily involves halting their industrial production and/or implementing very strict management of their release into the environment. Several regulatory actions have been undertaken, but these measures remain predominantly PFAS compound-specific (EU-Persistent Organic Pollutants Regulation,[7] EU-Classification, Labelling and Packaging Regulation,[8] EU-REACH Regulation[9]). In March 2026 the European Chemicals Agency (ECHA) followed Sweden Denmark, Germany, Norway and the Netherlands in their request for an EU-wide restriction. Since 2026, the new EU Drinking Water Directive set stricter thresholds (limit of 100 ng/l for sum of 20 specific PFAS and 500 ng/l for PFAS total).[2, 10]

It is also important to adequately manage individuals who may have been exposed to higher levels of PFAS. In December 2024, the Interministerial Conference (IMC) on Public Health tasked KCE to yield national recommendations for healthcare professionals so that they can best inform and care for their patients with a suspected or confirmed increased blood concentration of PFAS. Therefore, the KCE assessed the relevance of screening for PFAS contamination in order to best take care of screened individuals. Based on an ESRO[b] report,[11] a first set of recommendations was delivered in June 2025 (overview of ESRO results in Table 1).[2]

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[a] The International Agency for Research on Cancer (IARC) classifies PFOA as “carcinogenic to humans” based on strong evidence from mechanistic studies, sufficient evidence from animal studies and limited evidence regarding testicular and renal cell carcinoma in humans, and classifies PFOS as “possibly carcinogenic to humans” based on strong mechanistic evidence, limited evidence in animal studies and inadequate evidence in human studies.

A database of toxicological labels is available on the ECHA website (https://chem.echa.europa.eu/). Perfluorooctanoic acid (PFOA) and its salts are harmonised classified in Annex VI of Regulation (EC) No 1272/2008 as Repr. 1B; H360D ('May damage the unborn child'), indicating presumed human reproductive toxicity. PFOS and its salts are likewise classified as Repr. 1B; H360D under the EU CLP Regulation. PFHxS has been identified as a Substance of Very High Concern because it meets the criteria for reproductive toxicity under REACH. In 2025, a harmonised classification and labelling (CLH) proposal submitted to ECHA by the German competent authorities proposed classifying trifluoroacetic acid (TFA) as Repr. 1B (H360Df: "May damage the unborn child. Suspected of impairing fertility") based on reproductive and developmental toxicity data. At the time of writing, this proposal is under evaluation within the ECHA CLH process and does not yet constitute an adopted Annex VI harmonised classification.

[b] ESRO: the expedited scientific research was evidenced by a rapid review of literature starting from the NASEM report, with a focus on serious disease for which adapted medical follow-up was recommended. Therefore there was a focus on kidney cancer and breast cancer.

Table 1 – Overview of results of KCE report in July 2025[2]

MAIN RESULTS of ESRO report

1. There is currently no robust data to establish a gradation of individual pathological risk of cancer related to a defined level of PFAS in human blood.
   a. Kidney cancer: plausible link with PFOA, but inability to rule out chance, bias, or confounding with other PFAS.
   b. Breast cancer: inconsistent and contradictory results
2. The predictive value of current blood concentration thresholds is undetermined.
3. Analytical and technical parameters need to be clarified and standardised to result in a routine clinical test (e.g. list of PFAS that should be screened for, etc)
4. There is no robust data to determine the most appropriate medical management in the event of elevated blood levels of PFAS.

2 OBJECTIVE

In this second part of the KCE research project, the Interministerial Conference (IMC) on Public Health tasked KCE to yield national, evidence-based **recommendations on the optimal medical care for individuals potentially more susceptible to adverse health effects** either because they are exposed to high doses of PFAS due to their occupation, or because PFAS contamination occurs at critical times in fetal and infant development.

2.1 Research question

To provide adequate counselling and medical follow-up to patients contaminated by PFAS and susceptible to health consequences because of that exposure, such individuals need to be first identified. Therefore, the main research question translates into assessing the relevance of testing for PFAS contamination to inform clinical management. In this report, the target population was:

1. pregnant women, breastfeeding mothers and young children[c]
2. professionals particularly exposed to PFAS (e.g. firefighters)

Similarly to the former report, appropriateness of such testing was evaluated in reference to four crucial criteria[d]:

1. Is there strong evidence of an association between PFAS exposure and serious health conditions?
2. Is there a simple, safe, accurate, and validated screening test available?
3. Is there an appropriate threshold for defining a blood concentration that is harmful to health at the individual level?

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[c] offspring during the “first 1000 days” refers to the period from conception through a child’s second birthday. The “first 1000 days” allows linkage with the recent Belgian inter-federal initiative of integrated care.

[d] These are extracted from the guidance of the UK National Screening Committee (UK NSC) which extends the criteria of the framework proposed by Wilson and Junger. Our aim was not to assess the desirability of a national screening program for PFAS, but we considered 4 criteria to assess the clinical utility of screening for PFAS blood contamination.

4. Is there an effective intervention for screened patients, with evidence that intervention at a pre-symptomatic stage leads to better outcomes for the screened individual compared with usual care.

The following domains, while relevant and complementary, fall outside the scope of this research:

1. Interventions aimed at reducing population exposure to PFAS, such as monitoring regulatory standards for drinking water and food, banning the industrial production of PFAS, or cleaning up contaminated sites;
2. Interventions aimed at reducing occupational exposure (e.g. use of closed systems or alternative chemicals);
3. Interventions aimed at reducing individual exposure to PFAS (e.g. filtering water …);
4. Assessment of whether sufficient evidence exists to classify specific pathologies as occupational diseases in PFAS-exposed workers;
5. Measurement of PFAS in the environment, food, or drinking water;
6. Measurement of PFAS toxicity through mechanistic or animal studies, or to derive threshold values to judge toxicity[e]

3 METHODS

3.1 Evaluation of health outcomes in pregnant, breastfeeding women and young children

3.1.1 Selection of concerning health outcomes

Based on our previous research including expert consultation[f] the following concerning health outcomes were defined, including serious conditions (e.g. miscarriage) or worrying events for parents and health professionals. The review focused on direct clinical outcomes in pregnant women and their offspring. An exception was the reduced humoral response to vaccines in young children, as immune effects are currently considered one of the most sensitive and critical endpoints for PFAS, and used by international bodies (e.g. EFSA) as the critical effect to set PFAS health-based guidance values.

PRENATAL AND PERINATAL

- Preeclampsia
- Gestational diabetes mellitus
- Miscarriage
- Preterm birth
- Foetal growth restriction
- Congenital abnormalities (e.g. chromosomal abnormalities)

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[e] There is an ongoing WHO initiative to develop health-based guidance values for PFAS in food and water (see further in the report). This will include Systematic Evidence Collection and Evaluation of primary studies, including animal studies. However, their results will not be available before 2027

[f] The research and expert consultation during preparation of first KCE PFAS report indicated that early life exposure and outcomes were considered a priority.[2]

POSTNATAL

- Reduced humoral responses to some childhood vaccines
- Incidence of infectious diseases
- Leukaemia in children<2 years

The analysis prioritised health outcomes in the first 1000 days referring to the period from conception to a child's second birthday, which is also the focus of the new inter-federal integrated care plan.[g] Consistent with the Developmental Origins of Health and Disease (DOHaD) framework, pregnancy and early life represent critical windows of developmental vulnerability in which environmental exposures may have lasting effects on health. However, associations with health outcomes manifesting later in life, or even in the next generation, are more difficult to interpret due to longer causal pathways, cumulative exposures and effect modifiers, and are not part of this report.

Perinatal mortality (including stillbirths and early neonatal deaths) is generally considered a critically important health outcome. In this report we selected miscarriage, though did not select perinatal mortality as there was no indication or predefined association noted with PFAS exposure in our preliminary literature search.

Thyroid outcomes were not included as a separate endpoint because the review focused on direct clinical outcomes. Thyroid disruption is biologically plausible and has been reported in experimental and epidemiological studies, but the available human evidence in pregnancy and early life is heterogeneous, often based on intermediate biomarkers such as TSH, T4 or FT4 rather than clearly defined clinical infant outcomes.[12, 13]

An overview of excluded health outcomes can be consulted in Supplement 2.2.

3.1.2 Mixed method review

Similar to the former report, the four criteria to assess the appropriateness of testing from the UK National Screening Committee were used (see research question). We particularly focused on the first one, i.e. the causal association between PFAS contamination and increased risk of concerning health outcomes. Given the large number of health outcomes and the purpose of this research, we applied an expedited approach on some components of the project consistently with recommendations of the KCE process notes on ESRO methods.[11] First, we carried out an umbrella review, i.e. a review of systematic reviews.[14] We performed a literature search for recent systematic reviews with selection done according to predefined criteria (PECO see Table 2) by two independent reviewers (using the Covidence webtool). The search strategy and selection are in supplement. The quality of the systematic reviews was appraised with the AMSTAR-2 scale, and only good quality reviews could be included, i.e. if they had no critical limitation (see supplement section 3.1.1).[15]

Second, we limited the search to MEDLINE (Pubmed). Such an approach was considered appropriate, because results confirming an association between PFAS and health outcomes would most likely be published in highly ranked international journals, given the sensitive nature of the topic from a health policy perspective, and these journals are indexed in PubMed. Extending the search to other bibliographic databases would have been inefficient, and unlikely to improve the level of uncertainty that currently characterizes this field of knowledge. Furthermore, experts in the field were consulted to ensure that no important publications had been missed.

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g https://www.inami.fgov.be/fr/professionnels/info-pour-tous/plan-interfederal-soins-integres/programme-de-soins-integres-soins-et-accompagnement-des-femmes-enceintes-des-enfants-et-de-la-famille-qui-les-entoure-lors-des-premiers-1000-jours

Initially, PFAS contamination was defined when concentrations were above defined thresholds (e.g. German human Biomonitoring commission, EFSA, NASEM)[h], although they are not based on clear-cut risk of ill health (see PECO in Table 2 and previous KCE report[2]). However, most literature compares PFAS exposure between high and lower within-study exposure (either continuous via incremental exposure, or categorical high versus low based on quartiles/tertiles/quintiles), and therefore systematic reviews of such studies were also included in our umbrella review.

The need to update an existing systematic review with more recent primary studies was decided on a case-by-case basis, following criteria described in KCE report 386.[11] When no recent good-quality systematic review was available for a given health outcome, we reviewed primary studies.

Table 2 – Population, Exposure, Comparator, and Outcome (PECO) criteria for concerning health outcomes in pregnant, breastfeeding women and young children

PECOS	Inclusion	Exclusion
Population	Pregnant and lactating women, young children*	
Exposure	• Firstly: prenatal and early life exposure of PFAS as measured in serum, plasma, breast milk and cord blood above defined thresholds** • Secondary: within-study incremental PFAS concentration on a continuous or categorical scale (e.g. 4th quartile)	No individual-level exposure data
Comparator	• Firstly: no exposure to PFAS or exposure below defined thresholds* • Secondary : within-study lower PFAS concentration (e.g. first quartile)	
Outcome	Concerning health outcomes as defined in 3.1.1 with measures of association: OR, RR, HR, β and 95%CI	
Study type	• Firstly: **systematic reviews** of human epidemiological studies reporting on individual risk of health outcomes • Secondary: primary human epidemiological studies reporting on individual risk of health outcomes (prospective or retrospective cohort studies; case-controls studies) either to update an existing systematic review or to compensate the absence of a recent good quality one	• Ecological studies • Animal studies • Mechanistic studies • Consensus paper • Case report or case series • Narrative non-systematic reviews
Time horizon	• The focus was on recent SRs, from 2023 onwards. However if no good quality SR was identified, older SRs were considered. Search date was 5 January 2026 • -the time horizon for primary studies depended on the availability of SRs.	
Database	• Medline via Pubmed • Bibliography of included studies • Expert consultation	

**the selection of outcomes was based on outcomes relevant in early life with a focus on foetal development and infants/small children. However studies on children till 15y were considered. **There are several health based thresholds with considerable variation: > 5ng/ml for PFOA in women of childbearing age (HBM), > 6.9ng/ml for the sum PFOA, PFOS, PFHxS, PFNA in breastfeeding women (EFSA) . There is an ongoing WHO initiative to develop health-based guidance values for PFAS in water and food (see chapter 6 further in the report)*

h There are several health based thresholds with considerable variation: > 5ng/ml for PFOA in women of childbearing age (HBM), > 6.9ng/ml for the sum PFOA, PFOS, PFHxS, PFNA in breastfeeding women (EFSA). There is an ongoing WHO initiative to develop health-based guidance values for PFAS in food and drinking water (see chapter 6 in the report).

For the three other criteria from the UK National Screening Committee (availability of a validated test, existence of a suitable threshold, and presence of effective interventions to reduce health risks), our strategy was lighter as it was limited to grey literature search combining desk research with expert consultation. In addition we performed a grey literature search for international breastfeeding recommendations (see 3.3). Specifically for occupational exposure we performed a literature search for SRs and health effects (see 3.2).

3.1.3 How to quantify PFAS exposure in a meta-analysis

Most people have detectable levels of several PFAS in their blood, so exposure is typically assessed by comparing individuals with higher versus lower concentration, often expressed as an increment in concentration of a specific PFAS. Primary studies report these increases **using different measurement metrics,** including absolute changes (per ng/mL increase, or per IQR, per SD), and logarithmic transformations. A logarithmic transformation is commonly applied to accommodate right-skewed exposure distributions, characterized by a small proportion of individuals with very high exposure levels. Log transformation is also appropriate when exposures vary multiplicatively rather than additively and when the data span several orders of magnitude. Moreover, many statistical methods, including regression models, exhibit improved performance and more stable variance assumptions when applied to log-transformed variables.

Different logarithmic bases may be chosen depending on interpretability: the natural logarithm (ln) facilitates interpretation in terms of relative or percentage changes (e.g., an e-fold or approximately 2.7-fold increase), $\log_2$ corresponds to a doubling of exposure, and $\log_{10}$ reflects a tenfold increase. Consequently, reported effect estimates such as odds ratios (ORs) may represent the change in health risk associated with a doubling or a tenfold increase in PFAS concentration. In contrast, some studies report ORs per interquartile range increase, which complicates direct quantitative comparisons across studies due to differing exposure metrics and scaling conventions.

When data pooling is appropriate, effect estimates must be expressed on a common scale to ensure valid quantitative synthesis. More recently, some meta-analyses have therefore rescaled exposure–response estimates to an uniform metric,[16] and some applied re-expression methods—such as deriving continuous summary estimates from categorical exposure data—to facilitate pooling.[17, 18] These approaches also enable assessment of between-study consistency and heterogeneity across harmonized effect measures.

3.1.4 Impact of individual PFAS molecules and handling PFAS as a mixture

PFAS is a large group of molecules, a class of chemicals that includes more than 12,000 different compounds. Not all PFAS compounds relate to health outcomes in the same way. In epidemiological research, one compound may show a harmful association for a certain outcome in a study, while another compound is not associated, or suggests protective association.[19]

Most studies analyze associations with each PFAS separately, which creates consistency in how results are reported. However, this approach does not reflect how people are actually exposed to PFAS in real life, where multiple compounds occur together. PFAS exposure can be underestimated if combined exposure to multiple PFAS is not considered.[20] Moreover, concentrations of individual PFAS can be highly correlated with one another, making it difficult to disentangle the independent effects of specific PFAS.

Statistical methods for investigating the association of mixtures have been developed, specifically to account for high collinearity: Bayesian kernel machine regression (BKMR), quantile-based g-computation (G-Comp), and weighted quantile sum regression (WQS). Consequently, there has been a shift in observational epidemiology studies, with more researchers adopting a mixture-based approach often in complement to analyses of single compounds. Although multiple methods exist for examining exposure to PFAS mixtures (see Table 3), it remains unclear which method is the most

suitable for assessing the mixture effect for PFAS. All the available mixture methods have their own strengths and limitations, highlighting the complementary use of multiple mixture methods.[21, 22]

Table 3 – Overview of some common statistical approaches to analyse PFAS mixtures[21]

Key features	Strengths	Limitations
Bayesian Kernal Machine Regression (BKMR)		
Estimates the exposure-response function and identifies the individual components of the mixture responsible for health effects	It models nonlinearity and non-additive effects among mixture components	Exposure limited to continuous metric Does not produce a single regression coefficient or Odds Ratio
Quantile g-Computation (qgcomp)		
Ranks exposure importance by chemical weights	Gives an overall mixture effect Ideal for mixed directions and high collinearity	Data information loss due to data transformation to quantiles May not adequately capture the dose–response function if the underlying model is not smooth
Weighted Quantile Sum Regression (WQS)		
Assigns weights to mixture components which are interpreted as variable importance factors	Provides a single, summed estimate of the effect of the mixture	Assumes components of mixture have linear additive effects Requires that all exposures act in the same direction (are all harmful or all protective)

3.1.5 Rating the body of evidence according to GRADE methodology

In order to rate the level of certainty of the association between a PFAS contamination (single PFAS or in mixture) and a given health outcome, the GRADE methodology was applied (KCE guidelines [23] see Table 4).

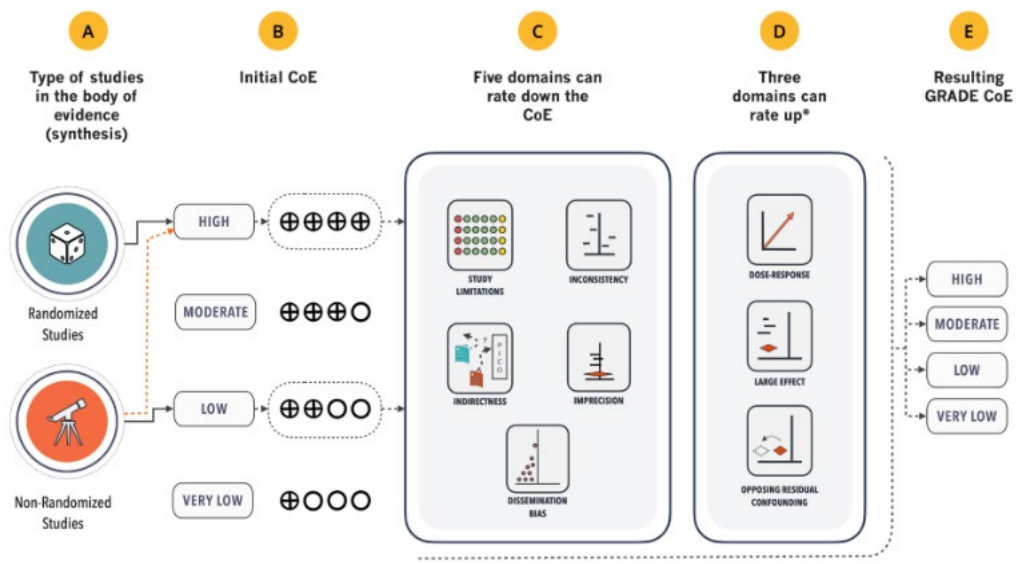
The epidemiological evidence on PFAS exposure and human health outcomes consists exclusively of observational studies (cohort, case–control, and cross-sectional). Under the GRADE framework for intervention studies—which is commonly applied when assessing causality—such evidence is rated low quality at baseline, and can be rated up if there is a large magnitude of effect, evidence of a dose-response gradient and if residual confounding would actually reduce the demonstrated effect.[24] Downgrading is opportune when there is high risk of bias, inconsistency in the results, indirectness, imprecision and evidence of publication bias. Ideally, these criteria apply to pooled estimates of effect for each health outcomes, and these estimates are derived from a meta-analysis. In the absence of a meta-analysis (for example in the case of too heterogeneous studies), the body of evidence was summarized narratively and its quality also assessed with the GRADE framework.

All quality assessments were conducted by a single investigator, and verified by a second one in case of doubt.

Table 4 – GRADE methodology on certainty of evidence[24]

Starting point	Downgrading or upgrading?	Certainty level	Interpretation
Observational human studies (cohort, case-control, cross-sectional) ~**low certainty** if focus is causation	Upgrading: large magnitude of effect, evidence of a dose-response gradient and if residual confounding	High	Very confident the true effect is close to the estimate
		Moderate	Moderately confident; true effect likely close but may differ
	Downgrading: risk of bias, inconsistency, imprecision, indirectness, publication bias	Low	Limited confidence; true effect may differ substantially
		Very Low	Very little confidence; true effect likely substantially different

Figure 1 – GRADE approach for rating certainty of evidence (CoE)[24]



Note: Observational human studies start at a low certainty of evidence and can be downgraded or upgraded.

3.1.5.1 Judging risk of bias

The OHAT risk of bias tool, developed by the U.S. National Toxicology Program for evaluating human and animal evidence in environmental health assessment,[25] has been recommended in the WHO initiative on systematic evidence reviews.[26] The judgement is narrative and does not provide an overall scoring.

When our analysis was based on an existing systematic review, we used the quality appraisal of the individual studies reported therein even when another tool had been used for bias detection. When we analyzed primary studies, we used the OHAT risk of bias tool.[25]

When in the GRADE approach the evidence from observational studies is considered low certainty from baseline, this inherently acknowledges the potential for confounding and selection bias is present.[24] Therefore, we only rated down the quality of the evidence by one level when more than half of the studies had a probably or definite high risk of bias in more than one domain.

3.1.5.2 Judging inconsistency

Inconsistency of the results across studies may justify downgrading the evidence quality.[24] Inconsistency of results about the association between PFAS (single or in mixture) and a specific health outcome is apparent when:

- The strength and/or direction of point estimates vary widely across studies and/or are dispersed on both sides of a relevant predefined threshold
- Confidence intervals show minimal or no overlap
- Statistically demonstrated heterogeneity (Cochran's Q test, $p<0.05$), particularly if I^2 value is greater than 50% (Higgins test) indicating the proportion of heterogeneity due to true differences across studies. This can be assessed only on pooled meta-analysed results.

Because different PFAS may exhibit distinct toxicological profiles, variation in the direction and the strength of the association across congeners is possible. Therefore, such variations do not lead to downgrading the evidence quality.

3.1.5.3 Judging indirectness

When there is a mismatch between the target PECO and PECO of included studies, the evidence is considered indirect and may be rated down.[24] Indirectness was not considered a major concern because our PECO criteria restricted inclusion to studies directly addressing the target population, exposure, and outcomes. When a study focused on a specific subgroup (e.g., women attending infertility clinics), or reported a narrower outcome subtype (e.g. placental preterm birth), this was reported transparently but did not warrant rating down for indirectness.

3.1.5.4 Judging imprecision

For judging imprecision, we used a simplified approach. First, when the pooled estimates of effect was statistically significant, we considered there was no imprecision even when the confidence interval was wide, because even a small increase of risk at the lower bound is relevant for public health. A same reasoning theoretically applies for statistically significant protective effect, even if the upper bound is close to unity. Second, when the confidence interval included unity, the evidence was rated down because with such results one cannot judge whether there is a reduction or increase of the risk. In case of a systematic review without meta-analysis, there was no rating for imprecision.

3.1.5.5 Judging publication/dissemination bias

In this report, only the publication bias assessment as reported in the systematic reviews was used.

3.1.5.6 Judging dose-response relationship

In general when there is a clear gradient of effect across exposure levels, which is consistent across studies, the certainty of evidence can be upgraded.[27] Most of the time this means searching for linear patterns, on a continuous scale (logarithmic increase implies a dose-response) or on a categorical scale (tertiles/quartiles/quintiles), and we applied this approach based on results retrieved in the literature. However, assessing a dose-response relationship for PFAS is particularly challenging, for both biological and methodological reasons. First, PFAS may yield non-linear dose-response patterns (steep effects at low exposures, plateau at higher exposure, threshold effects, non-monotonic effects, i.e. low and high exposures may have different or even opposite effects).[28] Thus fitting a linear function may miss a genuine dose-response effect. Second, studies often study a restricted exposure range, e.g. only compare high vs low exposure groups when categorical or a narrow exposure window when continuous, and then extrapolate the function beyond observed data, whereas the validity of such an approach is difficult to ascertain.

3.1.5.7 Judging large magnitude of effect

GRADE suggests considering rating up one level when methodologically rigorous observational studies, with low risk for confounding, show at least a two-fold reduction or increase in risk, and rating up two levels for at least a five-fold reduction or increase in risk.[24, 29] Of note is that while a large effect is an indication to upgrade the level of certainty, it does not necessarily mean there is greater confidence that the effect is indeed large.[29] If there was no pooling, we did not assess large magnitude of effect.

3.1.5.8 Judging residual confounding

In the GRADE framework, observational evidence may be upgraded when all plausible residual confounding would reduce the observed effect or suggest a spurious effect in the opposite direction. In such cases, the true association is likely stronger than estimated, increasing confidence in the findings. In environmental epidemiology, residual confounding due to co-exposure to other pollutants is prevalent (through diet, occupation, consumer products). For PFAS, there is the possibility of being correlated with other pollutants that also influence a health outcome. Because of this co-exposure risk, we assumed not to upgrade for residual confounding in this analysis.

3.1.6 Clinical impact discussion with clinical experts

In a dedicated meeting in March 2026, the preliminary results on concerning health outcomes were discussed with clinical experts and toxicologists (n=7, see colophon). The focus was on defining clinical impact and possible medical follow up. Of note, the experts did not point to any missing health outcomes of concern.

3.2 Evaluation of health outcomes due to occupational exposure

3.2.1 An umbrella review

The focus was on systematic reviews assessing the association between occupational PFAS exposure and health effects. The PECO is detailed in Table 5.

Table 5 – PECO criteria for occupational exposure

PECOS	Inclusion	Exclusion
Population	Adults with occupational exposure	
Exposure	Exposure to PFAS as measured in serum, plasma	No individual-level exposure data
Comparator	Firstly: no exposure to PFAS or exposure below defined thresholds* Secondary: within-study incremental PFAS concentration on a continuous or categorical scale (e.g. 4th quartile)	
Outcome	Health outcomes with measures of association: OR, RR, HR, β and 95%CI	
Study type	Systematic reviews of human epidemiological studies reporting on individual risk of health outcomes (prospective or retrospective cohort studies; case-controls studies, cross-sectional)	-Ecological studies -Animal studies -Mechanistic studies -Consensus paper -Case report or case series -Narrative non-systematic reviews

PECOS	Inclusion	Exclusion
Time horizon	Search date was 20 April 2026 (No time horizon was set)	
Database	- Medline via Pubmed - Bibliography of included studies	

**There are several health based thresholds with considerable variation: > 5ng/ml for PFOA in women of childbearing age (HBM), > 6.9ng/ml for the sum PFOA, PFOS, PFHxS, PFNA in breastfeeding women (EFSA) . There is an ongoing WHO initiative to develop health-based guidance values for PFAS (see further chapter 6)*

3.3 Grey literature search on guidance and ongoing initiatives

A grey literature search for guidance on breastfeeding, and on medical management of occupational exposure as well as for ongoing research was performed (on interventions to reduce PFAS in blood, on health-based thresholds). It was a combination of desk research searching for information on relevant websites and outreach to relevant expert organisations or individuals, mainly on the Belgian level (FEDRIS, Federal Public Service of Work, see colophon), as well as some international experts (WHO initiative, HAS, Société Française de Santé au Travail).

4 RESULTS

4.1 Umbrella review results on concerning health outcomes

The search for systematic reviews identified 288 references (after de-duplication). The flow chart of the selection process can be consulted in supplement 2.1. Twenty two SRs were included for selected *concerning* outcomes (see 3.1.1) and 1 SR on assessing exposure via breast milk, and one SR on PFAS mixture effects,[21] Overview of included SRs and excluded SRs (on other potential adverse health outcomes) are available in supplement section 2.2.

In the following sections the results are presented by health outcome, as well as a dedicated chapter on breast milk exposure.

4.2 Preeclampsia

4.2.1 Definition of the outcome

Pre-eclampsia is a hypertensive disorder of pregnancy defined by new-onset hypertension[i] after 20 weeks' gestation accompanied by proteinuria and/or maternal organ dysfunction and, utero-placental dysfunction that may lead to adverse pregnancy outcomes. Overall, preeclampsia complicates 3 to 5% of pregnancies.[30] Preeclampsia can be subdivided into early onset or late onset using 34 weeks as a cutoff, or preterm or term using 37 weeks of gestation as a cutoff (it can also develop in the weeks after delivery). Risk factors include a prior history of preeclampsia, diabetes, kidney disease, obesity, and high maternal age.[31] Because of their effects several pathophysiological mechanisms such as oxidative stress, endothelial toxicity or angiogenesis, PFAS have been suggested as risk factor for developing pre-eclampsia.[32]

[i] Systolic blood pressure sustained at ≥140 mm Hg or diastolic blood pressure sustained at ≥90 mm Hg, or both

4.2.2 Key points

- There was no recent good quality SR identified.
- We retrieved 15 primary studies on preeclampsia. They reported inconsistent results. Eight studies did not identify a statistically significant association between any PFAS and preeclampsia, while six studies identified an association with some types of PFAS, and one study in a specific subgroup of Hispanic participants.
- There was marked heterogeneity in outcome definitions, exposure assessment methods, and covariate adjustment strategies which prevented meaningful pooling of results.
- For these reasons, the overall certainty of evidence was rated very low based on GRADE (downgraded by 1 level for inconsistency).
- Therefore, we cannot conclude either the presence or absence of a link between PFAS contamination and preeclampsia.

4.2.3 Results of systematic reviews

Table 6 shows the overview of recent SRs including the outcome 'pre-eclampsia'. Two SRs were rated as critically low and low, while one SR was rated as low to moderate quality (according to AMSTAR-2 – see table and details in Supplement section 3.1.2).[33-35] All three studies used a search timeframe that was limited to the year 2022, and one SR considered only the period 2012-2022. All studies investigated the association of preeclampsia[j] with several types of PFAS: the overlap between studies included was consistent and is presented in Table 6 (two SR included 11 studies, while the other included 10 studies[k]). The three SRs performed meta-analyses and indicated a statistically significant association between PFOA and PFOS and preeclampsia, with limited pooled effects sizes (Table 6). Regarding the other types of PFAS, results were inconsistent. Regarding PFHxS, one SR/MA reported a statistically significant association, while the other two SRs showed a non-statistically significant association. Regarding PFNA, one SR identified a statistically significant association with the outcome while the other study did not (the third study did not assessed this type of PFAS). The other PFAS addressed in each SR are reported in Table 6 and were not identified as associated with the occurrence of preeclampsia.

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j One study considered all hypertensive disorders during the pregnancy and one study considered all endocrine-disrupting chemicals.

k Among these 10 studies, 7 were included in the meta-analysis since one study was excluded as PFAS measurement was performed on the placenta and not from the plasma, and the two other studies presented hazard ratio that were not pooled with odds ratio.

Table 6 – Systematic reviews and meta-analyses on preeclampsia

Systematic review	Included primary studies	Results	Remark	Quality appraisal (AMSTAR)
Abd Mutalib N, 2025[33]	• Starling 2014 (Norway) • Wilkström 2019 (Sweden) • Huang 2019 (China) • Rylander 2020 (Sweden) • Huo 2020 (China) • Borghese 2020 (Canada) • Bangma 2020 (US) • Bommarito 2021 (US) • Birukov 2021 (Denmark) • Liu 2022 (China) NB: ○ Stein 2009 outside the selected timeframe 2012-2022 ○ Preston 2022 not identified (published in June 2022 probably after completion of the search)	*Preeclampsia was found to have moderate association with maternal PFOA as well as PFOS exposure* **Pooled adjusted OR (CI%CI)- I^2** (7 studies)**:** • **PFOA:** 1.237(1.024-1.494)- I^2: 0.0%, p=0.745 • **PFOS:** 1.260 (1.050-1.511)- I^2: 0.0%, p=0.718 • **PFHxS:** 1.052 (0.734-1.508)- I^2: 68.8%, p=0.004	/	Critical limitations
Hirke A, 2023[34]	• Starling 2014 (Norway) • Wilkström 2019 (Sweden) • Huang 2019 (China) • Rylander 2020 (Sweden) • Huo 2020 (China) • Borghese 2020 (Canada) • Bommarito 2021 (US) • Birukov 2021 (Denmark) • Liu 2022 (China) • Stein 2009 (US) • Preston 2022 (US)	*The pooled results demonstrated that PFOA, PFOS, PFNA, were significantly associated with an increased risk of preeclampsia* **Pooled adjusted OR (CI%CI)- I^2:** • **PFOA** (8 studies)**:** 1.20 (1.04-1.39)- I^2: 0.0%, p=0.745 • **PFOS** (8 studies)**:** 1.23 (1.10-1.38)- I^2: 0.0%, p=0.48 • **PFNA** (6 studies)**:** 1.20 (1.03-1.40)- I^2: 0.0%, p=0.63 PFHxS, PFDA, PFHpA, PFUnDA : non statistically significant associations	Authors mentioned for PFOA: • unstable results in sensitivity analysis (leave-one out method) • publication bias detected for PFOA (funnel plot and Egger's test)	Critical limitations

Systematic review	Included primary studies	Results	Remark	Quality appraisal (AMSTAR)
Hu C-Y, 2023[35]	• Starling 2014 (Norway) • Wilkström 2019 (Sweden) • Huang 2019 (China) • Rylander 2020 (Sweden) • Huo 2020 (China) • Borghese 2020 (Canada) • Bommarito 2021 (US) • Birukov 2021 (Denmark) • Liu 2022 (China) • Stein 2009 (US) • Preston 2022 (US) • Stavitz 2012 (US)	*Low to moderate certainty of evidence of association between preeclampsia and exposure to PFOA, PFOS, and PFHxS* **Pooled adjusted OR (CI%CI)- I^2:** • **PFOA** (6 studies)**:** 1.39 (1.05-1.85)- I^2: 69% • **PFOS** (6 studies)**:** 1.51 (1.23-1.86)- I^2: 48% • **PFHxS** (6 studies)**:** 1.39 (1.10-1.76)- I^2: 79% PFNA, PFDA, PFDoA, PFHpA , PFUnDA : non statistically significant associations	Authors mentioned robust estimates for PFOA, PFOS and PFHxS using leave-one-out-method	Critical limitations

4.2.4 Results of primary studies

Because there was no recent good quality SR, a search for primary studies was conducted. The SR/MA from Hirke *et al.* (2023) was selected for extraction of the primary studies,[34] and an update was conducted on 13 January 2026, which resulted in 5 additional primary studies (search strategy in Supplement 1.2.1 and list of excluded studies in Supplement 2.3).

4.2.4.1 Characteristics of the primary studies identified from the systematic review and the update of literature

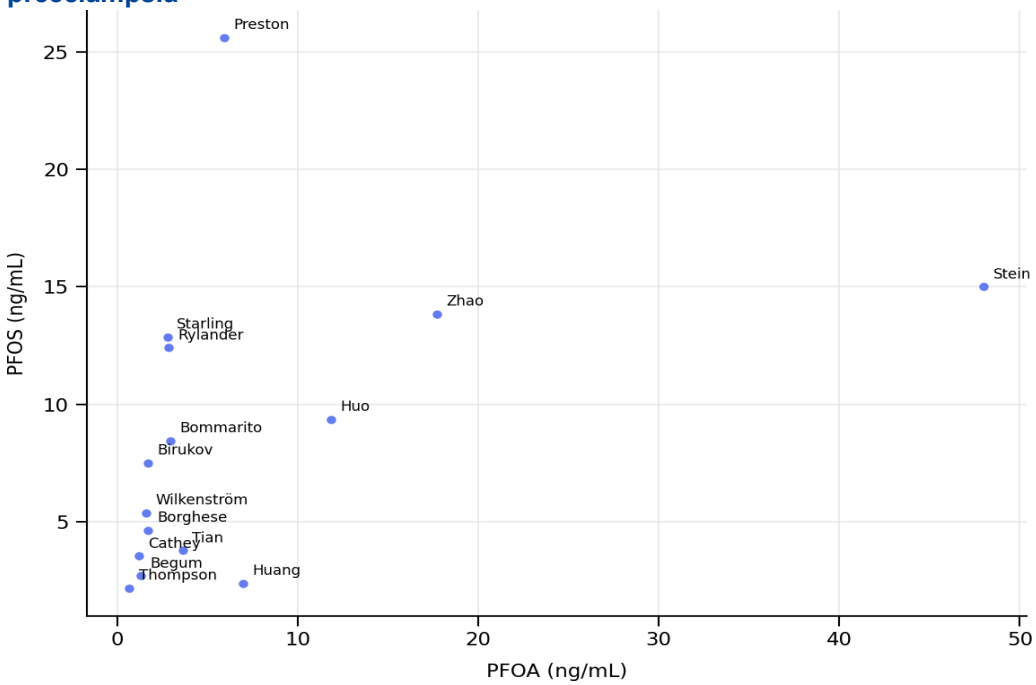
Together with the studies identified in the SRs, the total number of primary studies reporting on the association between PFAS and preeclampsia was 15 and their characteristics are provided in Supplement 4.1). All studies involved a measurement of PFAS from the plasma of pregnant participants, except one which assessed the PFAS concentration on the umbilical cord at delivery.[36]

A total of 8 cohort studies were identified[37-44] along with 4 case controls[45-48], 2 cross sectional studies[36, 49], and 1 ancillary study of a RCT.[50] The definition of the outcome was consistent in most studies and in line with the *American College of Obstetricians and Gynecologists* (ACOG) criteria. It is worth noting that 3 studies did not accurately defined the presence of proteinuria, mentioning only its identification, without defining the measured amount of proteins as it is the case in other studies.[36, 42, 44] One study did not mention the definition[50], and another study included self-reporting of the outcome for a proportion of the studied sample.[39, 49] The majority of the studies were conducted in the USA (n=6) , followed by China (n=4). The other studies were conducted in Sweden (n=2), Norway (n=1), Canada (n=1) and Denmark (n=1).

The types of PFAS investigated vary between studies, with the exception of PFOA and PFOS, which were measured in all selected studies. The timing for PFAS concentrations measurements varied across studies: 6 studies performed PFAS dosage during the first trimester of pregnancy, while 4 measured PFAS during the second trimester of pregnancy (Supplement 4.1) One study performed the measure at 32 weeks[50], one study at 1-2 days before delivery[48], and one study at delivery on the blood from umbilical cord.[36] One study did not mentioned the timing of measurement.[49], while another has several throughout the pregnancy (with missing timings).[39] The range of median PFOA and PFOS concentrations was fairly comparable across studies, except for two studies in which these concentrations were markedly higher.[41, 49] A summary of concentrations of PFOA and PFOS is presented in Figure 2.

To report the strength of the association, eleven studies reported adjusted odds ratio, while 2 studies provided adjusted hazard ratio. Four studies assessed the impact of a mixture of PFAS on the association with the outcome, using methods previously described (e.g. BKMR).[39, 41, 43, 50] Not all studies reported PFAS exposure using the same scale: the majority reported the OR per log-2 increase of plasma concentration, while the other studies used interquartile range (IQR) increase and other only reported on a categorical exposure scale comparing tertile, quartiles or a predefined cutoff value.

Figure 2 – Comparison of PFOA and PFOS blood concentrations in the 15 primary studies on preeclampsia



Note: Not all PFOA and PFOS concentrations were sampled at the same gestational age.

4.2.4.2 Main results in the primary studies

Results for PFAS individual analysis

Overall, the primary studies reported inconsistent results. Eight studies[l] did not identify a statistically significant association between PFAS and preeclampsia, while six studies identified an association with some types of PFAS (Table in Supplement 4.1):

- The cohort study from Wikström *et al*. reported a positive association with PFOS and PFNA concentrations performed during the first trimester of pregnancy (expressed as log-2 incremental units). It is however important to note that when PFNA was presented as highest versus lowest quartile of concentration, the finding was no more statistically significant.[44]
- The cohort study from Borghese *et al.* found an association only with PFHxS (PFOA and PFOS were not significantly associated with the occurrence of preeclampsia).[38]
- The nested case-control study from Bommarito *et al.* reported an association with PFOS and PFDA only in a subgroup of preeclampsia occurring after 34 gestational weeks.[45]
- The cohort study from Cathey et al. did not report statistically significant association with PFAS exposure and preeclampsia. However, in a subgroup analysis of Hispanic individuals, a statistically association was found with PFNA, PFDA and PFOA.[39]
- The nested case-control study from Zhao *et al.* conducted in a cohort of widely exposed participants, an association with PFOA and PFOS was reported when expressed as categorical expression of the concentration (having a concentration higher than a cut off value).[47]

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[l] The study from Cathey et al. (2026) identified an association between PFOA, PFDA and PFNA and preeclampsia in the subgroup of hispanic participants.

- Huang *et al.* did not show any association between PFAS and preeclampsia but using a logistic regression model considering the multiple interactions between PFAS (elastic net regression), PFBS was shown to be associated with the outcome.[36]
- A case-control study conducted in one hospital in China measured a panel of PFAS 1 to 2 days before delivery and reported a statistically significant association between PFOA, PFUnDA and 6:2Cl PFESA (chlorinated polyfluorinated ether sulfonate) and preeclampsia.[48] This study also showed that other PFAS were negatively associated with the occurrence of preeclampsia: PFHxS, PFHpA, 4:2fluorotelomer sulfonates and ADONA (3H-perfluoro-3-[(3-methoxypropoxy)propanoic acid]).
- In a cohort of highly exposed population (Mid-Ohio Valley), Stein *et al.* reported through a cross sectional design a statistically significative association of PFOS with preeclampsia. It has to be noted that this study has particular characteristics differing from the other studies included: the assessment of the outcome was self-reported; the study used the data on PFAS from the C8 project and data on pregnancy outcomes in the 5 year before enrolment; residency restrictions were used to ensure that PFOA concentrations measured at the enrolment would reflect the level at the time of pregnancy.[49]

Results for mixture of PFAS

Five studies performed mixture of PFAS analysis using BKMR or quantile based g-computation methods. Four of them did not show that plasma concentrations of PFAS mixture (including 4 to 8 PFAS) was associated with preeclampsia.[39, 41, 43, 50] One case-control study using a BKMR model (including 15 PFAS congeners) showed an association with preeclampsia.[48]

Analysis of dose response

Only 5 studies reported on a dose response analysis. Wikström et al reported on difference between Q4 and Q1 as indication for dose-response.[44] Huang et a. obtained a linear trend by treating the categorical PFAS variables as continuous variables in the regression model and concluded a dose-response pattern for PFBS.[36] Three studies used restricted cubic spline functions for modelizing the association. Starling et al. identified a weakly inversed relationship of PFNA, PFDA and PFUnDA with preeclampsia, while there was an increased association with PFHpS and possibly with PFOS.[42] Whereas Birukov et al. found no association using a comparable modeling approach,[37] the study that reported an association between preeclampsia and PFHxS also observed a significant association when applying this same modeling strategy.[38]

Table 7 – Summary of results on the association between PFAS and preeclampsia

Author (year)	Overall result	Author (year)	Overall result
Starling, 2014[42]	🔴	***Stein,** 2009*[49]	🟢 PFOS
***Wilkenström,** 2019*[44]	🟢 PFOS,PFNA	***Preston,** 2022*[41]	🔴
***Rylander,** 2020*[46]	🔴	***Begum,** 2024*[50]	🔴
***Huo,** 2020*[40]	🔴	***Thompson,** 2024*[43]	🔴
***Borghese,** 2020*[38]	🟢 PFHxS	***Cathey,** 2026*[39]	🔵
***Bommarito,** 2021*[45]	🟢 PFOS, PFDA	***Huang,** 2019*[36]	🟢 PFBS
***Birukov,** 2021*[37]	🔴	***Zhao,** 2023*[47]	🟢 PFOS, PFOA
Tian, 2023 [48]	🟢 PFOA, PFUnDA, 6:2PFESA		

🟢 Statistically significant association shown 🔴 Statistically significant association not shown
🔵 Statistically significant association shown only in specific subgroups

4.2.4.3 Consideration on pooling the evidence and review of the quality of evidence

Pooling of the evidence

- The studies identified from the meta-analysis and from our literature update yield divergent findings. Pooled estimates from the meta-analysis by Hirke *et al.* suggest a modest association between PFAS exposure (PFOA, PFOS, and PFNA) and preeclampsia, with the lower bound of the confidence interval lying close to 1.00, which is consistent with residual statistical uncertainty.[34] Since additional primary studies were identified, it is legitimate to consider undertaking a new meta-analysis based on the updated evidence base. Meta-analyses are appropriate only when the population, study design, exposure metric, and outcome definitions are sufficiently comparable. In the present case, several sources of between-study heterogeneity constitute substantive obstacles to performing a meta-analysis that would allow a reliable interpretation of its pooled estimate. In terms of outcome definition and assessment, although outcome definitions were quite consistent across studies, some applied less detailed diagnostic criteria than others (e.g., measurement of proteinuria). In addition, preeclampsia was assessed using heterogeneous methods (administrative coding, clinical confirmation, self-reporting). Most studies did not report the timing of pre-eclampsia onset and therefore did not distinguish early-onset from late-onset disease.
- In terms of the range of blood PFAS concentrations, even when concentrations appear quite similar across studies, comparability cannot be assumed for several reasons: maternal PFAS levels vary across gestation; concentrations may be modified by the haemodilution of pregnancy and reliance on a single time-point measurement may be not valid; identical concentrations of PFOA or PFOS can mask divergent mixture profiles, as PFAS are correlated. In addition, studied populations vary and similar average concentrations of PFAS do not imply comparable exposure across studies because sources of contamination may differ and environmental factors not addressed may influence both exposure profiles and risk. In that way an harmonisation of studies context and settings would therefore be required for estimating a credible overall effect in a meta-analysis.
- Recruitment of participants also differs across studies (national registries, clinical cohorts, subgroup of RCT), further limiting comparability across populations.
- PFAS measurement was performed at different gestational windows. These differences capture different periods and potentially address different pathophysiology pathways of preeclampsia, undermining comparability of exposure contrasts across studies.
- Heterogeneous metrics are reported across studies to report effect estimates (per continuous values of ng/mL, per interquartile range, per standard deviation, or on log-transformed scales, and expressed as ORs, RRs, or HR). These metrics are not directly combinable, and undertaking mathematical transformations (particularly from categorical to continuous values) without individual-level data offers insufficient assurance of accuracy.
- Adjustment covariates differed across studies. Although most analyses controlled for the main risk factors for pre-eclampsia, heterogeneity in covariate selection limits comparability and pooling effect estimates with different adjustment may compromise the validity of the combined effect.
- Some associations are observed only within particular subgroups. Pooling these effects would potentially lead to clinically relevant heterogeneity.
- Given potential interactions among PFAS and non-linear exposure-response relations, it may be questioned whether study-level estimates are directly comparable and interpreted individually. New statistical methods such as BKMR or quantile-g computation have been developed to take into account these characteristics.

Consideration on the quality of the studies

We assessed internal validity for the preeclampsia outcome using the OHAT risk-of-bias tool (see Supplement 3.2.1). The OHAT tool applies a domain-based assessment at the outcome level, with judgments expressed on a four-point scale (definitely/probably low vs probably/definitely high risk of bias):

- Cohort studies were generally of good internal validity, with most domains rated as 'probably low risk of bias'. One cohort study was rated as 'probably high risk of bias' for confounding and for outcome assessment (detection bias), because preeclampsia was partly based on self-reported outcomes.[39]
- The ancillary study from an RCT was rated as 'probably high risk of bias' in several domains: attrition (study group defined by availability of a blood sample), exposure assessment (detection bias; potential for reverse causation), and outcome assessment (detection bias; self-reported outcome recording).[50]
- For cross-sectional studies, Huang et al. (PFAS measured in umbilical cord blood) was rated as 'probably high risk of bias' for outcome assessment (detection bias), while Stein et al. was rated as 'probably high risk of bias' for confounding, attrition, and for detection bias in both exposure and outcome assessment.[36, 49]
- The case-controls studies were rated as 'probably high risk of bias' for attrition and selection domains, or detection (exposure)[45-48]

4.2.5 Certainty of evidence with GRADE

Inconsistency

The primary studies yielded inconsistent findings. Some studies reported an association between preeclampsia and some specific PFAS compound, while others did not observe any statistically significant association. Effect estimates varied across studies in both direction and magnitude (ORs ranged above and below 1.00), and this variability also differed by PFAS compound.

We should also note that studies that used mixture analyses (BKMR) did not indicate an association with preeclampsia in four studies among the five.

Accordingly, we rated down the certainty of evidence for serious inconsistency because effect estimates varied across studies, and no clear explanation for the heterogeneity in results could be established.

Risk of bias

Most evidence came from cohort studies (8/15), which were predominantly rated as probably low risk of bias across key domains, with isolated concerns in one cohort study regarding confounding and outcome ascertainment. In contrast, cross-sectional (2/15), case-control (4/15), and one ancillary analysis from an RCT (1/15) more frequently raised concerns, particularly for selection/attrition and exposure/outcome assessment. We did not rate down the certainty of evidence for the GRADE risk-of-bias domain.

Imprecision

Imprecision was not assessed since there was no pooled analysis.

Indirectness

While a minority of studies deviated from the prespecified PECO (e.g. differences in exposure measurement timing, or outcome ascertainment), the majority of studies were broadly consistent with the target PECO. Therefore, we did not rate down the certainty of evidence for indirectness.

Dose-response

Nor in the SRs nor in the primary studies a clear dose-response relationship was reported.

Magnitude of effect

No pooled effect estimate was considered for this analysis. Among studies reporting an association, the magnitude of the estimated effects was generally small (aOR <2.0).

Overall interpretation

Overall, using the GRADE approach, the certainty of evidence for an association between PFAS exposure and preeclampsia was rated as very low. Evidence started at low certainty (observational studies), and was rated down for serious inconsistency. Therefore, the available evidence does not support confident conclusions regarding either an association or no association between environmental PFAS exposure and preeclampsia.

Table 8 – GRADE assessment for preeclampsia

GRADE assessment								
No of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Magnitude of effect**	**Dose-response**	**Other considerations**	**Conclusion**
15 N= 22 963*	**Not serious.**	**Serious.** effect estimates for various PFAS compound varied across studies both positive and negative	**Not serious.** populations and outcomes were broadly applicable to the PECO	Not assessed (no pooling)	Not assessed (no pooling)	Dose-effect: inconsistent	Publication bias: Not assessed Residual confounding: Not applicable	**Very Low**

**cases 2295 and 20 667 controls*

4.3 Gestational diabetes

4.3.1 Definition of outcome 'gestational diabetes mellitus'

Gestational diabetes mellitus (GDM) is a form of glucose intolerance that is first recognized during pregnancy and is associated with increased risks for both mother and fetus (hypertensive disorders, preterm delivery, macrosomia, and the risk of developing type 2 diabetes post-pregnancy). It represents the most common medical complication of pregnancy, occurring in approximately 14% of pregnancies worldwide, with regional variability, and its incidence continues to increase globally.[51]

Diagnostic criteria recommended by the International Association of Diabetes and Pregnancy Study Groups and adopted by the WHO is a one-step approach and involves a fasting 75g oral blood glucose tolerance test (OGTT) at 24–28 weeks of gestation. The diagnosis is set when any of the following thresholds are met: fasting blood glucose ≥5.1 mmol/L, 1-h OGTT ≥10.0 mmol/L, or 2-h OGTT ≥8.5 mmol/L. In Flanders, an expert consensus guideline recommends to measure fasting glucose before 20 weeks gestation.[52] When test results indicate 95-125 mg/dL (5.3-6.9 mmol/L), the diagnosis should be made. When the test results of fasting glucose indicate < 95mg/dl (<5.3 mmol/l) women should receive a two-step approach: a 50g glucose challenge test which should be followed by a 75g OGTT

when ≥130mg/dl.[52] In case of risk factors (obesity, history of GDM), a 75g OGTT should be performed between 6-20 weeks.

Risk factors include elevated pre-pregnancy BMI, advanced maternal age, a history of GDM, and certain metabolic or family-history profiles.

4.3.2 Key points

- The certainty in the effect of PFOA on gestational diabetes mellitus (GDM) is moderate, and low for PFNA and PFDA. For other PFAS, the confidence level is very low.
- Our analysis is primarily based on a good quality SR (Quan 2026) reporting on consistent findings for PFOA in pooled data for different exposure assessments (10 studies pooled for categorical and 14 studies for logarithmic increase) as well as a linear dose-response relationship for PFOA. For other PFAS there was less consistency and more imprecision.
- Significant associations between PFNA and PFDA and GDM were identified exclusively in analyses where PFAS exposure was expressed as ln-increment increases.
- However a recent publication by Starling et al. including 5 229 pregnant women in the United States (the largest cohort to date)—examining individual PFAS exposure as well as mixture PFAS did not identify a significant association with GDM (even protective effect for PFOA and other PFAS congeners). In this study the PFAS measurement and outcome assessment were done closely together during pregnancy and the authors found that the timing of exposure measurement influenced the observed association (possible influence of physiologic changes during pregnancy with greater plasma-volume expansion and slightly lower PFAS concentrations). Given the possible risk of bias for this study we did not rate down for inconsistency.

4.3.3 Results of systematic reviews

The literature search identified four SRs (as shown in Table 9).[16, 53-55] The most recent (search date February 2025), most complete SR with a good quality was Quan et al 2026, including 21 unique studies on the outcome GDM, and reported also on OGTT results as separate outcome (see Table 9).

Table 9 – Systematic reviews and meta-analyses on gestational diabetes mellitus

Systematic review	Included primary studies	Reported Result	Remark	Quality appraisal (AMSTAR)
Quan 2026[16]	In total 28 unique studies Outcome GDM diagnosis: 21 studies • Zhang 2015 (USA) • Shapiro 2016 (Canada) • Matilla Santander 2017 (Spain) • Valvi 2017 (Denmark) • Wang 2018 (China) • Wang 2018 b (China) • Liu 2019 (China) • Rahman 2019 (USA) • Preston 2020 (USA) • Xu 2020 (China) • Yu 2021 (China) • Xu 2022 (China) • Huang 2023 (China) • Peterson 2023 (USA) • Trowbridge 2023 (USA) • Zhang 2023 (China) • Zhang 2023 b (China) • Mao 2024 (China) • Qi 2024 (China) • Soomro 2024 (Canada) • Yang 2024 (China)	*ln-transformed stable and significantly positively associated with the risk of GDM* • *PFOA, OR = 1.23 (95 % CI: 1.15–1.32)* • *PFNA, OR= 1.24 (95 %CI: 1.14–1.34)* • *PFDA, OR= 1.19 (95 %CI: 1.12–1.26)* *Highest versus lowest* • *PFOA, OR = 1.70 (95 % CI: 1.34–2.16)* • *PFNA, OR= 1.16 (95 %CI: 0.77–1.73)* • *PFDA, OR= 1.16 (95 %CI: 0.85–1.59)* *Dose-response: Only PFOA showed linear positive association with GDM risk, Compared with no exposure, ORs were 3.00 (95 % CI: 1.11–8.09), 5.05 (95 % CI: 1.33–19.23), and 6.19 (95 % CI: 1.51–25.46) at concentrations of 5, 10, and 15 ng/mL PFOA* *findings **suggest** that prenatal PFAS exposure increased the risk of GDM and may selectively affect postprandial glucose regulation rather than basal glucose homeostasis*	OR, HR, or RR reported in log2 or log10 scales were converted to ln-unit changes Pooling is done separately three types of OR for GDM: • Per ln increase (logarithmic) • Per ng/ml unit increase (absolute) • Highest Q4 vs lowest Q1 (categorical)	No critical limitations

Systematic review	Included primary studies	Reported Result	Remark	Quality appraisal (AMSTAR)
Wang 2025[55]	12 studies included • Zhang 2015 (USA) • Wang 2018 (China) • Yu 2021 (China) • Xu 2020 (China) • Shapiro 2016 (Canada) • Zhang 2023 (China) • Xu 2022 (China) • Matilla-Santander 2017 (Spain) • Valvi 2017 (Denmark) • Zhang 2023 b(China) • Liu 2019 (China) • Preston 2020 (USA)	Result for association in multivariate analysis based on 8 studies **PFOA:** *aOR for high level exposure 1.625 (95%CI 1.282, 2.06)* *aOR for increased exposure per SD 1.289 (1.057,1.571)* **PFOS:** *aOR for high level exposure 1.213 (0.949,1.549)* *aOR for increased exposure per SD 1.001 (0.902, 1.111)* **PFBS:** *aOR for high level exposure 1.349 (95%CI 0.982, 1.853)* subgroup analysis showed that only Chinese studies showed association *"high levels of PFOA and PFBS had significantly increased risk of GDM with ORs of 1.513 and 1.436"*	Pooling is done separately • for SMD (comparing how much SD higher concentration in cases and controls are) • for OR High exposure level • for OR for increased exposure per SD Rahman 2019 not included	Critical limitations
Pang 2024[53]	12 studies • Liu 2019 (China) • Matilla-Santander 2017(Spain) • Preston 2020 (USA) • Shapiro 2016 (Canada) • Trowbridge 2023 (USA) • Valvi 2017 (Denmark) • Wang 2018a (China) • Wang 2018b • Xu 2020 (China) • Yu 2021 (China) • Zang 2023 (China) • Zhang 2015 (USA)	Pooling 11 studies for PFOA: OR = 1.45 (95%CI: 1.07–1.94) 11 studies for PFHxS: OR = 1.16 (95%CI: 1.00–1.36) 4 studies for PFBS: OR = 1.44, (95% CI: 1.16–1.79) 2 studies for PFHpA: OR = 1.41 (95%CI: 1.10–1.82)	Pooling is done highest versus lowest exposure(categorical) Adjusted risk estimates. Subgroup analysis shows heterogeneity based on study type, region and sample size For PFOA and PFHxS: Only pooling from 7 Asian studies show significant association (not the 4 non-Asian), only the 5 case	No critical limitations

Systematic review	Included primary studies	Reported Result	Remark	Quality appraisal (AMSTAR)
		No significant association was observed between exposure to PFOS, PFNA, PFDA, PFUnDA, PFDoA, and GDM	control studies and only the 5 studies with sample size < 1000 Rahman 2019 (USA) not included because	
Yao 2023[54]	13 studies on PFAS • Zhang 2015 (USA) • Shapiro 2016 (Canada) • Matilla-Santander 2017 (Spain) • Valvi 2017 (Denmark) • Wang 2018 (China) • Wang 2018 b (China) • Liu 2019 (China) • Rahman 2019 (USA) • Xu 2020 (China) • Preston 2020 (USA) • Li 2020 (China) • Yu 2021 (China) • Xu 2022 (China)	Pooling 13 studies for PFOA: OR 1.19 (0.99-1.43) 13 studies for PFOS: OR 1.10 (0.91,1.33) 10 studies for PFHxS: OR 0.95 (0.74,1.33) 10 studies for PFNA: OR 1.06 (0.91,1.22) Pooling all together: OR=1.10 (1.01,1.19) Sensitivity analysis shows large impact of Xu 2022 Subgroup analysis shows that only Chinese studies have statistical significant association no dose-response relationship was found. *Meta-analysis result indicate PFAS exposure was associated with higher risk of GDM. Additional high quality large sample prospective studies are needed*.	When the pooled effects are presented per PFAS molecule, none of the associations is significant. It is only when they pool the different PFAS molecules with a random effect model it becomes borderline significant. But this pooling of all individual PFAS compounds into one summary is not opportune.	Critical limitations

Quan et al. identified 21 studies exploring the association between prenatal PFAS exposure and risk of GDM. Twelve Chinese studies, five from US, two from Canada, one from Denmark and one from Spain. The median exposure to PFOA in the included studies ranged from 0.76 ng/ml (in a US study) to 11.56 ng/ml (in Chinese study), and for PFOS from 1.30 ng/ml (US study) to 27.2 ng/ml (Denmark). This relates to environmental (background) exposure, i.e. no specific studies on elevated exposure due to occupational or contaminated zones. Most studies adjusted for potential confounding factors such as age, BMI, education, and parity. The pooling in *Quan 2026* was done per individual PFAS and separately for studies reporting OR per incremental increase on logarithmic scale (per ln-unit increase), absolute scale (per ng/ml unit increase) and categorical scale (highest versus lowest quartiles).

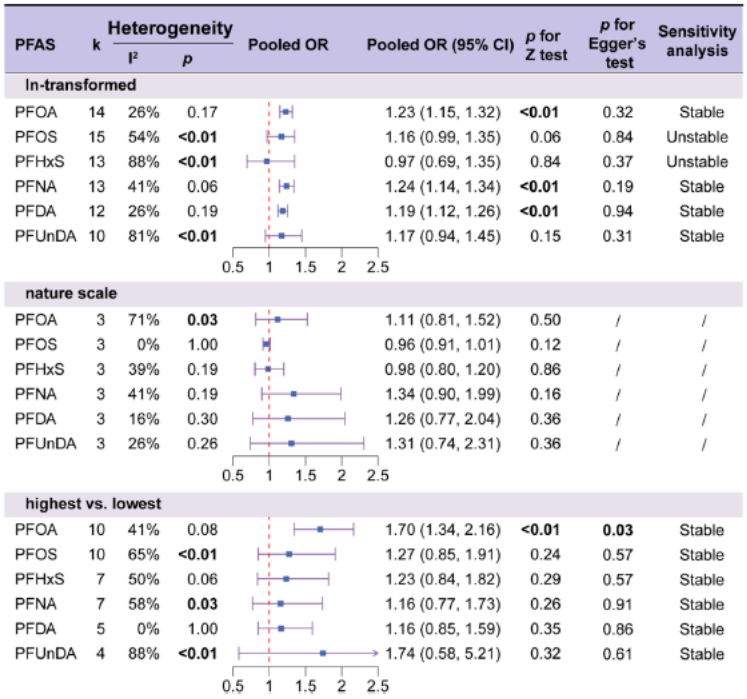
There was a statistically significant association for PFOA both for logarithmic increase (n= 14 studies: OR=1.23, 95%CI: 1.15,1.32) and in the categorical analysis of high versus low exposure (n= 10 studies: OR=1.70, 95%CI: 1.34, 2.16). Such association was not retrieved for the absolute increase but that could be explained by the small number of studies (n=3). Sensitivity analysis (leave one out) showed that for PFOA the result was stable. For PFNA and PFDA stable significant associations were reported only for logarithmic increase, respectively OR=1.24 (95%CI 1.14,1.34) and OR= 1.19 (95%CI 1.12,1.26) (see Figure 3).

Oftentimes, region based subgroup analyses reveal significant difference between China and Western countries, as also evidenced in the several other SRs.[53-55] However, in Quan, the subgroup analysis per region showed that for PFOA both Chinese studies (n=8) and Western studies (n=6) had a significant association with GDM for logarithmic increase, OR 1.27 (95%CI 1.13,1.44), and 1.21 (95%CI 1.11, 1.32) respectively. But this was not significant in Western studies with PFOA exposure as a categorical variable (OR 1.03 (95%CI 0.68, 1.57).

Subgroup analysis per study design showed that in the 8 case-control studies the significant association with GDM risk and increasing PFOA exposure remained (OR=1.27, 95%CI 1.18,1.37), but not in the 5 cohort studies (OR=1.11, 95%CI 0.92,1.34) or the cross-sectional study (OR=1.01, 95%CI 0.76,1.34). This heterogeneity by study design was also noted in meta-analyses of *Pang et al*.[53]

Quan et al. also reported a linear positive dose-response relationship for PFOA based on a meta-analysis of studies reporting effect estimates at fixed exposure percentiles (10th, 50th, and 90th percentiles of the PFAS concentration distribution) which translated for PFOA into of 5,10, and 15 ng/ml.

Figure 3 – Meta-analysis for pooled estimate OR for gestational diabetes mellitus as reported in Quan 2026[16]



Note: k denotes the number of study data included, fourteen using log-transformed and three using nature scale, five reported OR for both log-transformed and categorized PFAS variables, while only four categorized variables, and one provides OR in first trimester and second trimester, respectively. The red dashed line indicates OR= 1, with the blue squares symbolizing the pooled estimate of β, and the purple line across the blue squares represents 95 % CI, the arrow indicates that the upper confidence limit extends beyond the x-axis

4.3.4 Certainty of evidence with GRADE

Inconsistency

The evidence from the good quality SR indicated that for PFOA a consistent significant association with increased GDM was observed when pooling the data for continuous exposure (14 studies on ln-unit-increase) as well as on categorical exposure (10 studies). As the SR by Quan did not report effect sizes on individual study level we could not assess inconsistency of individual studies, though there was a certain level of heterogeneity when considering study design (only significant associations in case-control, and not in cohort studies).

Although we did not conduct an update of the SR by Quan et al. because of its recent search (February 2025), we did identify a newly published cohort study—the largest to date, including 5 229 pregnant women in the United States—examining individual PFAS exposure as well as mixture PFAS.[56] This study reported no significant association with PFAS, even a negative association between PFOA exposure and GDM prevalence, and a negative association between the 6-PFAS mixture and GDM prevalence (see Table 10). These results did not change in the different sensitivity analyses, indicating robustness. No linear or non-linear dose–response relationship was detected when PFAS concentrations were modelled in quartiles. The authors suggested that PFAS levels in the ECHO cohort may have been too low to reveal an association. The overall median PFAS concentrations of women enrolled between 1999 and 2021 (PFOA 1.1 ng/ml and PFOS 3.41 ng/ml) were similar to those reported in US representative sample of women in 2011-2018.

The OHAT quality assessment indicated that there is a probably high risk for confounding as previous GDM diagnosis was not considered (see supplement 3.2.2). Moreover the exposure and outcome

were measured very closely together, and it was not always clear whether the diagnosis of GDM was before or after PFAS measurement, indicating a possible high risk for detection bias. The authors also noted that the timing of serum PFAS measurement during pregnancy may influence study findings. In a sensitivity analysis restricted to PFAS measurements obtained before 24 weeks of gestation, the inverse associations were attenuated toward the null. One proposed explanation was that GDM might be associated with greater plasma-volume expansion later in pregnancy, which could lead to slightly lower measured serum PFAS concentrations. The recent study by Starling contrasts with the pooled estimate for PFOA reported by Quan, and thus increases the overall uncertainty in the evidence base, though we did not downgrade for inconsistency because pooled estimate showed low heterogeneity (I^2=26%).

Table 10 – Recent identified primary study on gestational diabetes mellitus[56]

	Study details	Result	Quality assessment (OHAT)
Starling 2026 [56]	5 229 singleton pregnant women from 16 cohorts in USA (ECHO Cohort consortium) Exclusion of women with diabetes outside pregnancy (but no exclusion of women with previous GDM diagnosis) 383 with GDM and 4 846 without 14 PFAS measured during pregnancy 2nd trim (1999–2021) Outcome: self-report or medical diagnosis of GDM Analysis generalized estimating equation (GEE) models fit with a Poisson distribution (prevalence per doubling of each PFAS concentration) Mixture: quantile- based g-computation	In single-pollutant models, prevalence ratios generally did not differ from the null, except for the association between PFOA and GDM, which was negative (prevalence ratio [PR] 0.92; 95% CI 0.86, 0.98 per doubling in PFOA) The six-PFAS mixture was negatively associated with the prevalence of GDM (PR 0.75; 95% CI 0.58, 0.96)	Most domains indicate low risk of bias. Only for confounding bias it may be probably high because previous GDM diagnosis was not considered as confounder. The exposure and outcome were measured very closely together (during pregnancy) sensitivity analysis restricted to PFAS measurements before 24 weeks of gestation, negative results were closer to the null, suggesting a possible bias due to reverse causality in the main results Lack of data on timing of GDM diagnosis, and thus not possible to conclude whether PFAS measured before or after diagnosis.

Risk of bias assessment

The risk of bias assessment in Quan was based on the NOS scale, with all studies indicating low risk of bias.

Indirectness

The populations and outcomes were broadly applicable to the PECO.

Imprecision

There was no noted imprecision for the pooled estimate for PFOA. Pooled effect size for PFOA did not include null-effect and CI were narrow when expressed in ln-increase. Similarly for PFNA and PFDA there was no noted imprecision when PFAS was expressed in ln-increase. For other PFAS there was imprecision, for which downgrading was opportune.

Publication bias

No publication bias reported by the SR Quan 2026

Dose-response

The SR Quan 2026 reported a linear dose-response relationship for PFOA, which warrants upgrading the evidence.

Magnitude of effect

In terms of effect sizes, the pooled OR of 1.23 relates to a 23% (95%CI 15% to 32%) higher odds relative to baseline when the PFOA concentration is increased by 2.7 times (~RR of 1.19). Expressed in absolute terms, this corresponds to an increase in risk from a baseline probability of 14% to an estimated 16.7%. When considering the categorical exposure, a 70% higher odds (95%CI 34% to an 116% increase) of GDM was noted when highest exposure was compared against lowest exposure. We did not rate up for magnitude of effect.

Table 11 – GRADE assessment for gestational diabetes

GRADE assessment								
No of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Magnitude of effect**	**Dose-response**	**Other considerations**	**Conclusion**
21 **(n= 16 212 women)** ***(in SR Quan 2026)***	Not serious.	Not serious.	Not serious.	PFOA: Not serious PFNA, PFDA: Not serious **Other PFAS: Serious**	PFOA: No large effect size	PFOA: linear dose response relationship	No Publication bias reported Residual confounding: Not applicable	**PFOA: Moderate** **PFNA and PFDA: low** **PFOS and other PFAS: very low**
+1 cohort[56] ***(n= 5 229)***	Possible risk of bias	Increases inconsistency because 'protective' effect of PFOA, and other PFAS						

4.4 Miscarriage

4.4.1 Definition of the outcome 'miscarriage'

"Miscarriage" or "spontaneous abortion" is generally defined as the loss of an intrauterine pregnancy before viability. Although the definitions and allocated timeframe of miscarriage or spontaneous abortion vary, it is generally from 6 to 20 weeks (after that timeframe it is considered stillbirth and before that timeframe it is considered biochemical pregnancy loss). The European Society of Human Reproduction and Embryology states that it is loss before viability (around 22-24 weeks).[57] The term Recurrent Spontaneous Abortion (RSA) is used when two or more consecutive miscarriages occur, although some guidelines define it as three or more.[58]

Approximately 15 % of pregnancies confirmed at medical facilities end in miscarriage.[59]

4.4.2 Key points

- Overall, the certainty of evidence on the effect of PFAS on miscarriage was rated very low, due to inconsistency across studies, as well as a *probably high risk of bias* in most studies.
- This high risk of bias was due to confounding by reproductive history, i.e. past miscarriage both influences the chance of subsequent miscarriage, and can also lower the PFAS concentration in the blood. This also points to the importance of timing of the PFAS measurement as PFAS concentration decreases with each miscarriage and birth, and measuring PFAS after the miscarriage may misleadingly suggest that women who miscarried had lower PFAS exposure.
- Although the evidence base is relatively large (n=13 studies) marked heterogeneity in outcome definitions, exposure assessment methods, and covariate adjustment strategies prevented meaningful pooling of results.
- Most studies reported an association with at least one PFAS compound, but the specific PFAS implicated were not consistent across studies. Four studies reported no significant associations, and some even observed inverse (protective-appearing) associations.
- More recent analyses using PFAS mixture models also failed to demonstrate a consistent pattern of association with miscarriage.
- Future research should focus on prospective cohorts with pre-conceptional sampling, and detailed reproductive history (stratified for nulligravid).

4.4.3 Results of systematic reviews

The umbrella search identified six SRs that reported on miscarriage (see supplement 2.2). We focused on the two most recent SRs (the other four had a search date before 2021[60-62]).

Table 12 shows characteristics of the two most recent SRs.[63, 64] None of the two analysed SRs and MA were rated as high quality (according to AMSTAR-2 – see table and details in supplement 3.1.4). For PFOA, Haimbaugh indicated a weakly increased odds for miscarriage,[63] while the other SR by Liu did not report any association with PFOA.[64] In Haimbaugh the conclusion of an association was based on a narrative reporting of two of the three included studies.[65, 66] Haimbaugh limited the inclusion of primary studies to those with low risk of bias, which resulted in including only three studies.[65-67] However, there was no transparency on this selection process. Liu et al included nine studies, and generated pooled odds ratios for each individual PFAS, integrating estimates based on heterogeneous exposure contrasts, including categorical comparisons and continuous measures on a logarithmic scale. Across these pooled analyses, they did not report any significant association of any individual PFAS with miscarriage.[64] However, when they pooled all individual PFAS into one pooled estimate they did report on a significant association. However this pooled estimate is very difficult to interpret because several individual odds ratios are derived from overlapping study populations, reducing the independence of the data.

The quality of the SRs necessitates cautious interpretation of their findings. The literature was updated through an analysis of primary studies.

Table 12 – Systematic reviews and meta-analyses on miscarriage

Systematic review	Included primary studies	Result	Remark	Quality appraisal (AMSTAR)
Haimbaugh 2024[63]	• Liew 2020 (Denmark) • Wang 2021 (China) • Wikstrom 2021 (Sweden)	Narrative *In sum, there is weak or no evidence for an association between most PFAS and miscarriage. In two of the three studies, PFOA was associated with weakly increased odds of miscarriage, especially in parous women*	Only included studies with a low risk of bias (as assessed by NOS). But not clear why some studies were not considered	Critical limitations
Liu 2024[64]	• Stein 2009 (USA); • Darrow 2014 (USA) • Jensen 2015 (Denmark); • Louis 2016 (USA); • Liew 2020 (Denmark); • Wikstrom 2021 (Sweden); • Wang 2021 (China) • Nian 2022 (China) • Mi 2022 (China)	Pooling *Positive correlation of maternal PFAS exposure and miscarriage (OR 1.09, 95%CI 1:00-1.19)*	When the pooled effects are presented per PFAS molecule, none of the associations is significant. It is only when they pool the different PFAS molecules with a random effect model it becomes borderline significant. This statistical method to provide an overall summary PFAS statistic is not the best way to pool the data.	Critical limitations

4.4.4 Results of primary studies

On 21 April 2026 we performed a search for primary studies published after those included in the existing SRs (see supplement 1.2.2). We identified five additional studies—three from China,[68, 69,19] one from Japan,[70] and one from Norway.[71] Together with the studies identified in the SRs, the total of primary studies was 15, of which 13 reported effect estimates.

4.4.4.1 Characteristics of the primary studies

Of the 15 identified primary studies, four were cohort studies,[65, 67, 72, 73] 2 cross-sectional[49, 74] and 9 (nested) case-control studies.[19, 66, 68-71, 75-77] Overview of characteristics and results of primary studies in supplement 4.2.

The most recent studies were conducted in China (6/15),[19, 67-69, 76, 77] one in Japan,[70], a very recent study from Norway,[71] one from Sweden,[65] three from Denmark,[66, 74, 75] and three from the USA.[49, 72, 73]

In terms of population, six studies were conducted in the framework of a birth cohort (Odense child cohort[75], US LIFE cohort[73], national Danish birth cohort[66], Swedish SELMA cohort,[65] Japan Environment and Children's study, [70] Norwegian Mother, Father and Child Cohort Study[71]), while Chinese studies were conducted in the context of a reproductive hospital,[19, 68, 69, 76, 77] and one study recruited infertile women undergoing IVF treatment.[67] There were two studies including the same population with higher PFOA exposure near the DuPont facility.[49, 72] Because Stein conducted a cross-sectional analysis and Darrow performed a more recent analysis, our discussion prioritized the latter as the most up-to-date evidence.

There is a clear difference in outcome definitions. While some studies reported on miscarriage in general (before 24 weeks of gestation,[68], before 22 weeks,[71, 75] before 21 weeks,[73] before 20 weeks[72], 'in first trimester',[65]), some focused on early miscarriage (before 12 weeks,[69] or preclinical abortion[67]), while two reported on late miscarriage (12-22 weeks)[66, 70]. Two Chinese studies focused on recurrent spontaneous miscarriage.[19, 77]

In term of exposure measurement, most of the time the same legacy PFAS (PFOA, PFOS, PFNA, PFDA, PFHxS) were measured in women's blood. Some studies also investigated a larger range, including newer PFAS (Mi 2022-32 PFAS, Wang 2024–30 PFAS, Liu 2025-25 PFAS, Tatsuta 2025-28 PFAS and Nian 2022-35 PFAS). More than half of the women were pregnant during the PFAS measurement (Jensen 2015, Liew 2020, Wikström 2019, Wang 2024, Tatsuta 2025, Mi 2022, Grindstad 2026), and in the other half the measurement was pre-conception (Liu 2025, Darrow 2014, Louis 2016, Wang 2021). A cross-sectional study measured PFAS after miscarriage had occurred and concluded that levels of most of the PFAS in the pregnant women's serum decreased with more (≥2) previous miscarriages.[74] This points at the importance of timing of PFAS measurement and risk of reverse causation, as well as the importance to adjust for reproductive history.

To report the strength of the association, eleven studies reported adjusted odds ratio, while one study provided adjusted hazard ratio,[73] and one study adjusted relative risk.[67] Liu et al performed a PFAS environment-wide association study.[68] Eight studies assessed the impact of a mixture of PFAS on the association with the outcome, using methods previously described (e.g. BKMR).

Comparison of effect measures is difficult as different exposure scales were used to express the incremental increase (see supplement 4.2). Not all studies reporting continuous exposure used the same scale: the majority reported the OR per ln increase[68, 72, 75] or per doubling[65, 66, 71] which is somewhat comparable. Wang 2024 and Tatsuta 2025 reported an OR per 10 fold increase, and Louis et al 2016 per standard deviation increase. Some studies only reported on a categorical exposure scale: Wang 2021 and Mi 2022 compared high versus low exposure with the median as cutoff.

Important aspect in interpreting the effect measure is whether confounders were taken into account. Most studies had adjusted effect measures. In addition to age, reproductive history is an important factor to consider when discussing risk/odds of miscarriage. Parity is often considered in adjusted analyses or stratified for (except not in Liu 2025, Wang 2021). Moreover stratified analyses showed in some studies that the association was only present in parous women and not in nulliparous women (Liew 2020 and PFOA, and Wikstrom 2021 with PFOA), while in others it was only present in primipara (Darrow 2014 and PFOA). In addition to parity, also the info on previous miscarriages is important as they are associated with increased miscarriage risk, while at the same time they can lower a women's PFAS level.[72, 74] Therefore it is crucial for a study to perform stratified analysis on gravidity, or to only select nulliparous women with no miscarriage history in both case and controls (nulligravid women). Some studies performed sensitivity analyses only including women with no history of previous miscarriages (nulligravid).[70, 72] In the Norwegian study by Grindstad, only nulliparous women from a pregnancy cohort were included to account for reproductive history.[71] However, because miscarriage was assessed retrospectively among women who were currently pregnant, those who experienced a miscarriage and did not have a subsequent pregnancy were not captured. Some studies did consider parity but no previous pregnancy loss (Jensen 2015),[75] others used previous pregnancy loss as an exclusion criterium in the control group, and as an inclusion criteria in the cases (Liu 2025),[68] and another study adjusted for gravidity but not parity (Nian 2022).[77]

Considerations on the quality of the studies

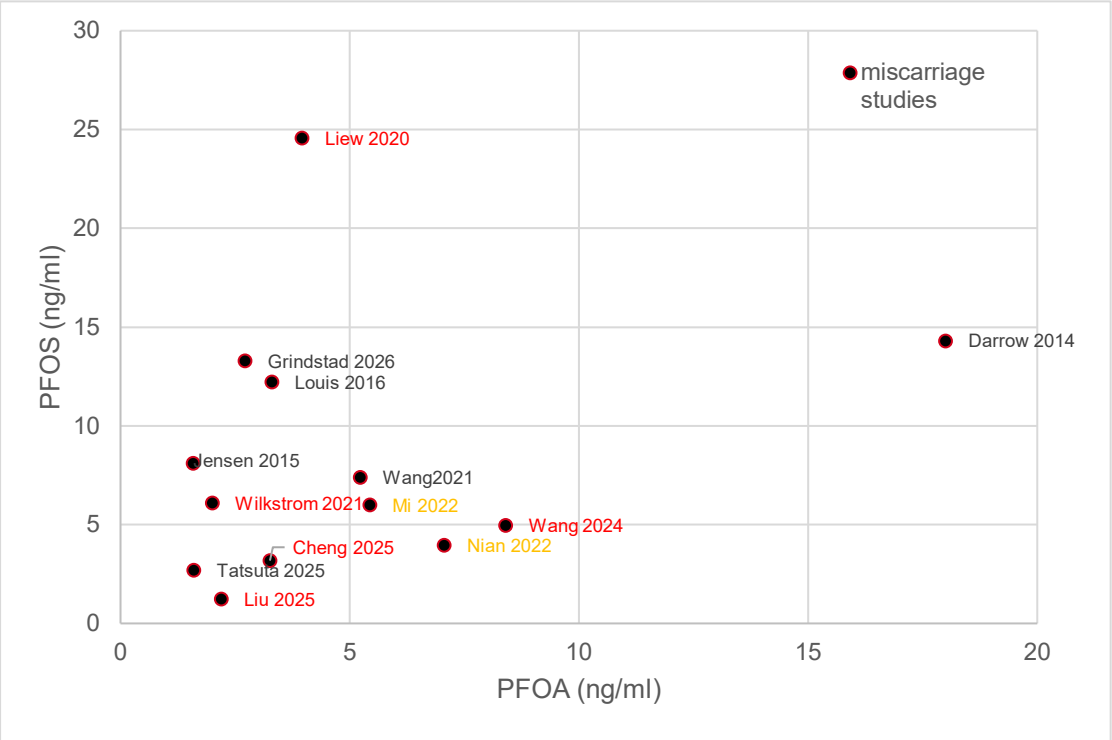
OHAT risk of bias assessments are available in supplement 3.2.3. All studies performed complete-case analysis (only inclusion of individuals with complete exposure and outcome data). For example in a large birth cohort, only those with both PFAS blood concentrations and information on the outcome were included. However, with miscarriage as outcome it is plausible that individuals with this outcome leave the birth cohort or do not join a birth cohort and introduce selection bias. Selection bias was present in studies applying different inclusion and exclusion criteria among cases and controls (exclusion of recurrent miscarriages only in the cases in Wikstrom 2021, while exclusion of previous miscarriage only in the controls in Liu 2025, excluding women with no subsequent successful pregnancy in Grindstad 2026), or when the control group was drawn from a particular population (in Wang 2024 and Cheng 2025 the controls were women searching for pregnancy termination, in Nian 2022 the control group were those with at least 1 live birth).

Confounding due to reproductive history is important to consider. Therefore, the studies that performed a stratified analysis for those women with no prior pregnancy or no prior miscarriages were considered the lowest risk of bias for confounding by reproductive history.[70-72] Moreover these studies were the studies that did not report significant associations between PFAS and miscarriage.

Residual confounding cannot be ruled out, especially when there is the risk of confounding by co-exposure (the case in specific contamination zones, industry, occupation, Darrow 2014). In none of the studies, other pollutants such as heavy metals, pesticides, etc were taken into consideration.

There is a low risk of detection bias. All studies except three (Darrow 2014, Louis 2016, Grindstad 2026) have the outcome confirmed by clinical diagnosis/clinical record. Most studies use the same method or timing of PFAS blood concentrations in both the cases and controls (except Wang 2024, Cheng 2025, Nian 2022, and Grindstad 2026).

Figure 4 – PFOS and PFOA concentrations in the primary studies on miscarriage



The concentration expressed are medians (ng/ml). The studies indicated in red are those that identified a significant association with either PFOS or PFOA. The studies indicated in orange did not identify a significant association with PFOS or PFOA, but with at least another PFAS compound.

4.4.4.2 Main results of primary studies

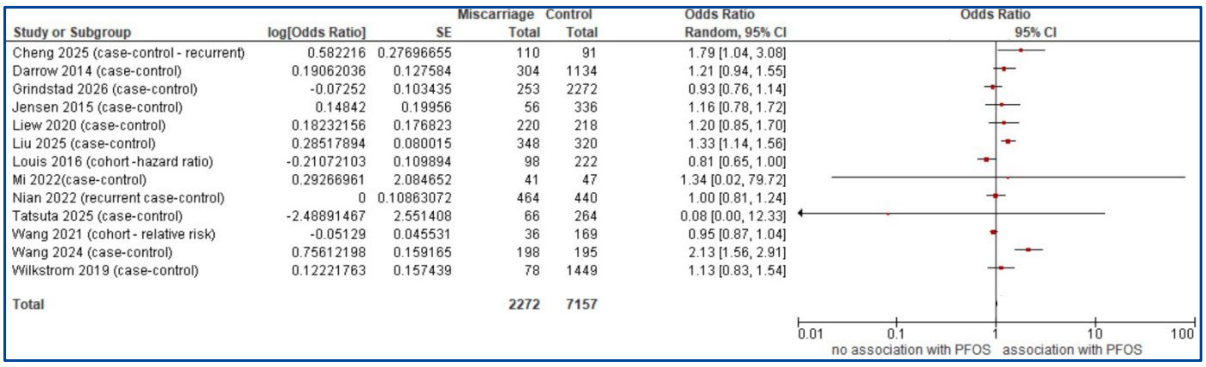
Results for PFAS individual analysis

The results of the primary studies show **non-consistent findings**. Four studies concluded that none of the PFAS examined show a significant association (Grindstad 2026, Tatsuta 2025, Wang 2021, Louis 2016), while nine studies identified an association with some types of PFAS, in some subgroups.

- In the cohort near the US Dupont facility PFOA was borderline associated with miscarriage in a subgroup of nulligravid women at enrolment, and PFOS in the subgroup of first pregnancy after enrolment (not specifically nulligravid or primipara).[72]
- In the Danish Odense child cohort a significant association was reported for PFNA and PFDA (not for PFOS and PFOA).[75]
- In the nested case control in the Danish birth cohort a borderline significant association with PFOA in continuous analyses (per log2-unit increase) as well as in categorical analyses (Q4 versus Q1), and borderline for PFHpS.[66] Stratified analysis on parity showed that PFOA was only significant in parous women.
- The Swedish cohort identified a statistical significant association with PFOA in continuous analyses (per log2-unit increase), but not in categorical analysis. Similarly the stratified analysis on parity indicated only significant association with PFOA in parous women.[65]
- The small case-control study in a Beijing hospital indicated a significant association with PFDA and PFUda when exposure was higher than the median.[76]
- A nested case-control study within a cohort from a Chinese reproductive center applied an environment-wide association study (EWAS) framework and identified statistically significant associations between six PFAS compounds and the outcome per log-unit increase in exposure. In this particular analysis parity was not adjusted for.[68]
- The case control in a Shanghai centre on the particular outcome of 'missed miscarriage' showed significant association with 13 PFAS, with higher odds in nulligravid. For this particular outcome PFAS was measured after miscarriage had occurred but prior to uterine evacuation.[69]
- On the particular outcome of *recurrent miscarriage* a Chinese case control study identified a significant association with PFAS alternative HFPO-DA (GenX) in continuous and categorical analysis,[77] while another Chinese study on this outcome identified associations with PFBA and PFDoDA in both continuous and categorical analysis, and for PFOS, PFHpS, and PFNA, only in continuous analysis (per ln unit increase).[19] In both studies the exposure was measured after the outcome.

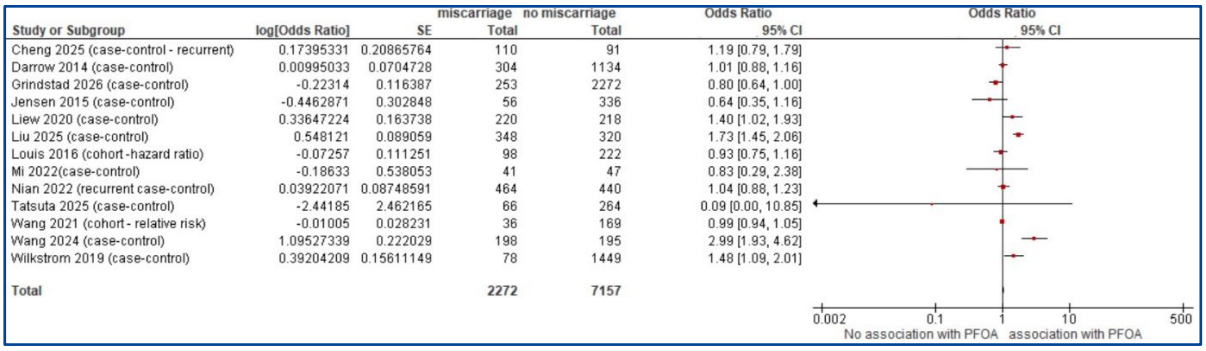
Figure 5 and Figure 6 show the effect measures for PFOS and PFOA as reported in the primary studies. Most of the ORs in the figures express a continuous exposure, i.e. ln or log2-increase (no rescaling or transformation was done). Among the 13 primary studies, two recent Chinese studies[68, 69] showed a statistically significant association with PFOS and PFOA. Another Chinese study focused on *recurrent miscarriages*, and reported a significant association with PFOS.[19] The exposure profiles differed: in Wang 2024, PFOA concentrations (not PFOS) were moderately higher than those observed in most other studies, whereas Liu and Cheng reported comparatively lower exposure levels than the broader evidence base (see Figure 4). Figure 5 and 6 show that some studies suggest 'protective effects' of PFOA and PFOS.

Figure 5 – PFOS descriptive forest plot without pooling



OR are those reported in the primary study (no rescaling nor transformation); Stein 2009 not shown as the population has been included in Darrow 2014. Bjerregaard-Olesen not shown as the study did not provide an effect estimate. 95% CI of Tatsuta 2025 shows 0 but this is due to rounding.

Figure 6 – PFOA descriptive forest plot without pooling



OR are those reported in the primary study (no rescaling nor transformation); Stein 2009 not shown as the population has been included in Darrow 2014. Bjerregaard-Olesen not shown as the study did not provide an effect estimate. 95% CI of Tatsuta 2025 shows 0 but this is due to rounding.

Dose-response analysis

Five studies reported on a dose-response analysis. Wikström reported on an indication of a monotonic dose response association for PFOA.[65] Liew concluded that the quartile analysis showed monotonic dose-relationship for PFOA and PFHpS.[66] Two studies performed restricted cubic spline analysis, and failed to show non-linear associations.[76, 77] Two studies reported that the visualisation of the BKMR shows a dose-response relationship.[19, 69]

Table 13 – Overview of reported associations with individual PFAS in primary studies on miscarriage

Study	Results
Grindstad 2026 (Norway)[71]	
Tatsuta 2025 (Japan)[70]	
Liu 2025 (China)[68]	PFPeS, PFOA, PFOS, PFNA, PFHxS, PFPeA (but not when stratified per age)
Wang 2024 (China)[69]	PFOA, PFNA, PFDA, PFOS, PFUdA,
Mi 2022 (China)[76]	PFDA, PFUda
Wikstrom 2021 (Sweden) [65]	PFOA (only statistical significant in parous women)

Study	Results
Wang 2021 (China) [67]	
Liew 2020 (Denmark) [66]	PFOA (only statistical significant in subgroup parous women)
Louis 2016 (USA) [73]	Suggesting protective effect
Jensen 2015 (Denmark) [75]	PFNA, PFDA
Darrow 2014 (USA) [72]	PFOA Only in primipara, PFOS in subgroup of first pregnancy after enrolment
Cheng 2025 (China) [19]	Recurrent miscarriage - PFBA, PFDoDA, PFNA, PFOS
Nian 2022 (China) [77]	Recurrent miscarriage – HFPO-DA (GenX)

Red - no statistical significant association with any PFAS in the study, green – statistical significant association, blue – only significant association in certain subgroup

Results for mixture of PFAS

Eight studies, mainly the more recent ones, performed mixture analyses (see Table 14). The results were inconsistent, with three studies reporting an association between PFAS mixture and miscarriage risk,[66, 69, 76] while five did not.[19, 67, 70, 71, 77]

Table 14 – Overview of mixture analyses in primary studies on miscarriage

Study	Results + mixture method used
Grindstad 2026 (Norway) [71]	quantile-based g-computation
Tatsuta 2025 (Japan) [70]	BKMR
Liu 2025 (China)[68]	No mixture analysis
Wang 2024 (China) [69]	BKMR indicates PFOA and 1m PFOS as predominant components
Mi 2022 (China)[76]	Principal component analysis (PFOS substitutes and perfluoroalkyl carboxylic acids)
Wikstrom 2021 (Sweden) [65]	No mixture analysis
Wang 2021 (China) [67]	BKMR
Liew 2020 (Denmark) [66]	Weighted Quantile Sum Regression
Louis 2016 (USA) [73]	No mixture analysis
Jensen 2015 (Denmark) [75]	No mixture analysis
Darrow 2014 (USA) [72]	No mixture analysis
Cheng 2025 (China) [19]	quantile-based g-computation, Weighted Quantile Sum Regression BKMR
Nian 2022 (China) [77]	quantile-based g-computation, BKMR

The red indicates there is no association of the mixture with the outcome reported. BKMR: Bayesian Kernal Machine Regression, EWAS: Environment-Wide Association Study

4.4.5 Certainty of evidence with GRADE

Inconsistency

Nor the analysis of individual PFAS nor the mixture analyses showed consistent findings (see Table 13 and Table 14). The PFAS analyses showed indications of harmful as well as protective effects. Accordingly, we rated down the certainty of evidence for serious inconsistency.

Risk of bias

Given the importance of confounding by reproductive history, and possible risk of selection bias, resulting in more than half of the studies having a probably high risk of bias in more than one domain (7/13), we downgraded for risk of bias.

Indirectness

There are some studies focussing on a dedicated population, for example women visiting reproductive hospitals, a study on IVF, and studies on recurrent spontaneous abortion (all Chinese studies). However we did not rate down for this GRADE domain as this population was also considered relevant.

Imprecision

As we did not perform a pooling there is no single risk estimate to judge imprecision.

Dose-response

There was no consistent reporting on a dose-response relationship.

Magnitude of effect

No pooled effect estimate was considered for this analysis. Among studies reporting an association, the magnitude of the estimated effects was generally small (aOR <2.0), with some exceptions in individual studies (Jensen 2015 for PFNA and PFDA; Cheng 2025 for PFBA, Wang 2024)

Table 15 – GRADE assessment for miscarriage

GRADE assessment								
No of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Magnitude of effect**	**Dose-response**	**Other considerations**	**Conclusion**
13 (n= 9429)	**Serious** confounding by reproductive history, and possible risk of selection bias	**Serious** because nor the analysis of individual PFAS nor the mixture analyses showed consistent findings	**Not serious** Studies in birth cohorts, but also studies on specific populations (fertility clinics)	Not assessed, because no pooled estimate	Not assessed, because no pooled estimate	Dose-effect: inconsistent	Publication bias not assessed Residual confounding: Not applicable	**very low**

4.5 Prematurity

4.5.1 Definition of the outcome 'prematurity'

Preterm birth (PTB) is defined by the WHO as any delivery that occurs before 37 weeks of pregnancy or less than 259 days following the start of a woman's last menstrual cycle. PTB is a risk factor for apnoea, jaundice, cerebral palsy, psychological problems, school difficulties and other deleterious short- and long-term health outcomes.[62]

The mechanisms possibly linking PFAS and PTB are not yet clearly understood. PFAS can induce inflammatory responses. For example, PFOS can activate the NF-κB signaling pathway, leading to the secretion of several proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α),

interleukin-1 beta (IL-1β), and interleukin-6 (IL-6).[78] This hyperinflammatory state could contribute to the mechanism behind PFAS-induced preterm birth. Other mediation mechanisms could involve placental IGF1 signaling,[79, 80], specific types of DNA methylation,[81] or perturbed tissue neogenesis, neuroendocrine function, and redox homeostasis.[82]

4.5.2 Key points

- Current evidence suggest a possible but not definitive association between PFAS exposure and preterm birth (PTB), with important variability across studies and compounds.
- PFOS shows the most consistent signal, as apparent in a systematic review including 14 studies and half of the 6 more recent primary studies. These newer studies also indicate potential associations for PFNA, PFOA, PFUnDA and PFAS mixtures.
- Effect sizes are generally small to modest (OR is around 1.2–1.5 in many analyses), although higher estimates are occasionally reported in specific subgroups or exposure contrasts.
- Results are not fully consistent across PFAS congeners, populations, or study designs, reflecting substantial heterogeneity.
- Exposure assessment affects results, with differences observed by biological matrix (maternal vs cord blood), timing of sampling, and exposure levels.
- Effect modification is likely, with emerging evidence for roles of fetal sex, maternal nutritional status, and possibly other susceptibility factors.
- Mixture-based analyses often detect stronger or more coherent signals than single-pollutant models.
- The certainty of evidence was rated very low for all studied PFAS.

4.5.3 Results of systematic reviews

Among the six SRs retrieved, the one by Yang et al. 2022 was selected to be described in detail because the most recent one (search strategy up to 21 March 2021) with an acceptable quality level (see AMSTAR 2 table in the Supplement).[62] Another SR was published that same year by Gui et al., but the reporting on the included studies and computation of results was incomplete.[m83] A more recent systematic review by Haimbaugh et al. 2024 was also available (see AMSTAR 2 table in the Supplement).[63] However, it included fewer studies than the one by Yang et al. 2022 and the reason for this difference was not clearly documented. The SR by Liu et al 2024 included 21 studies, and generated pooled odds ratios for each individual PFAS, integrating estimates based on heterogeneous exposure contrasts, including categorical comparisons and continuous measures on a logarithmic scale. The quality appraisal was low considering critical limitations (see also miscarriage). They reported significant association for PFOS and prematurity, and not for other PFAS, though there was high heterogeneity in the pooled estimate. The umbrella review by Xing et al. 2024 was also excluded because the association with prematurity was based on an unique systematic review published in 2021 (Gao et al 2021).[3]

Yang et al. 2022 included 14 studies on prematurity: 12 cohort studies, 1 nested case-control, and 1 cross-sectional study with a total of 21 935 participants.[n] Four studies were conducted in China, 5 in

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[m] Detailed results are reported in Excel sheets (supplementary online material) which reading is difficult (e.g. no name for the studies, no clear explanation for the computations)

[n] The total number of studies and included population differs per PFAS compound. The highest number is used (often PFOS, or PFOA)

Europe, and 5 in the Americas. One study used cord blood and the other studies used maternal blood for the PFAS exposure assessment. A total of 20 PFASs were measured, 4 of which were associated with sufficient data and used for subsequent analyses (PFOS, PFOA, PFHxS, PFNA).[o] All included studies were rated high-quality by the authors of the review who used the Ottawa New Castle scale.[62] Egger tests showed that publication bias was only observed in the meta-analysis of PFNA (p=0.004).

Results showed high heterogeneity within and between PFAS. **There was a statistically significant association only for PFOS (OR=1.54; 95% CI: 1.20, 1.98; I^2=63.4%, p=0.001; 14 studies),** as summarized in Figure 7. Of note, when primary studies investigated the associations of PFAS exposure and birth outcomes using the first quartile of PFAS concentration as a reference, the estimate with the largest effect was selected. Therefore, the meaning of the pooled OR is unclear, and it should serve as an indication of a significant association, not for a numerical estimation of the risk increase. There was substantial heterogeneity across studies reporting on specific PFAS (for example, see Figure 8 for PFOS; for PFOA I^2 = 58.8%; for PFHxS I^2 = 55.9%). The authors reported the following contributors to this heterogeneity:

- The associations between PFAS and PTB varied across geographical regions, with PFOS displaying a pooled OR of 1.44 (95% CI 1.19–1.76) in the Americas, compared with 1.55 (0.89–2.71) in Europe and 1.73 (0.89–3.36) in Asia, while PFNA was significantly associated with PTB only in the Americas (OR 1.86; 95% CI 1.11–3.11) but not in Europe.
- The timing of exposure assessment also influenced results: for PFOS, associations were observed both in early pregnancy (OR 1.45; 95% CI 1.01–2.08) and in late pregnancy (OR 2.88; 95% CI 1.15–7.17), suggesting possible sensitive windows. For PFOA, the effect estimates differed more clearly by timing, with a weaker association in early pregnancy (OR 1.23; 95% CI 0.88–1.72) and a stronger association when measured later (OR 2.25; 95% CI 1.07–4.74), with timing explaining part of the heterogeneity.
- The biological matrix also contributed to heterogeneity: PFOA was associated with PTB when measured in maternal blood (OR 1.29; 95% CI 1.01–1.66), and sample type significantly explained between-study variability (p=0.009).

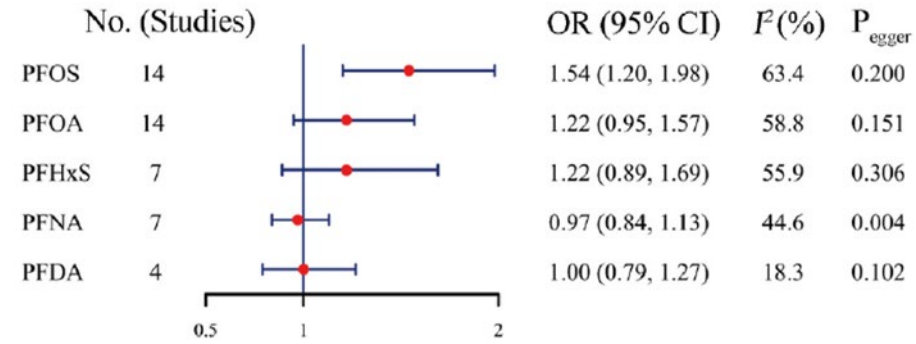
Overall, these findings indicate that variability in region, timing of exposure measurement, and biological matrix play a key role in explaining inconsistencies across studies, rather than the absence of a true association.

Study design (case-control or cohort), groups compared (terciles or quartiles), mean or median PFAS concentration, and level of adjustment for confounding factors represented potential additional sources of variation.[62]

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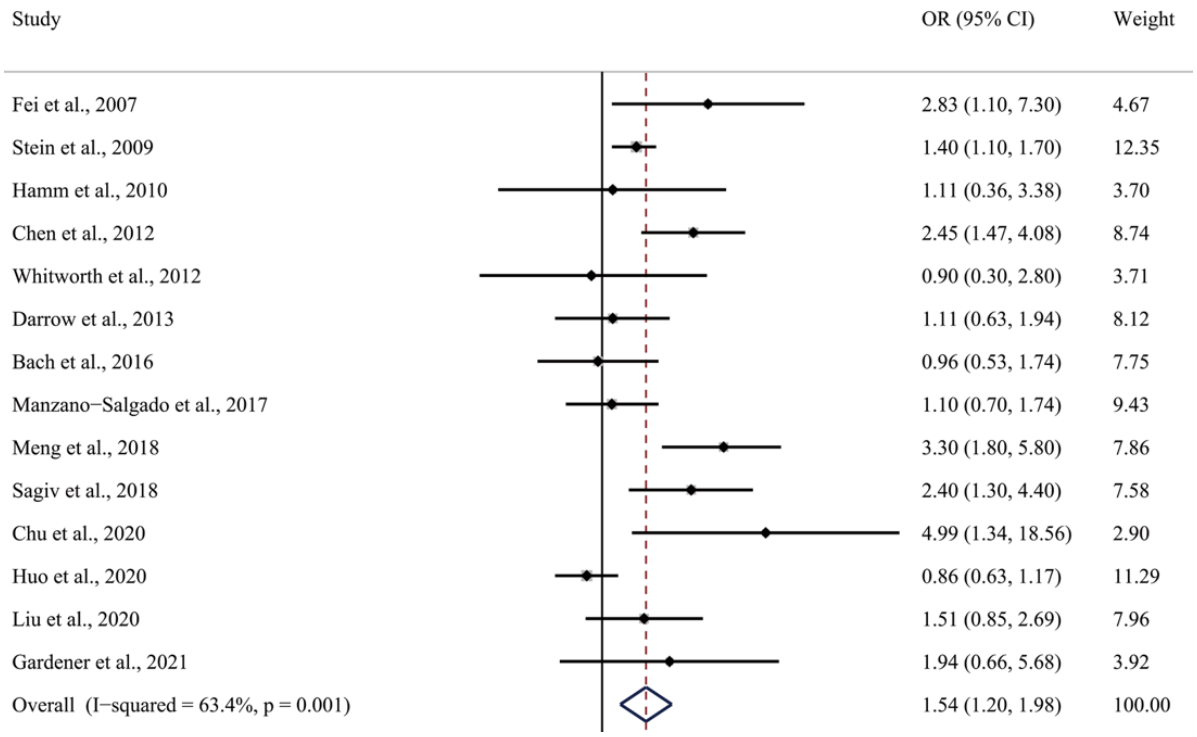
[o] Results for PFDA were also reported by the authors, but excluded from our report because only 4 studies were available. The pooled OR was 1.00 (95%CI: 0.79, 1.27).

Figure 7 – Association of individual PFAS with preterm birth as reported in Yang et al. [62]



Note : the OR, RR, HR estimate with the largest effect was selected. Therefore, the meaning of the pooled OR is unclear, and it should serve as an indication of a significant association, not for a numerical estimation of the risk increase.

Figure 8 – Meta-analysis of the association between maternal PFOS and preterm birth as reported in Yang et al. [62]



Note : the OR, RR, HR estimate with the largest effect was selected. Therefore, the meaning of the pooled OR is unclear, and it should serve as an indication of a significant association, not for a numerical estimation of the risk increase.

4.5.4 Results of primary studies

The updated search on 9 March 2026, resulted in six additional primary studies published after March 2021 (search strategy and excluded studies in supplement). Their quality appraisal can be found in Supplement 3.2.4.

4.5.4.1 Description of the recent primary studies

Overall, the studies were conducted in two main geographic settings, namely China (Hu et al., Liao et al., Shen et al., Yu et al.)[84-86] and the United States (Siwakoti et al., Zhang et al.),[87-89]reflecting both Asian and Western populations (see Supplement 4.3.2).

In terms of study design, most investigations relied on observational cohort-based approaches. Two studies (Liao et al., 2022; Zhang et al., 2023)[85, 89] were large prospective birth cohorts, while Hu et al. (2025), Siwakoti et al. (2023), and Yu et al. (2022) used nested case-control designs within established cohorts.[84, 87, 88] Shen et al. (2022) conducted a smaller birth cohort study.[86] Sample sizes varied substantially, ranging from 501 participants in Siwakoti et al. (2023) to approximately 1,400 mother–infant pairs in Zhang et al. 2023, with most studies including several hundred participants. Case-control studies explicitly compared preterm births with term controls, whereas cohort studies analyzed outcomes across the full study population.

Most studies measured PFAS in maternal blood collected during pregnancy, typically in early gestation (around 9–10 weeks) for Hu et al., Siwakoti et al., and Zhang et al.,[84, 87, 89] or before 12 weeks in Liao et al.[85] Shen et al. collected maternal blood samples during pregnancy, although the timing was later and less clearly standardized.[86] Yu et al. included a more comprehensive exposure assessment by measuring PFAS in maternal, paternal, and neonatal cord blood, allowing evaluation of multiple exposure windows.[88] Across studies, a broad range of PFAS compounds was analyzed, including commonly studied substances such as PFOA, PFOS, PFNA, and PFHxS, as well as less common long-chain and emerging compounds.

Statistical analyses were primarily based on multivariable regression models. All studies also applied mixture-based approaches, including weighted quantile sum (WQS) regression, Bayesian kernel machine regression (BKMR), and quantile g-computation, to account for correlated PFAS exposures.[84-89]

The definition of preterm birth (PTB) was consistent across studies as delivery before 37 weeks of gestation; however, the classification of PTB subtypes varied. Some studies (e.g., Shen et al., 2022; Zhang et al., 2023; Liao et al., 2022; Yu et al., 2022) treated PTB as a single binary outcome without further distinction.[85, 86, 88, 89] Others used more detailed classifications. Siwakoti et al. (2023) distinguished between spontaneous PTB and placental PTB, the latter defined by the presence of conditions such as preeclampsia or intrauterine growth restriction, reflecting a pathophysiological categorization.[87] Hu et al. (2025) classified PTB into spontaneous and iatrogenic PTB, where iatrogenic PTB refers to medically indicated preterm delivery initiated by clinicians, typically through induction of labor or cesarean section due to maternal or fetal complications.[84] These differences illustrate variation between biological (placental PTB) and clinical (iatrogenic PTB) classifications across studies.

In terms of methodological quality, two studies (Liao et al., 2022; Zhang et al., 2023) were rated high quality with the OHAT risk of bias tool (see quality appraisal tables in Supplement 3.2.4).[p85, 89] The remaining studies were rated moderate quality.

4.5.4.2 Main results of recent primary studies

The results are presented in detail in Supplement 4.3.3. The studies do not point equally strongly to every PFAS. **PFOS** appears to be one of the most reproducible compounds for PTB risk (in three of the six studies there was a significant association), consistently with the results in Yang et al. (2022).[62]. In Yu 2022, maternal PFOS was strongly associated with PTB, with an OR of 2.07 per 1 ln-ng/mL increase, whereas paternal PFOS showed an inverse association and cord blood PFOS was null, underlining that the biologically matrix matters.[88] In Liao 2022, PFOS was also positively associated with PTB, including an elevated risk for the third quartile versus the first quartile and a significant

[p] A study was rated high quality when all OHAT domains were judged definitively low risk of bias or probably low risk of bias. Study with at least one domain presenting probably high risk of bias were judged moderate quality. When the majority of domains were probably high risk of bias or definitively high risk of bias, the study was rated low quality.

positive trend per 1 log10-unit increase.[85] Hu 2025 also reported a positive continuous association for PFOS with overall PTB, spontaneous PTB and iatrogenic PTB.[84]

As regards **PFOA**, in contrast with the pooled estimate from the systematic review by Yang et al. (2022),[62] a significant positive association was found in four studies over six. Hu 2025 reported a strong positive association with overall PTB (OR=2.08 (95% CI 1.52–2.85))and with both spontaneous and iatrogenic PTB, and the risk increased across exposure quartiles.[84] Yu 2022 similarly found a positive association for maternal PFOA, but not for paternal or cord blood PFOA.[88] Shen 2022 also reported a positive association between PFOA and PTB.[86] However, Zhang 2023 did not show a clear association with PTB, even when stratified by folate status, and Liao 2022 described PFOA as inversely associated in adjusted models. This inconsistency may reflect exposure range, timing, population differences, or outcome definition.[85, 89]

The evidence for **PFNA**, **PFDA**, and **PFUA/PFUnDA** is noteworthy because the associations became stronger when analyses moved beyond overall PTB. Siwakoti 2023 found significant associations of PFNA, PFDA and PFUA with **placental PTB**, with particularly large estimates among male offspring, including an OR of 4.01 for PFNA and 2.53 for PFDA in males.[87] Hu 2025 also showed strong quartile gradients for PFNA and PFUnDA for overall PTB and subtypes.[84] Yu 2022 found positive maternal and cord blood associations for PFNA, and a high family exposure profile dominated by PFNA and PFDA was associated with substantially increased PTB risk.[88] These results suggest that some of the newer or less historically emphasized PFAS may be particularly relevant for placental or subtype-specific pathways. The one study that stands somewhat apart is Liao 2022, which reported both positive and inverse associations across different PFAS.[85] PFOS, PFHpA and PFBS showed positive associations, but PFUnA and some other compounds showed inverse associations. This mixed pattern may reflect true heterogeneity, but it may also indicate the difficulty of interpreting single-pollutant models in the presence of correlated PFAS exposures, regional exposure profiles, and non-linear dose-response patterns. Indeed, Liao explicitly reported a non-linear relationship for PFBS and found positive mixture effects in WQS and BKMR.[85] This illustrates the complexity of PFAS epidemiology.

The **mixture findings** are one of the strongest aspects of the evidence base. Hu 2025 concluded that both individual PFAS and PFAS mixtures increased PTB risk, with PFOA, PFNA and PFUnDA as major contributors.[84] Liao 2022 also found a positive association for the PFAS mixture, with PFOS, PFHpA and PFBS being the main contributors.[85] Yu 2022 reported that the highly exposed family profile, characterized especially by PFNA and PFDA, had more than double the odds of PTB.[88] Even when exact pooled ORs are not always available from BKMR, the direction of the evidence is fairly consistent: PFAS rarely occur alone, and mixture-based analyses often detect stronger or more coherent signals than single-pollutant models.

4.5.5 Discussion

Yang et al. (2022) pooled 14 studies and reported a significant association between PFOS exposure and preterm birth (PTB), with a pooled odds ratio (OR) of 1.54 (95% CI 1.20–1.98), while pooled associations for PFOA, PFHxS and PFDA were not statistically significant, and PFNA showed no overall association.[62] Importantly, Yang et al. (2022) highlighted substantial heterogeneity, showing that associations for PFOS and PFNA varied by geographic region, and that timing of exposure assessment and biological matrix contributed to between-study variability. These findings suggested that methodological and contextual differences may partly explain inconsistent results across studies.

Our updated synthesis based on six more recent primary studies is broadly consistent with Yang et al.[62] for PFOS, which remains the most consistently associated PFAS with PTB across populations. However, the newer studies suggest that earlier pooled estimates may have underestimated the role of other PFAS, particularly PFNA, PFDA and PFUA/PFUnDA. This likely reflects differences in study design and analytical approaches: many earlier studies focused on overall PTB as a single outcome, included a limited number of PFAS congeners, and rarely considered mixture effects. In contrast, more recent studies—particularly Siwakoti et al. (2023) and Hu et al. (2025)—have incorporated PTB

subtypes and mixture-based models, showing that PFNA and PFDA are more strongly associated with placental or iatrogenic PTB pathways than with overall PTB.[84, 87]

Consistent with Yang et al. (2022), the present review supports the importance of exposure characterization and biological matrix in explaining between-study heterogeneity. Yu et al. (2022) demonstrated that associations differ according to biological matrix, with divergent results observed for maternal, paternal, and cord blood PFAS concentrations, highlighting that "PFAS exposure" is not a single construct.[88] Evidence from cord blood remains limited and heterogeneous: while Yang et al. 2022 identified only one study using cord blood (precluding pooled analysis and not showing a clear positive association), Yu et al. reported compound-specific results, with positive associations for some PFAS (e.g., PFBA, PFHxA, PFNA) and null or weaker associations for others (e.g., PFOA, PFOS).[88] This suggests that differences in toxicokinetics, placental transfer, and timing of exposure measurement may influence observed associations. In addition, Zhang et al. (2023) identified maternal folate status as a potential effect modifier,[89] while Siwakoti et al. (2023) reported stronger associations among pregnancies with male fetuses, suggesting sex-specific susceptibility.[87] Together, these findings indicate that heterogeneity across studies may reflect underlying biological complexity rather than inconsistency.

Overall, the current body of evidence suggests that PFAS do not exert a uniform class-wide effect on PTB. Instead, a subset of compounds (most notably PFOS, and increasingly PFNA and PFDA) appear to drive the association.. In this context, the newer studies do not contradict the findings of Yang et al. 2022, but rather refine them by highlighting the importance of exposure level, mixture effects, and outcome heterogeneity in understanding PFAS-related reproductive risks.

4.5.6 Certainty of evidence with GRADE

Inconsistency

In the systematic review by Yang et al. 2022,[62] there was substantial heterogeneity across studies for each PFAS, with only a limited proportion reporting a statistically significant association and high I^2 statistics reflecting variations by geographic region, timing of exposure assessment and biological matrix, but also possibly the various way of computing the OR at the study level. Results from the 6 more recent studies were in the same line as significant associations were reported in some studies only. For these reasons, we rated down the certainty by one level for all PFAS.

Risk of bias

All included studies included in the systematic review by Yang et al. 2022 were rated high-quality by the authors who used the Ottawa New Castle scale.[62] None of the 6 more recent primary studies that we reviewed had one domain at high risk of bias on the OHAT scale. Therefore, the evidence was not rated down for risk of bias.

Imprecision

For PFOS, no downgrading for imprecision was applied because the pooled estimate reported in the systematic review by Yang demonstrated a statistically significant association, a finding that is further supported by consistent significant associations in the more recent primary studies.[62]

For PFOA, Yang's pooled estimate did not report a significant association. It was however borderline significant, i.e. OR=1.22 (95%CI: 0.95-1.57). Moreover, 4 over the 6 more recent primary studies reported an association statistically significant. For these reasons, the evidence was not downgraded for PFOA neither.

The evidence for all other PFAS was downgraded for imprecision.

Dose response

The existence of a dose-response relationship was not assessed in the systematic review by Yang et al. 2022.[62] In the 6 additional primary studies, a statistically significant linear relationship was reported for MPAH (1 study), PFBA in maternal serum and cord blood (1 study), PFHpA (1 study), PFHP (1 study), PFHxA in paternal serum and cord blood (1 study), PFHxS in cord blood (1 study), PFNA (3 studies, for specific outcomes), PFNS (1 study), PFO5D0A (1 study), PFOA (4 studies), PFOS (3 studies), PFUA/PFUnA/PFUnDA (2 studies).

Given the methodological challenges explained in the methods section, we did not rate up the evidence for a dose-response effect.

Interpretation of effect size -magnitude of effect

While acknowledging that even moderate relative risks can translate into substantial absolute increases at the population level, particularly given the widespread exposure to PFAS, we did not retrieved effect size big enough to justify rating up the evidence. Moreover, in the systematic review by Yang et al. 2022, the numerical significance of the pooled OR is unclear as individual study-level ORs were computed in various way.

Limitations of current knowledge

Despite growing evidence, several important limitations remain. First, most epidemiological studies (including those synthesized by Yang et al. 2022) rely on pooled estimates that assume a homogeneous exposure–response relationship, which may not be appropriate for PFAS. Recent work by Guo et al. 2025 suggests that PFAS–health outcome associations may be non-linear and dependent on exposure level, with potential threshold or saturation effects.[q] [28] This implies that pooled ORs may obscure important differences between low-, moderate-, and high-exposure populations. Second, substantial exposure heterogeneity exists across regions and time periods, both in terms of absolute concentrations and PFAS mixtures, limiting comparability. Third, mixture effects remain difficult to interpret, as different statistical approaches (e.g., WQS, BKMR, quantile g-computation) capture different aspects of combined exposure and are not directly comparable across studies. Fourth, the increasing focus on PTB subtypes introduces a degree of indirectness, as findings for placental or iatrogenic PTB cannot be directly extrapolated to overall PTB risk. Finally, residual confounding, particularly by socioeconomic, dietary, or environmental factors, cannot be excluded in observational designs. These findings suggest that further epidemiological evidence is still needed for assessing the relationship between PFAS exposure and the odds of preterm delivery.

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[q] It was reported that in subgroup analysis, the summary ORs for preterm birth were positive and larger for studies when the referent group levels were low (≤5ng/m; OR=1.65;95%CI,1.08-2.52) or high (>10ng/mL; OR=1.54;95%CI,1.08-2.19), and the association was null for moderate referent group levels (>5-10ng/m; OR=0.95;95%CI,0.68-1.37).[28.]

Table 16 – GRADE assessment for prematurity

GRADE assessment								
No of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Magnitude of effect**	**Dose-response**	**Other considerations**	**Conclusion**
14* (n=21 935) *in Yang 2022* [62] + *6 primary studies* *(n=5260)	Not serious	**Serious**	Not serious. populations and outcomes were broadly applicable to the PECO	PFOS: Not serious PFOA: Not serious All **other PFAS: serious**	No large effect size	Not demonstrated	No Publication bias reported in the systematic review Residual confounding: not applicable	**PFOS: very low** **PFOA: very low** **Other PFAS: very low**

4.6 Birth weight and small for gestational age

4.6.1 Definition of outcome

PFAS can cross the placenta, raising concerns about direct effects on foetal development during critical windows of growth. The potential impact of maternal PFAS exposure can be measured by a decrement of birth weight on a continuous basis, or by categorical data to which an increased risk of health complications is associated, i.e. low birth weight (LBW, birth weight<2500 grams) or small-for-gestational age (SGA, birth weight <10th percentile for that gestational age and sex). A growing body of longitudinal evidence indicates that LBW and SGA are associated with adverse long-term outcomes, including impaired neurodevelopment, impaired growth trajectories, hypertension and increased cardiometabolic risk.[90-92] In addition, altered foetal growth is associated with long-term changes in body composition, including increased visceral adiposity, insulin resistance, and unfavorable lipid profiles, particularly when followed by rapid postnatal catch-up growth.[93, 94]. Given the ubiquity of PFAS exposure, even modest effects on fetal growth could translate into substantial public health impacts.

Mechanistic pathways linking maternal PFAS exposure and birth weight remain unclear. PFAS may affect infant birth weight through a reduction in IGF2 methylation, disruption of maternal and neonatal thyroid hormone function, activation of peroxisome proliferator-activated receptor-α, and changes in epigenetic composition. Placental mRNA levels of insulin-like growth factor 1 (IGF1) and IGF1 receptor (IGF1R) might be mediators.[79] PFAS could also affect human placentation and placental-specific functions.[95]

The third trimester was identified as the critical window of vulnerability to PFAS exposure that affects birth weight and birth length.[96] The transplacental transfer efficiencies (TTE) of 29 PFAS were comprehensively assessed, and a "U"-shaped trend in TTE values with increasing molecular chain length of perfluoroalkyl carboxylic acid (PFCA) was observed in this study.[96]

4.6.2 Key points

- The evidence base on decremental birth weight was large, with PFOS (n=53 studies), PFOA (n=23), PFHxS (n=27), PFHxS (n=27), PFNA (n=27) as the most studied maternal PFAS.
- In good quality systematic reviews, these PFAS were consistently associated with a decrement of birth weight in the range of 30 grams (95%CI: ≈-40, ≈-20) per ln-unit ng/ml increase of PFAS concentration, except for PFHxS (≈-8 grams).
- The confidence in the effect for PFOS, PFOA and PFNA is rated moderate with GRADE, because the plausible dose-response relationship triggered an upgrade by one level. However, it is still to be demonstrated that the linearity of results is not an artifact.

- The clinical significance of such birth weight decrements is not straightforward. The evidence base on better defined risk factors, namely low birth weight (<2500 g) and small for gestational age, is much thinner. In the systematic review included, only PFOS increased significantly LBW risk (1.52; 95%CI: 1.19-1.94; I^2=19.1%), and this association was rated low certainty. All the other associations were inconclusive and very low quality.
- The association between maternal PFAS concentration and reduced birthweight may be confounded by the timing of sample collection due to pregnancy-related changes in maternal physiology, although convincing evidence to confirm or refute this hypothesis is still lacking.
- It is also necessary to study other PFAS, either individually or in mixture, and determine the best moment to measure them (repeated measurements ? measurement in blood cord?).

Table 17 – Main results on the association between maternal PFAS and birth weight

PFAS	Systematic review	Nb studies	Overall effect on birth weight	Effect in earlier pregnancy
PFOS	Wright 2025	53	-30 g (95% CI: -41.6, -18.9; I^2 = 42.4%) per ln-unit ng/ml increase	-23.6 g (95% CI: -38.7, -8.6; 18 studies) per ln-unit increase. No significant gradient across time windows
PFOA	Fu 2025	24	-81.3 g (95% CI: -126.1, -36.4; 23 studies; I^2 = 64.1%) per log10 unit ng/ml increase	-97.9 g (95% CI: -181.8, -13.9; 8 studies) per log10 unit increase. Gradient not tested
PFHxS	Ru 2024	27	-7.9 g (95% CI: -15.0 to -0.7; I^2 = 0%) per ln-unit ng/ml increase	-7.6 g (95% CI: -16.2, 1.1; 7; 12 studies) per ln-unit ng/ml increase. No significant gradient across time windows
PFNA	Wright 2023	27	-32.9 g (95% CI: -47.0, -18.7; I^2 = 36%) per ln-unit ng/ml increase	-22.0 g (95% CI: -40.1, -4.0; 11 studies) per ln-unit ng/ml increase. No significant gradient across time windows

4.6.3 Results of systematic reviews

The umbrella review identified several SRs on birth weight, foetal growth, low birth weight and small for gestational age (see supplement 2.1). The most comprehensive and most recent evidence synthesis was available for birth weight, with dedicated SRs per individual PFAS (PFOS,[17] PFOA,[97] PFHxS,[97] and PFNA[98]). Common confounders in most primary studies: maternal age, parity, BMI, pregnancy weight gain, ethnicity, parental education, socioeconomic status, maternal smoking, maternal alcohol intake, gestational age, fetal sex.

For each PFAS, we based the analysis on the most recent high-quality systematic review. There was no attempt to update these reviews because they were recent and included a great number of studies (for example, there were 53 studies in the review by Wright et al. 2025 on PFOS,[17] i.e. additional primary studies were unlikely to add extra information.

Reviews on LBW and SGA newborns were much rarer. Therefore, contrary to the approach used to analyse birth weight where a different systematic review was used for each PFAS, our analysis on LBW and SGA was based on one common review by Yang et al. 2022 (search date up to March

2021).[62] Another SR was published that same year by Gui et al., but the reporting on the included studies and computation of results was incomplete.[r83]

We present here the methods of this review by Yang et al. 2022, whereas the results were dispatched per PFAS. The AMSTAR-2 quality appraisal can be found in Supplements 3.1.6. Yang et al. 2022 meta-analysed for the outcome small for gestational age 9, 10, 4, and 6 studies for respectively PFOS, PFOA, PFHxS and PFNA, including 7155 pregnant women, recruited from China (3 studies), Europe (6), and the Americas (1). Participants were general pregnant women, with no restriction on ethnicity or region, reflecting real-world settings. For the outcome low birth weight 7, 7 and 3 studies were meta-analysed for respectively PFOS, PFOA and PFNA.

Exposure assessment relied mainly on maternal blood (20 studies), with 2 studies using cord blood and 1 using modelled equivalent cord concentrations. Regarding timing of exposure measurement, it was early pregnancy (before pregnancy, 1st or 2nd trimester) in 16 studies, late pregnancy (3rd trimester to delivery) in 3 studies, cord blood at delivery in 2 studies, and the timing was unspecified in 2 studies. All studies reported adjusted effect estimates, and all were rated as high quality using the Newcastle–Ottawa Scale.

Subgroup analyses were conducted (≥3 studies) according to: geographical region, timing of exposure and biological sample type (maternal vs cord blood). In this meta-analysis, the odds ratios (ORs) correspond to higher vs lower exposure to PFASs within each study population. In most studies, exposure was categorized (e.g., quartiles or tertiles of PFAS levels), and the lowest category served as the reference group. When multiple exposure categories were available, the authors selected the estimate with the largest effect (i.e., highest exposure vs lowest) for the meta-analysis. Some studies may have used continuous exposure metrics, but these were harmonized into comparable effect estimates (OR/RR/HR) before pooling. So, the pooled ORs do not represent a standardized dose increase (e.g., per ng/mL), but rather a contrast between higher vs lower exposure levels, which may differ between studies. This is important because it introduces heterogeneity in exposure definition, which partly explains variability in results. More importantly, this approach jeopardizes a straightforward interpretation of the pooled results, i.e. an OR above one is a qualitative signal of an association but the effect size does not relate to a clear-cut entity.

4.6.4 PFOS

4.6.4.1 Methods

The most recent high-quality systematic literature review (search date until 18 April 2024) included 53 epidemiological studies on the association between maternal PFOS concentration and birthweight, comprising 31 cohort studies, 12 cross-sectional studies, and 10 case-control studies, and representing more than 70,000 mother–child pairs across multiple regions.[17]

Most studies relied on maternal blood (serum or plasma) collected during pregnancy (43 studies), while a smaller subset used cord blood samples collected at delivery (10 studies) to reflect fetal exposure.

Sampling timing varied and was explicitly categorized into three groups. Eighteen studies were classified as early pregnancy sampling, including preconception and first trimester. Twenty-three studies were classified as late pregnancy sampling, corresponding to second or third trimester. The remaining 12 studies used post-partum samples, including maternal samples collected after delivery and neonatal samples, among which 10 were based on umbilical cord blood.

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[r] Detailed results are reported in Excel sheets (supplementary online material) which reading is difficult (e.g. no name for the studies, no clear explanation for the computations). The article indicates that details of the results on LBW and SGA are presented in Supplementary Table 12, but this table is not provided on the website of the journal.

To enable quantitative synthesis, the authors applied extensive harmonization procedures. Effect estimates were standardized to a common metric, namely grams of birth weight per ln-unit increase in PFOS concentration. Estimates reported on different scales (e.g., log10, per ng/mL, per IQR, or categorical comparisons) were converted to this common scale using change-of-base transformations and re-expression methods. Concentrations measured in whole blood or dried blood spots were converted into serum-equivalent concentrations using established factors. Additional steps included digitizing graphical data when necessary and converting standardized outcomes into absolute birth weight differences.

The AMSTAR-2 appraisal can be found in Supplement 3.1.6. Another recent meta-analysis was available, and although it was not selected because it included only 23 studies, we used its results as a comparison point.[97] This study served as the reference review for PFOA and is described in the corresponding section.

4.6.4.2 Main results

Main results are presented in Supplements 4.4. Overall, a 30-gram birthweight deficit (95%CI: −41.6, −18.9; I^2 = 42.4%, p< 0.0001) was seen with each increasing ln-unit (i.e. each time the PFOS concentration was increased by 2,73 fold). This result was not significantly affected by the quality of the primary studies. The range of median PFAS contamination was quite broad from less than 2ng/mL (11 studies) to more than 10ng/mL (16 studies). There was a small non-significant decrement in average change in BW across studies with increasing median PFOS level (β =−1.4 g; 95%CI: −2.9, 0.1) per unit increase).

To evaluate the potential impact of pregnancy hemodynamic on the results, the outcome was analysed according to the sample timing. There was no evidence of a gradient of BW deficits across sample timing (β range: −24 to −39 g per ln-unit increase). Deficits were larger for the 23 late sample (β =−38.9 g; 95%CI: −59.7, −18.2) than the 12 post-partum sample studies (β =−30.6 g; 95%CI: −60.5, −0.6) and the 18 early sampled studies (β=−23.6 g; 95%CI: −38.7, −8.6). Of note, time windows could overlap as the early-pregnancy group was defined as studies with blood samples taken either in the 1st trimester, a combination of 1st and 2nd trimester, or a combination of 1st, 2nd and 3rd trimester. However, results were not substantially different (β =−21.5 g; 95%CI: −42.8, −0.2) based on the subset of nine studies with PFAS measured ≤10 gestational weeks.[s] These results suggest that observed deficits for PFOS are not (entirely) attributable to pregnancy hemodynamic changes.

In the systematic review by Fu et al. 2025,[97] the birthweight was decreased by 71.5g (95%CI: -114.5, -28.6; 23 studies; I^2=64.1%) for every log10 unit ng/ml increase in PFOS exposure, a result quite close to the one expected from the more extensive systematic review by Wright et al. 2025[17] (-30g for each increasing ln-unit of PFOS exposure). Of note, there was not significant impact of maternal PFOS exposure in earlier pregnancy measures (β=−22.2 g; 95%CI:−68.3, +23.8; 7 studies)

For LBW and SGA newborns, Yang et al. 2022 reported that based on 7 and 9 studies, the pooled OR of PFOS on LBW and SGA were 1.52 (95%CI: 1.19-1.94; I^2=19.1%) and 1.22 (95%CI: 0.92-1.61, I^2=74.3%), respectively.[62]

[s] Birth weight deficits were slightly smaller when this window was extended to 13 studies with ≤13 gestational weeks (β=−16.9 g; 95%CI:−31.2, −2.6)

4.6.5 PFOA

4.6.5.1 Methods

The most recent systematic review by Fu et al. 2025 (search strategy up to March 2024) included 24 studies (19 prospective cohort, 5 cross-sectional studies) with a search strategy up to March 2024.[97] Geographically, the studies were distributed across Asia (13 studies), Europe (6 studies), North America (4 studies), and Oceania (1 study), reflecting a predominance of Asian populations. All included studies assessed maternal exposure, with PFAS measured in serum or whole blood samples collected from pregnant women.

Sampling timing was explicitly categorized into three groups: pregnancy, including pre-pregnancy or first trimester (n=7); mid-to-late pregnancy, corresponding to second and/or third trimester sampling (n=8); samples collected after delivery, reflecting maternal or perinatal measurements at or shortly after birth (n=9).

All studies were considered high-quality based on Newcastle–Ottawa Scale and AHRQ assessments, although heterogeneity remained substantial due to differences in exposure timing, transformation methods, and study populations.

The AMSTAR-2 appraisal can be found in Supplement 3.1.6.

4.6.5.2 Main results

There was a significant negative correlation association between maternal PFOA exposure and neonatal birth weight (β= −81.3 g; 95 %CI= −126.1, −36.4) for every log10 unit ng/ml increase in PFOA exposure, with great heterogeneity across studies (I^2=67.2%, p<0.0001).

In subgroup analyses by timing of exposure, the association varied. In mid-to-late pregnancy, PFOA exposure was significantly associated with reduced birth weight (β = −85.9 g; 95% CI: −139.3, −32.5) per log10 unit increase. In contrast, no statistically significant association was observed in early pregnancy or after delivery. The pooled estimates were consistent across regions (Asia versus other countries). Unfortunately, results were not stratified by type of studies (cross-sectional vs. cohort studies).

For LBW and SGA, Yang et al. 2022 reported that based on 7 and 11 studies, the pooled OR of PFOA on LBW and SGA were 1.02 (95%CI: 0.80-1.29; I^2=0%) and 1.08 (95%CI: 0.93-1.27, I^2=0%), respectively.[62]

4.6.6 PFHxS

4.6.6.1 Methods

The high quality review by Ru et al. 2024 (search strategy up to April 2023) including 27 studies was selected.[99] Most were cohort studies (n=23), with a smaller number of cross-sectional studies (n=4). Sample sizes ranged widely, from fewer than 100 to more than 3,500 participants. Exposure assessment relied mainly on maternal blood with a few studies using cord blood serum (n=3) to capture fetal exposure.

Sampling timing was categorized into three predefined windows: early pregnancy included samples collected before conception or during the first trimester, or spanning the first trimester (e.g., T1 only, T1–T2, or T1–T3) (n=12). Mid-to-late pregnancy included samples collected from the second trimester onward (e.g., T2 only, T2–T3, T3 only, or T2–T3 plus delivery) (10 studies). Post-partum comprised samples collected at delivery, at birth, or after birth, including both maternal and cord blood measurements (5 studies). Study quality was assessed using the US EPA IRIS-based framework, evaluating domains such as participant selection, exposure measurement, confounding, and analysis.

Among the included studies, 12 were rated high confidence, 11 medium confidence, and 4 low confidence, indicating an overall moderate-to-high quality evidence base.

We acknowledge the existence of a more recent systematic review by Fu et al. 2025 including 15 studies (11 cohort studies and 4 cross-sectional) with a search strategy up to March 2024.[97] However, it was not selected because it included much fewer studies than Ru et al. 2024. Ru et al. included substantially more PFHxS studies than Fu et al. because they applied a broader evidence-identification strategy, including EPA systematic-review procedures, grey-literature screening, and extensive harmonisation of effect estimates. Ru et al. also reconstructed overall-population estimates from sex-specific analyses and retained studies across high, medium and low confidence categories, excluding only studies deemed uninformative. In contrast, Fu et al. restricted inclusion to studies directly reporting regression coefficients suitable for quantitative synthesis and excluded low-quality studies.

4.6.6.2 Main results

Ru et al. 2024 reported a −7.9 g (95% CI −15.0 to –0.7; I^2=0%) BW decrease per ln ng/mL PFHxS increase.[99] The 11 medium confidence studies (β=−10.0 g; 95% CI −21.1 to 1.1) showed larger deficits than the 12 high (β=−6.8 g; 95% CI −16.3 to 2.8) and 4 low confidence studies (β=−1.5 g; 95% CI −51.6 to 48.7). However, there was no statistically significant difference (p=0.82) in effect size among these three strata of study quality. The 10 studies with mid-pregnancy to late-pregnancy sampling periods showed smaller deficits (β=−3.9 g; 95% CI −17.7 to 9.9) than 5 post-partum studies (β=−28.3 g; 95% CI −69.3 to 12.7) and 12 early sampling studies (β=−7.6 g; 95% CI −16.2 to 1.1). The results showed that while some mean BW deficits differed in magnitude by sampling window, especially in contrast to postpartum strata, statistical significance (p=0.30) was not observed when testing the hypothesis for differences across any strata.

For SGA newborns, **Yang et al. 2022** reported that based on 4 studies, the pooled OR of PFHxS on SGA was 1.38 (95%CI: 0.86-2.22; I^2=58.3%). No studies reporting on the risk of LBW were presented.[62]

4.6.7 PFNA

4.6.7.1 Methods

This analysis is based on the results of a high-quality systematic review published by Wright et al. in 2023 (search date up to July 2022) and including 27 studies.[98] The quality appraisal based on AMSTAR-2 can be found in Supplement 3.1.6. We acknowledge the existence of a more recent review by Fu et al. 2025, which was not selected because it included only 14 studies, but used as a comparison.[97]

The review included 27 observational epidemiological studies examining the association between PFNA exposure and birth weight.[98] Among these, 22 were cohort studies and 5 were cross-sectional studies, with no case-control designs represented. Sample size varied widely across studies, generally ranging from approximately 100 to over 2,000 participants.

Most studies measured PFNA in maternal serum or plasma collected during pregnancy (n = 22). A smaller subset used umbilical cord blood collected at delivery (n = 5), providing a measure of fetal exposure at birth.

Sampling timing was categorized into three groups: early pregnancy (11 studies), mid-to-late pregnancy (10 studies), and post-partum (5 cord blood, 1 maternal blood). Early pregnancy included preconception and first-trimester sampling, while mid-to-late pregnancy covered second- and third-trimester measurements. The post-partum category comprised both cord blood studies and maternal samples collected at delivery.

Study quality was evaluated using a structured framework derived from the US EPA IRIS methodology. Each study received an overall confidence rating based on expert judgment. Among the 27 studies, 12 were classified as high confidence, 10 as medium confidence, and 5 as low confidence.

To ensure comparability across studies, the authors applied extensive data harmonization procedures.[t] Stratified analyses by sampling timing and study confidence were done, as well as meta-regression using gestational age at sampling and multiple sensitivity analyses to assess the robustness of the findings.

4.6.7.2 Results

A mean decrease of −32.9 g (95%CI: −47.0, −18.7; I^2=36%) birthweight per each ln ng/mL increase in PFNA was observed.[98] The twelve high confidence studies yielded a smaller pooled effect estimate (β = −28.0 g; 95%CI: −49.0, −6.9) than the ten medium (β = −39.0 g; 95%CI: −61.8, −16.3) or four low confidence (β = −36.9 g; 95%CI: −82.9, 9.1) studies.

The stratum-specific results based on earlier pregnancy sampling periods in 11 studies showed smaller deficits (β = −22.0 g; 95%CI: −40.1, −4.0) compared to 10 mid- and late-pregnancy (β = −44.2 g; 95%CI: −64.8, −23.5) studies and six post-partum studies (β = −42.9 g; 95%CI: −88.0, 2.2). Despite a substantial differences across these strata and a gradient in deficits across timing, the hypothesis test for differences across any strata was not statistically significant (p = 0.14). When restricted to high quality studies, β coefficient was −14.6 grams (95% CI: −38.4, 9.2) in earlier samples as compared to β −59.1 g (95% CI: −91.0, −27.1) in mid-/late samples. Thus, birthweight deficits that were detected across all strata did not appear to be fully explained by potential bias due to pregnancy hemodynamics from sampling timing differences.[98].

In contrast, another recent good quality systematic review based on a more restricted sample of studies reported no overall significant change in birthweight in relation with maternal PFNA exposure (β=3.95; 95 %CI= −10.41, 18.31; I2=40.6%; 14 studies).[97] However, the results showed that for every log10 unit ng/ml increase in PFNA exposure, the birth weight of offspring decreased by 90.4 g in the mid-to-late pregnancy (β= −90.4; 95%CI= −152.9, −27.9, 4 studies), whereas such effect was not observed in earlier pregnancy or after delivery.[97]

For LBW and SGA newborns, Yang et al. 2022 reported that based on 3 and 6 studies, the pooled OR of PFNA on LBW and SGA were 0.87 (95%CI: 0.68-1.12; I^2=0%) and 0.96 (95%CI: 0.82-1.11, I^2=8.4%), respectively.[62]

4.6.8 Certainty of evidence with GRADE

Table 18 – Elements for grading evidence on decrement of birth weight, per PFAS

	PFOS	PFOA	PFHxS	PFNA
Author	Wright 2025[17]	Fu 2025[97]	Ru et al. 2024[99]	Wright 2023[98]
N studies	53	24	27	27
Risk of bias	Not serious. Results were robust across all study confidence levels	Not serious. All studies rated high on NOS scale	Not serious. Although the effect was smaller for the 12 high confidence studies, the difference among strata of study quality was not	Not serious. Results were robust across all study confidence levels

[t] Birth weight outcomes were standardized to grams, and all effect estimates were converted to a common metric of change in birth weight per ln(ng/mL) increase in PFNA concentration.

	PFOS	PFOA	PFHxS	PFNA
			statistically significant	
Inconsistency	Not serious.	Not serious, although I^2=67.2% this can be explained by difference in methods	Not serious (I^2=0%)	Not serious (I^2=36%)
Indirectness	No	No	No	No
Imprecision	Not serious. Average decrement was -30g (95%CI: - 41.6, -18.9) per ln-unit ng/mL	Not serious. Average decrement was -81.3g (95 %CI: −126.1, −36.4) per log10 unit ng/ml. The large CI doesn't question the presence of an effect	Serious. Average decrement was −7.9 g (95% CI: –15.0 to –0.7) per ln-unit ng/mL, i.e. the upper bound is close to 0	Not serious. Average decrement was −32.9g (95%CI: −47.0, −18.7) per ln-unit ng/mL
Publication bias	Not serious. Possibly 4 unpublished studies but little impact on pooled estimate	None detected	None detected	None detected
Magnitude of effect	Moderate average effect, with unclear clinical significance	Moderate average effect, with unclear clinical significance	Small average effect, with unclear clinical significance	Moderate average effect, with unclear clinical significance
Dose-response	Plausible. The birth weight decrement was per 1 ln-unit PFOS increase	Plausible. The birth weight decrement was per 1 $\log_{10}$ unit PFOA increase	Plausible. The birth weight decrement was per 1 ln-unit PFHxS increase	Plausible. The birth weight decrement was per 1 ln-unit PFNA increase

From a GRADE perspective, the overall quality of evidence on the association between PFAS contamination and birth weight was rated moderate for most of the compounds assessed (low for PFHxS). The plausible dose-response relationship with birth weight triggered an upgrade of the quality by one level. However, it is still to be demonstrated that the linearity of results is not an artifact (see discussion below). Moreover, the clinical impact of such decrements is still unknown as studies on LBW and SGA were rare, and an association was found only for PFOS and LBW. Regarding LBW and SGA, the quality of evidence was found very low for all compounds, except the association between PFOS and LBW which was judged low quality.

Table 19 – GRADE assessment for birth weight and small for gestational age

GRADE assessment								
No of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Magnitude of effect**	**Dose-response**	**Other considerations**	**Conclusion**
Birth weight								
PFOS (53 studie)[17]	Not serious	Not serious	Not serious	Not serious	Moderate	Plausible	Plausible publication bias, but no impact Residual confounding not demonstrated	**Moderate**
PFOA (24 studies)[97]	Not serious	Not serious	Not serious	Not serious	Moderate	Plausible	No publication bias Residual confounding not demonstrated	**Moderate**
PFHxS (27 studies)[99]	Not serious	Not serious	Not serious	**Serious** The upper bound of the CI is close to 0	Small	Plausible	No publication bias Residual confounding not demonstrated	**Low**
PFNA (27 studies)[98]	Not serious	Not serious	Not serious	Not serious	Moderate	Plausible	No publication bias Residual confounding not demonstrated	**Moderate**
Low birth weight < 2500g								
PFOA (n=7), PFOS (n=7), PFNA (n=3) in SR Yang 2022[62]	Not serious All studies rated high with NOS	Not serious	Not serious	**Serious** for PFOA and PFNA (CI includes unity) Not serious for PFOS	Undetermined*	Not assessed	No publication bias Residual confounding not demonstrated	**PFOS: low** **PFOA: very low** **PFNA: very low**
Small for gestational age								
PFOA (n=11), PFOS (n=9), PFHxS (n=4), PFNA (n=6) in SR by Yang 2022[62]	**Not serious** **All studies rated high with NOS**	**Serious for PFOS & PFHxS (I^2 above 50%)**	**Not serious**	Serious for all (CI includes unity)	Undetermined*	Not assessed	No publication bias Residual confounding not assessed	**PFOS: very low** **PFOA: very low** **PFHxS: very low** **PFNA: very low**

** When studies investigated the associations of PFASs exposure and birth outcomes using the first quartile of PFASs concentrations as a reference, the estimate with the largest effect was selected. Therefore, the numerical value of pooled estimates is difficult to interpret*

4.6.9 Discussion

Maternal PFAS contamination (PFOS, PFOA, PFHxS, PFNA) was consistently associated with a moderate decrement of birth weight. For example, PFOS, which was the most studied PFAS (53 studies included in the review by Wright et al. 2025[17]) yielded a 30 g decrement (95%CI: -41.6, -18.9; I^2=42.4%) per ln-unit ng/ml. The decrement linked to PFOA and PFNA was in the same range, whereas it was much smaller for PFHxS.

The clinical significance of such decrements is not straightforward. Data on LBW and SGA newborns were meta-analysed in one systematic review, and only PFOS yielded a statistically significant increased risk of LBW.[62]

Although these results undoubtedly constitute a warning signal of PFAS toxicity during pregnancy, their validity must be tested along two lines of questioning: the role of physiological changes in pregnancy as a confounding factor and the statistical limitations encountered in the studies.

4.6.9.1 *Confounding by physiologic changes (renal function, plasma expansion) related to pregnancy.*

The association between maternal PFAS concentration and reduced birthweight may be confounded by the timing of sample collection due to pregnancy-related changes in maternal physiology that impact both serum PFAS concentrations and birthweight.[100] PFOA and PFOS are primarily found in the plasma bound to albumin and are slowly excreted by the kidney (PFOA and PFOS half-lives are 2.8 and 4.8 years, respectively) making plasma (or serum) PFAS concentrations inversely related to renal function.[101] Renal function and plasma volume increase 50 % and 45 % during pregnancy, respectively, and both the glomerular filtration rate (GFR) and plasma volume are positively associated with birthweight. Thus, it would be expected that women with a greater GFR and plasma volume would have larger infants and lower circulating PFAS levels. Results from the meta-analysis on PFOS[17] and PFNA[98] showed that the birthweight decrement was smaller in studies with early sampling. However, there was some overlap between group designations which may have blurred the picture; for example, in review by Wright et al. 2023 the “early” strata included studies that sampled from both trimesters 1 and 2, whereas studies that sampled in trimester 2 only are included in the “late” group.[98] Moreover, PFAS concentration was measured often once during pregnancy.

The hypothesis of results confounding by sample timing was recently tested by Wu et al. in two prospective cohort studies where PFOA, PFOS, PFNA, PFDA, PFHpS, PFHxS, individually and all together, were measured several times during the pregnancy.[u100] Except for PFHxS, the association between each PFAS and birthweight was generally null or slightly inverse in the 1st trimester and became more strongly inverse for measurements in the 3rd trimester. For instance, each SD increase in log2-transformed PFOA concentrations in the 1st trimester was associated with a 6-gram decrease in birthweight (95 % CI: -35, 22), while 3rd trimester concentrations were associated with a 26-gram (95 % CI: -54, 3) decrease.[100] Moreover, while concentrations of PFOA, PFNA, PFDA, PFHpS, PFHxS, and PFOS all declined between the 1st and 3rd trimester, they did so at a greater rate among women who gave birth to larger infants.

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[u] The first one was led in 728 Chinese women in whom nine serum PFAS concentrations were measured in each pregnancy trimesters. The second one in 70 American women in whom PFAS concentrations were measured in 2nd trimester.[100]

These findings seem consistent with a confounding effect of maternal physiological changes during pregnancy. However, other studies reported contradictory findings.[v102-104] Therefore, more studies are needed on PFAS and neonatal outcomes that should either incorporate repeated PFAS measurements or biomarkers of maternal kidney function (e.g., serum creatinine) to distinguish physiological adaptations during pregnancy from potential toxicological effects of PFAS.[100]

Additional research is also needed to better understand transplacental transfer of PFAS and to enable more analyses of homogeneous subgroups that may better delineate the potential impact of hemodynamics from other determinants.[17] Also, as mentioned in the introduction, there is limited information on mechanisms of fetal growth restriction, which could include epigenetic changes, maternal circulating nutrients (e.g., glucose, gestational diabetes), as well as reproductive, adinopekine, and thyroid hormones.[98] Whether these elements are effect modifiers or mediators is unclear, as is the proportion of birthweight variation that can be attributed to these factors.

4.6.9.2 Statistical considerations

Data analysis are based on the assumption of linearity, and this assumption may not hold, i.e. the ln-unit change at higher exposure levels may be much larger than that at lower exposure levels.[17] For PFOS, there was a small nonsignificant decrement in average change in birthweight with increased median PFOS.[17] It is possible that further exploration of exposure-response curves could provide additional information and explain some of the heterogeneity across studies. In another more ancient systematic review, a similar observation was reported where in the high median PFOS concentration group (>6.6 ng/ml, n = 3), PFOS exposure showed a statistically significant negative association with infant birthweight (β=−107.2; 95% CI: −171.1 to −43.4, p < 0.001), while studies with low median PFOS concentration did not observe such a significant negative association (β=−29.15; 95% CI: −63.61 to 5.30, p=0.10, 13 studies).[105] However, such an effect modification by median PFAS concentration was not retrieved for PFOA or PFHxS).

Furthermore, inverted U-shaped associations were found between PFASs and health effects, indicating a low-dose exposure to PFASs might be more harmful than a high-dose exposure.[28] The practical consequence is that the level of association observed in the studies may not apply to specific populations or specific individuals with different levels of contamination. Using meta-analysis without accounting for exposure range could contribute to literature inconsistency for exposure-induced health effects and impede evidence-based policymaking. Therefore, investigating result heterogeneity by exposure range is recommended.[28]

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[v] In the Project Viva study, serum PFAS concentration (median PFOA: 5.8 ng/mL and median PFOS: 26 ng/mL) measured early in pregnancy (median: 9 weeks) were inversely associated with birthweight and the associations were unchanged when controlling for pregnancy hemodynamics (GFR and plasma albumin).[102.] In the Atlanta African American Maternal-Child Cohort; 1 st and 2nd trimester maternal PFOA concentrations were non-significantly inversely associated with birthweight z-scores, whereas 3rd trimester concentrations were positively and significantly associated with birthweight (median PFOA ~ 0.5 ng/mL).[103]. Finally, maternal preconception PFAS concentrations were inversely associated with birthweight among participants recruited from a fertility clinic in Boston (median PFOA: 1.8 ng/mL and median PFOS: 3.7 ng/mL).[104].

4.7 Congenital abnormalities in infants.

4.7.1 Definition of the outcome

Congenital abnormalities is a broad definition including structural or functional anomalies, including congenital chromosomal abnormalities that occur during intrauterine life and are present at birth.[106] Approximately 3%–6% of infants are born with congenital birth defects worldwide every year.[107] Congenital heart disease is a structural abnormality, and is one of the most prevalent congenital malformations. These malformations span a wide spectrum and their severity varies from people having no symptoms during their lifetime to others needing urgent surgery.

4.7.2 Key points

- In total 10 primary studies on congenital abnormalities were identified. Most examined only a single outcome—such as cerebral palsy, chromosomal abnormalities, congenital hypothyroidism, or cryptorchidism—and were largely anecdotal, often based on small sample sizes.
- However for the outcome 'congenital heart disease', there were three Chinese studies (total n=1312) that reported significant associations with at least one PFAS congener. Two of the studies reported a significant association with PFDA and 6:2 Cl-PFESA. Two studies reported a significant association with the PFAS mixture in general.
- However, the certainty of evidence for congenital heart disease was rated very low, due to downgrading for risk of bias

4.7.3 Results of systematic reviews

The umbrella search identified two SRs reporting on PFAS and congenital abnormalities (see supplement 2.1). Both the SR by Bernardo on endocrine disruptors and surgical congenital malformations,[108] and the SR by Elhassan on endocrine disruptors and congenital heart disease did not focus on PFAS in particular and were rated low quality by AMSTAR-2 criteria.[109]

Table 20 – Overview of systematic reviews on congenital abnormalities

Systematic review	outcome	Included primary studies	Reported Results	Quality appraisal (AMSTAR)
Bernardo 2025[108]	Surgical congenital malformations	Not fully transparent which studies on PFAS were included • Yang 2018 (crossectional) • Rapazzo 2017(review) • Bach 2015 (review)	*PFAS compounds showed moderate associations, with PFOA linked to chromosomal abnormalities (OR: 1.67, 95 % CI: 1.08—2.58) (Bach 2015) and PFOS to endocrine alter ations (OR: 1.54, 95 % CI: 1.02—2.33) (Rapazzo 2017)*	critical limitations
Elhassan 2024[109]	Congenital heart diseases	In the large list of 59 studies included for all kinds of pollutants, the ones focused on PFAS: • Ou 2021 • Li 2024	*Ou 2021 OR=1.68 (95%CI 0.99,2.85)* *Li 2024 OR=2.07 (95%CI 1.32, 3.25)* *Pooling the two studies resulted in OR 1.90 (95 % CI 1.34-2.67)*	critical limitations

4.7.4 Results of primary studies

The search for primary studies on 5 March 2026 identified 10 studies (see Table 21, and details of search in supplement 1.2.4). One on birth defects in general,[110] one on congenital cerebral palsy,[111] two on congenital cryptorchidism (i.e. born with one or both testicles not fully descended into the scrotum),[112, 113] one very small study on congenital hypothyroidism,[114] three on congenital heart disease,[115-117] one on chromosomal abnormalities,[118] and one on structural malformations including chromosomal abnormalities and heart disease.[119]

4.7.4.1 Outcome: variety of congenital abnormalities

As shown in Table 21, the studies on congenital cryptorchidism did not report an association with PFAS,[112, 113] nor the study on general birth defects and PFOA.[110] The study on congenital hypothyroidism is very small in sample size (n= 27 cases and 13 controls).[114] The study on cerebral palsy suggests a possible link with only the increasing concentration of PFOA showing a significant association limited to boys (relative risk of 2.1 per ln increase, 95% CI: 1.2-3.6).[111] The Japanese study on chromosomal abnormalities suggests potential association between PFAS as mixture, and specifically PFOS and PFNA.[118]

Table 21 – Overview of primary studies on congenital abnormalities and PFAS

Study	Outcome	Study characteristics	Result
Stein 2014[110]	Birth defects	Case- control in the C8 Health Project cohort in Mid-Ohio Valley, USA 325 isolated birth effects and 63 multiple defects on a total of 10 262 live births for analysis Exposure: PFOA measurement at study enrolment and via a pharmacokinetic estimated serum for the year of conception Outcome: self-reported birth defect (down, eye, genital, urinary tract, nose, oral clefts, sickle cell, spina bifida, marfan syndrome, other) Result: only adjusted for year of conception OR per log IQR increase Brain defects (13 cases): OR: 2.6 (95% CI 1.3, 5.1) Heart defects: OR (60 cases): 1.2 (95% CI 0.8, 1.7) Genitourinary (31 cases): OR: 1.0 (95% CI 0.6, 1.7)	Generally no association between estimated PFOA concentration and birth defects, with the possible exception of brain defects. As this was based on 13 cases and may represent a chance finding, further investigation of this potential association may be warranted. The median PFOA concentration was 10.4 (IQR: 5.0-44.8) ng/ml
Liew 2014[111]	Congenital cerebral palsy	Case-cohort in the Danish national Birth cohort with 83 389 mother child pairs 156 cases identified and 550 randomly selected controls Exposure: prenatal maternal 6 PFAS in first trim Outcome: confirmed cerebral palsy (linkage with register) Result: adjusted RR per ln increase **in boys**: PFOS: 1.7 (95% CI: 1.0-2.8) PFOA: 2.1 (95% CI: 1.2-3.6) PFHxS : 1.2 (95% CI: 0.9-1.7) PFNA : 1.2 (95% CI: 0.6-2.5) PFHpS : 1.5 (95% CI: 1.0-2.2) PFDA : 1.1 (95% CI: 0.7 -1.7)	*Dose-response–like association between prenatal exposure to some PFAS and the risks of cerebral palsy in boys, but the finding is novel and replication is needed.* high PFOS and PFOA exposure median PFOS 28.90 ng/ml in cases boys and 27.60 ng/ml in control boys median PFOA 4.56 ng/ml in cases boys and 4.00 ng/ml in control boys
Vesterholm Jensen 2014[112]	Congenital cryptorchidism	Nested Case-control in a Danish and Finnish birth cohort 29 Danish cases + 48 Finnish cases Matched control by year of birth 30 Danish and 78 Finnish Exposure: PFAS in cord blood Outcome: diagnosis at birth Result: adjusted OR (birth weight, gestational age and parity) per ln increase PFOS: 0.83 (95% CI 0.44–1.58) PFOA: 0.51 (95% CI 0.21–1.20)	*We found no statistically significant association between cord blood PFOA and PFOS levels and congenital cryptorchidism;* *however, study was small and larger studies are warranted*

Study	Outcome	Study characteristics	Result
Kim 2016[114]	Congenital hypothyroidism	Case control in South Korean hospital 27 infants with congenital hypothyroidism, and 13 healthy infants Exposure: 16 PFAS in blood sample of infant in the 1-3 months after birth Outcome: congenital hypothyroidism not specified Result: PFOA, PFNA, PFDA and PFUnDA concentrations were higher in case group than in the control group.	*Concentrations of serum PFOA, PFNA, PFDA, PFUnDA, were significantly higher in the case group than the control group.* *This is a very small sample size study.*
Desalegn 2021[113]	Cryptorchidism (congenital, etc)	Case cohort in Norwegian Human Milk Study (2606 mother-infant pairs, of which 1326 mother-son and 641 with data on PFAS exposure) 26 cases of congenital cryptorchidism – 485 controls Exposure: PFAS and other EDCs in breast milk Outcome: self-reported by mothers	*There were no associations for individual PFASs with any of the cryptorchidism definitions.*
Ou 2021[115]	Congenital heart disease	Nested case–control in a Chinese hospital cohort of 11 578 live births (2014-2018) 158 cases and 158 controls matched by maternal age and parity (some cases had been excluded because of not enough specimen for PFAS analysis, and some had chromosomal malformations, syndromes) Exposure: 27 PFAS in maternal plasma just before birth Outcome: cardiologist-confirmed prenatal CDH (major lesion) after delivery Result: maternal age, parity, infant sex adjusted OR for categorical exposure: high (>75percentile) versus low exposure. Total PFOS: 1.61 (95% CI:0.91,2.84) Linear PFOS : **2.02 (95% CI 1.12,3.62)** Branched PFOS : 1.36 (95% CI 0.80,2.30) PFOA : 0.64 (95% CI 0.34,1.21) PFDA : **1.83 (95% CI 1.07,3.12)** PFHxA : 0.57(95% CI 0.31,1.04) PFNA : 1.33 (95% CI 0.75,2.35)	*Suggest gestational exposure to linear PFOS and PFDA may be associated with CHD. These results should be considered preliminary and interpreted with caution, and need to be confirmed in larger studies*
Hasegawa 2024[118]	Chromosomal abnormalities	Nested case control in Japan Environment and Children's Study Birth cohort study (JECS) 44 cases/ 24 653 non-cases (and 27 unconfirmed) Exposure: prenatal PFAS in first trim	*Study **suggest** potential association between PFAS (specifically PFOS), but selection bias cannot be ruled out.* *Although the study accounted for non–live-birth cases collected in JECS,*

Study	Outcome	Study characteristics	Result
		outcome: chromosomal abnormalities confirmed via test in all births (incl. abortions, miscarriages, stillbirth, live birth) Result: age and parity adjusted OR per doubling increase in concentration (log 2) for PFOS: 2.05 (95% CI: 1.38-3.05) for PFNA: 1.78 (95% CI: 1.22-2.58) No other PFAS showed significant association (PFDA, PFOA, PFunA, PFHxS, PFTrDA) **Mixture analysis**: OR per doubling increase in PFAS mixture = 2.22 (95% CI: 1.25, 3.96)	*pregnancy loss before recruitment (12 weeks gestation) was not included.*
Li 2024[116]	Congenital heart disease	Case control multicentre study on pollutants in China (2016-2021) 185 cases (211 excluding 26 who had also other anomalies) and 247 controls (matched for residence and gestational weeks, but the pairs not used because insufficient blood volume) Exposure: 13 PFAS in maternal plasma in 3th trim Outcome: prenatal major structural CHD Result: age, BMI, parity, fetal sex,…adjusted analysis showed increased OR when comparing above median and below median: PFOA: 1.00 (95%CI 0.97-1.02) PFOS : 1.01 (95%CI 0.93-1.09) **PFNA 1.30 (95% CI: 1.07-1.58),** **PFDA 2.07 (95% CI: 1.32-3.26),** **PFUnD 2.86 (95% CI: 1.45-5.65)** **6 :2 Cl PFESA : 1.15 (95%CI 1.01-1.3°)** Mixture analyses : BKMR model, indication of linearity qgcomp model : Prenatal exposure to the seven PFAS mixture was associated with an increased prevalence of CHD (**OR = 1.29**, 95%CI: 1.05–1.59), PFDA with the highest weight	*PFNA, PFDA, PFunDA significantly associated with risk for CHD.* *Multipollutant models (BKMR model and qgcomp) identified that a significant positive association between the PFAS mixture and risk for CHD, with PFDA one of the major contributors.*
Jiao 2025[117]	Congenital heart disease	Hospital-based cross-sectional case–control in China 282 cases (cardiac surgery) and 282 healthy matched controls on age, sex and race exposure: 19 PFAS **in children** before cardiac surgery outcome: children with CHD undergoing surgery	*Exposure to **PFAS mixtures** was associated with an increased risk of CHD in children, with 6:2 Cl-PFESA, 8:2 Cl-PFESA, PFBA, PFHxA, and PFTeDA*

Study	Outcome	Study characteristics	Result
		Result: Age and sex adjusted OR per ln increase **PFOA: 1.64 (95% CI: 1.27, 2.13)** **n-PFOS: 1.12 (95%CI 0.95, 1.31)** **6:2 Cl-PFESA: 1.65 (95% CI: 1.40, 1.94)** **8:2 Cl-PFESA : 1.92 (95% CI: 1.69, 2.19)** PFDA : 1.01 (95% CI 0.86, 1.19) **PFBA : 2.68 (95% CI: 2.28-3.15)** **PFBS : 2.38 (95% CI:1.77-3.22)** **PFHxA : 2.62 (95% CI:1.99-3.45)** **PFTeDA : 2.18 (95% CI:1.81-2.63)** Mixture analyses : BKMR model, including 6:2 Cl-PFESA, 8:2 Cl-PFESA, PFBA, PFHxA, and PFTeDA, all with PIPs of 1.00 WQS model : OR 3.49 ($q < 0.001$) with a one-quartile increase in the weighted sum of PFAS exposures. Restricted cubic spline curves indicate non-linear relationship	
Wu 2025[119]	congenital structural malformations	Nested case control in the cohort of mothers and infants in Chinese city 46 cases (incl. 11 circulatory system, 3 chromosomal abnormalities, etc) and 50 controls Exposure: 13 PFAS in maternal blood in early pregnancy Outcome: confirmed diagnosis of congenital structural malformations (ICD codes) Result: adjusted OR per ln increase concentration (adjusted for age at menarche and history of harmful factors before or during pregnancy)Linear PFDA: 4.79 (95% CI 1.55-18.52) Mixture analyses: BKMR model PFDA, PFOA, 9Cl_PF3ONS, and PFNA being significant contributors to the mixture effect.	*prenatal exposure to PFDA and PFAS mixtures was significantly linked to a heightened risk of congenital structural malformations with PFDA, PFOA, 9Cl-PF3ONS, and PFNA emerging as key contributors to the overall mixture effect* *Very small study, additional studies are necessary to confirm these results*

4.7.4.2 Outcome: congenital heart disease

Three Chinese studies focussed on serious congenital heart disease (major lesion CHD,[115] prenatal major structural CHD,[116] children needing surgery[117]). Another Chinese study on structural malformation also included 11 cases with congenital heart disease, but did not report on that outcome in particular,[119] and one US study reported on self-reported congenital heart defects.[110]

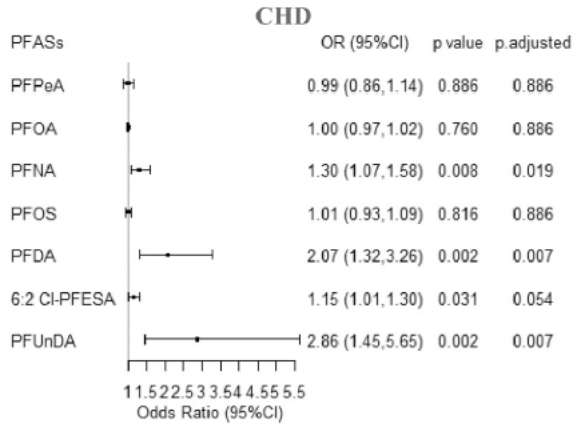
In 2021, Ou et al suggested gestational exposure to linear PFOS and PFDA may be associated with septal defects and conotruncal heart defects.[115] The authors indicated that these results in 158 cases and 158 matched controls should be considered preliminary and interpreted with caution. In 2024, Li et al concluded that gestational exposure to PFNA, PFDA, PFunDA was significantly associated with risk for congenital heart disease.[116]. They performed stratified analyses and their findings remained stable. They also performed multipollutant models (BKMR and qgcomp) and identified a consistent association between higher exposure and congenital heart disease (OR=1.29, 95%CI 1.05-1.59), with PFDA as largest contributor.[116]

The 2025 Chinese cross-sectional study on 282 cases and 282 healthy matched controls measured PFAS exposure in children's blood (no maternal blood) before surgery and indicated that a wide range of PFAS (PFOA, 6:2 Cl-PFESA, 8:2 Cl-PFESA, PFBA, PFBS, PFHxA, PFHpS, PFHxS and PFTeDA) was associated with congenital heart disease.[117] The restricted cubic spline curves revealed nonlinear relationships. Also the mixture analyses showed significant associations. The BKMR model identified significant contributors to the overall association, including 6:2 Cl-PFESA, 8:2 Cl-PFESA, PFBA, PFHxA, and PFTeDA). The weighted quantile sum regression reported an OR of 3.49 representing for each quartile increase in the overall PFAS mixture, the odds of CHD increase by 249%. However, the cross-sectional study design and the absence of adjustment for key confounding variables substantially limit the interpretability of the reported associations, a limitation also acknowledged by the authors.[117]

A Chinese nested case control study in 46 children with congenital structural malformations did include 11 cases with malformations in the circulatory system but did not conclude separately on this outcome.[119] No conclusions can be drawn based on this small study. The US study in the mid-Ohio valley on birth defects included 60 cases of self-reported heart defects and reported separately on this outcome, but did not identify an association with increasing PFOA.[110]

In conclusion, three studies with a total sample size of 1312, exclusively conducted in China, reported a positive association between congenital heart disease and increasing PFAS exposure. In these studies, the observed significant associations involved different PFAS compounds, with no consistent pattern emerging across individual PFAS analytes, though PFDA was mentioned in both the Li and Ou study.[115, 116] The studies by Li et al. and Ou et al. primarily identified long-chain perfluoroalkyl carboxylic acids (PFCAs), whereas Jiao found associations with some long-chain compounds (PFTeDA), and significant roles for emerging alternatives (e.g., 6:2 and 8:2 Cl-PFESA) as well as short-chain PFAS. The two studies that performed mixture analyses consistently reported a significant association with the PFAS mixture.[116, 117]

Figure 9 – Odds ratio for major structural congenital heart disease and individual PFAS as reported in Li 2024[116]



4.7.5 Certainty of evidence with GRADE

4.7.5.1 Congenital abnormalities in general

The studies on different congenital abnormalities were anecdotal (single studies with often small sample sizes). Therefore no GRADE assessment was performed for congenital cerebral palsy, chromosomal abnormalities, congenital hypothyroidism and congenital cryptorchidism. Further research with larger and methodologically rigorous studies is required.

4.7.5.2 Congenital heart disease

Inconsistency

Given the very limited evidence base—only three studies (n=1312 included), one of which had a clear high risk of confounding bias—it was difficult to reliably assess inconsistency.

There is some consistency in direction of a harmful effect, especially for the PFAS-mixture and PFDA and 6:2 Cl-PFESA (2 studies), therefore no rating down for inconsistency.

Risk of bias

Risk of bias analysis showed definite high risk for confounding bias and detection bias for Jiao (e.g. only adjusted for children's age and sex, and not maternal factors), as well as the study by Ou had probably high risk of bias for selection and confounding, and the study by Li had probable high selection bias (see supplement 3.2.5). This warranted a downgrading for risk of bias.

Imprecision

As we did not perform a pooling there is no single risk estimate to judge imprecision.

Indirectness

The studies focused on serious congenital studies which is in concordance with the PECO focussing on concerning health outcomes.

Dose-response analysis

Two studies reported on dose-response relationship. The one indicating linearity and the other non-linear relationships. However, no clear indication for upgrading.

The magnitude of effect.

There was no pooled estimate and no rigorous observational study with low risk of confounding to judge magnitude of effect. The individual studies reported for some individual PFAS an effect size larger than 2: PFOS in Ou 2021, PFDA and PFunD in Li 2024, PFBA,PFBS, PFHxA, PFTeDA in Jaio 2025.

Table 22 – GRADE assessment for congenital heart disease

GRADE assessment								
No of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Magnitude of effect**	**Dose-response**	**Other considerations**	**Conclusion**
3 (n= 1312)	**Serious**	Not serious	Not serious	Not assessed, because no pooled estimate	Not assessed, because no pooled estimate	No clear effect *	Publication bias not assessed Residual confounding: not applicable	**very low**

** two studies reported on dose-response relationship. The one indicating linearity and the other non-linear relationships.*

4.8 Vaccine response

Assessing the link between PFAS exposure and vaccine immune response is highly relevant because vaccine-induced antibodies are a functional measure of immune competence, not just a biochemical marker.[120] A reduced response to vaccination may indicate a broader impairment of the adaptive immune system, particularly in children during critical developmental periods. Evidence suggesting that PFAS may lower antibody titers raises concerns about reduced vaccine effectiveness and increased susceptibility to infections.[120, 121] This issue has gained regulatory importance, as the European Food Safety Authority (EFSA) identified decreased vaccine response as the critical effect for deriving health-based guidance values for PFAS (EFSA, 2020).[122] This represents a shift from earlier focus on metabolic endpoints such as cholesterol to direct human functional outcomes. Evaluating this association therefore helps inform risk assessment, public health policy, and exposure limits.[122] It is also essential for identifying vulnerable populations, such as infants and children, who may be more sensitive to immunotoxic effects.

Several recent mechanistic studies provide biological explanations for how PFAS may impair vaccine-induced immune responses. First, PFAS have been shown to disrupt B-cell development and function, including alterations in key signaling pathways such as NF-κB and NFAT, which are essential for antibody production. This can directly reduce the ability to generate vaccine-specific antibodies.[123]

Second, PFAS exposure can impair adaptive immunity more broadly, with experimental and in vivo data showing reduced T-cell responses and impaired coordination between T and B cells following immune challenge.[124] Since effective vaccination relies on T-cell–dependent antibody maturation, this mechanism is particularly relevant.

Third, PFAS may alter cytokine signaling and immune balance, including shifts in Th1/Th2 responses, which can weaken the quality and durability of vaccine-induced immunity. These alterations can lead to less effective immune memory formation. In addition, PFAS are known to act as immunomodulatory chemicals targeting multiple immune compartments, including lymphoid organs and circulating immune cells, resulting in broad immune dysregulation rather than a single pathway effect.[125]

4.8.1 Key points

- A recent good quality SR (Crawford 2023[18])[120] meta-analysed 14 studies on the effect of PFOS, PFOA, PFHxS, PFNA, and PFDA on the IgG antibody titers after vaccination (diphtheria, haemophilus influenza b, influenza A H1N1, measles, rubella, tetanus). Only 4 studies assessed the effect of gestational PFAS exposure on antibody titers in childhood.
- Results were heterogeneous across PFAS. No statistically significant associations were reported for PFNA or PFDA, suggesting either a lack of effect or insufficient evidence. Results were also heterogeneous within PFAS, with statistically significant associations only for some of the vaccines. PFOS and PFOA displayed the most frequent inverse associations with antibody concentrations, particularly for diphtheria, tetanus, and rubella.
- These associations were expressed in $\log_e$(antibody concentration) unit per doubling of PFAS concentration. Although the effect size was generally modest, a dose-response pattern cannot be excluded. The clinical significance of these small antibody reductions remains unclear.
- The level of confidence based on the GRADE framework was low for PFOS, PFOA and PFHxS, and very low for PFDA and PFNA.

4.8.2 Results of systematic reviews

Two recent systematic reviews were identified.[120, 121] According to AMSTAR-2 (See Supplement 3.1.8), Antoniou et al. (2024) showed several methodological limitations. In contrast, Crawford et al. (2023) met most AMSTAR-2 criteria, including comprehensive literature search, duplicate processes, and advanced multilevel meta-analytic methods, and can be considered high methodological quality. The two reviews rely on a largely overlapping set of core epidemiological studies, particularly the Faroese and European birth cohorts. Therefore, our analysis was based on Crawford 2023.[120]

4.8.2.1 Characteristics of the SR

This systematic review and meta-analysis included 14 reports (2012–2022), representing 13 unique study populations, identified through searches of PubMed and Web of Science up to May 2022. Eligible studies were observational (10 longitudinal, 4 cross-sectional) and conducted in humans of all ages (five reports were about adults), 4 reports included mother–child pairs), with exposure defined as serum or plasma concentrations of five PFAS (PFOA, PFOS, PFHxS, PFNA, PFDA). Apart from a report about Africa and another on from Greenland, nine reports were about populations in Europe (including the Faroes) and four were about populations in the U.S. Some studies contributed multiple publications, notably the Faroe Islands cohort. Across all 14 reports, the smallest number of subjects was 12, and the largest was 2,351. The total included population was 4 830 including both children and adults.

Exposure assessment relied primarily on blood-based biomarkers, although modeled serum concentrations were accepted when validated pharmacokinetic models were available. The level of blood PFAS concentration varied across studies. In two studies, the median PFOA level was high (31.6 ng/ml and 14.5 ng/ml), whereas eight reports had central PFOA levels that were 2.0–4.4 ng/ml.

Outcomes were IgG antibody concentrations following vaccination, measured on a continuous scale and expressed or re-expressed as differences in $\log_e$-transformed antibody levels per doubling of PFAS. The frequency of studies of a given antibody was Tetanus (n = 7); followed by Diphtheria (6); Measles (4), Rubella (3); *Haemophilus influenzae* type b and Influenza A H1N1 (2 each); and Hepatitis A, Hepatitis B, Influenza A H3N2, Influenza B, and Mumps (1 each). The span of time from vaccination or disease to antibody measurement, where presented, varied from days to years. The assays used were standard and generally well-accepted.

Study quality was assessed at the individual study level using a domain-based risk-of-bias tool, which evaluated potential biases related to exposure assessment, outcome measurement, confounding, participant selection, and statistical analysis (Morgan framework for non-randomized studies of exposure[126]). The overall RoB for each of the included reports was judged as low, moderate, or serious. In addition, the overall certainty of the evidence across studies was evaluated using the GRADE framework, providing a structured assessment of confidence in the pooled results. In this review, the certainty of evidence was initially rated as high. This approach differs from the conventional starting point for observational studies in the GRADE framework, because the review incorporated a structured risk-of-bias assessment tailored to non-randomized studies of exposure (Morgan et al., 2019[126]). Under this framework, the starting level reflects the assumption that, in the absence of important limitations, the body of evidence could provide a reliable estimate of the association. The certainty was then downgraded based on predefined criteria, including risk of bias, inconsistency, and imprecision, rather than being determined solely by study design .

4.8.2.2 Results

The main results are presented in Table 23. β units are differences in $\log_e$(antibody concentration) per doubling of PFAS. Multiplying the β coefficients by 100 gives a rough approximation of the percent difference in antibody concentration per PFAS doubling.[120]

Table 23 – Statistically significant results on the association between PFAS and antibody titers (Crawford 2023[120])

PFAS	Outcome	Life-stage group	Beta	95% CI	Certainty GRADE (Crawford 2023)
PFOA (n=13)	All antibodies treated as one type	All ages	**−0.06**	**−0.10 to −0.01**	Moderate
PFOA (n=8)	All antibodies treated as one type	Children	**−0.10**	**−0.16 to −0.03**	Moderate
PFOA (n=4)	Diphtheria antibody	Children	**−0.12**	**−0.23 to −0.00**	High
PFOA (n=3)	Rubella antibody	All ages	**−0.09**	**−0.17 to −0.01**	Moderate
PFOA (n=5)	Tetanus antibody	Children	**−0.12**	**−0.24 to −0.00**	Moderate
PFOS (n=13)	All antibodies treated as one type	All ages	**−0.06**	**−0.11 to −0.01**	Moderate
PFOS (n=8)	All antibodies treated as one type	Children	**−0.10**	**−0.18 to −0.03**	Moderate
PFOS (n=3)	Rubella antibody	All ages	**−0.09**	**−0.15 to −0.03**	High
PFOS (n=2)	Rubella antibody	Children	**−0.12**	**−0.20 to −0.04**	High
PFHxS (n=10)	All antibodies treated as one type	All ages	**−0.03**	**−0.06 to −0.00**	Moderate
PFHxS (n=7)	All antibodies treated as one type	Children	**−0.05**	**−0.09 to −0.00**	Low
PFHxS (n=2)	Rubella antibody	Children	**−0.07**	**−0.11 to −0.02**	High

For associations where results are presented for all ages and children, the effect modification by life stage was not statistically significant ($p > 0.10$). The units for β were difference in $\log_e$(antibody concentration) per doubling of PFAS. The certainty level is the one reported by the authors of the systematic review. Of note, the initial rating was high quality, an unusual approach for observational studies in the GRADE framework.

It should be noted that the evidence was very scarce for young children. PFAS were measured in maternal serum in only 4 studies (Grandjean 2012, Granum 2013, Grandjean 2017b, Timmermann 2022), and antibody response before age 5 years in only 3 studies (Granum 2013, Abraham 2020, Timmermann 2020). In Table 23 only results with a statistically significant association are listed, i.e. many associations between PFAS exposure and vaccine antibody titers were not statistically significant, indicating substantial variability across compounds, outcomes, and life stages. For children, there was a significant association with specific vaccines only for PFOA and diphtheria and tetanus, for PFOS and rubella, and for PFHxS and rubella. Moreover, it can be seen in the table that the upper bound of the confidence interval is often close to 0 (numbers rounded to two digits). Nevertheless, a consistent pattern emerges for PFOS and PFOA, which display the most frequent inverse associations with antibody concentrations, particularly for diphtheria, tetanus, and rubella. These associations are generally modest in magnitude but are observed across multiple cohorts and exposure windows, supporting their robustness. In contrast, PFHxS shows weaker and less consistent associations, with only a few significant findings, mainly for combined antibody outcomes or rubella in children. Importantly, no statistically significant associations were reported for PFNA or PFDA, suggesting either a lack of effect or insufficient evidence. The significant results are often restricted to specific life stages, particularly childhood exposure, highlighting the importance of timing. Crawford et al. did not report a meta-analysis specific to maternal-child pairs, but associations between specific PFAS and antibody titers are reported for individual studies in their Table 4 (p9). Here again, results varied a lot across PFAS and vaccine.

Overall, the findings suggest that only a subset of PFAS is associated with reduced antibody responses, while the broader class effect is not supported. These results underscore the need to consider compound-specific effects rather than PFAS as a homogeneous group.

4.8.3 Discussion

Crawford et al. found that PFAS exposure was associated with small reductions in vaccine antibody concentrations, with the clearest signals for PFOA, PFOS, and to a lesser extent PFHxS. The strongest and most consistent results concerned PFOA and PFOS, especially for diphtheria, tetanus, and rubella antibodies, whereas PFNA and PFDA showed no statistically relevant associations. Effects were expressed as changes in $\log_e$ antibody concentration per doubling of PFAS, and most significant estimates were modest, generally around −0.03 to −0.12 $\log_e$ units, with the upper bound of the confidence interval often ≤-0.03. Of note, in animal studies the lowest serum PFAS concentration resulting in an effect was 92 ng/ml PFOS, and 18 ng/ml was the no observable adverse effect concentration.[120] Levels of contamination in this systematic review were much lower.

A doubling of PFAS concentration was used as the comparator. This meant, on an arithmetic scale, exposure metrics were not comparable across reports, i.e., a doubling in one report expressed in ng/ml PFAS could be very different than in another report. The authors acknowledge that their results could have been substantially affected by this choice of comparator.[120]

The quality of evidence in Crawford 2023 was not uniform. The quality of evidence varied across compounds and outcomes, and was judged high only for the associations of PFOA and diphtheria in children, PFOS and rubella (both for all ages and for children), and PFHxS and rubella in children. All the other associations were rated moderate or low, despite the quite unusual approach of initially rating high all observational studies. If the authors had used GRADE in the usual way, that is, by initially classifying observational studies as low quality, the quality level of the studies found would be even lower. This is what we report in Table 24, with low confidence level for PFOS, PFOA and PFHxS, and very low confidence for PFDA and PFNA. Initially rating the studies low quality seems justified here as confounding by other pollutants and other factors was little assessed.

Antoniou 2024 reported broadly consistent findings: gestational PFAS exposure was associated with decreases in antibody responses, but the decreases were statistically significant only for some PFAS

and for some antibody titers[w]. [116] The number of studies was limited. The numerical comparisons between the two systematic reviews is difficult because Crawford et al. used stricter harmonization procedures, i.e. the effect sizes seem lower in the latter.

A central limitation is the uncertain clinical significance of these small antibody reductions. A statistically significant decrease in antibody titer does not necessarily mean loss of clinical protection, especially if antibody levels remain above accepted protective thresholds. Treating all antibodies as one type increased the statistical power of the meta-analysis, but rendered the clinical interpretation even more complex. However, even small downward shifts in antibody distributions could matter at the population level, particularly for children with lower baseline responses, incomplete vaccination, waning immunity, or higher exposure burdens. But this still needs to be confirmed. While antibody response may be a reasonable endpoint, the evidence that clinical infectious disease outcomes are related to serum concentration of PFAS is not clear.[120]

The findings are nevertheless important because vaccine antibody response is a functional immune endpoint, not merely a biomarker. This helps explain why regulatory discussions, including EFSA's PFAS assessment, gave substantial weight to vaccine response as a critical endpoint rather than relying only on metabolic outcomes such as cholesterol. Crawford's results support this shift, but also show that the evidence is strongest for selected PFAS and selected vaccines, not for all PFAS uniformly.

Further studies should include larger cohorts with repeated PFAS measurements, standardized vaccine-response timing, antibody thresholds linked to clinical protection, and assessment of actual infection outcomes (see section 4.9 on infections). More work is also needed on mixtures and newer PFAS.

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[w] Based on the percent difference in vaccine antibody response, there is *high certainty of confidence* in the results which suggest *no association* between:

- PFOS and measles, mumps (evidence from one study), and rubella (evidence from one study).
- PFOA and measles and Hib.
- PFHxS and tetanus and measles.
- PFNA and tetanus, mumps (evidence from one study), and diphtheria.
- PFDA and tetanus and diphtheria.

Based on the percent difference in vaccine antibody response, there is low confidence of evidence in the results

which suggest an association between:

- PFOS and tetanus, diphtheria, Hib.
- PFOA and tetanus, and diphtheria, and rubella (evidence from one study)
- PFHxS and diphtheria, rubella (evidence from one study), and Hib (evidence from one study).
- PFNA and measles (evidence from one study) and rubella (evidence from one study).
- PFUnDA and measles.

4.8.4 Certainty of evidence with GRADE

Table 24 – GRADE assessment for vaccine response

GRADE assessment								
No of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Magnitude of effect**	**Dose-response**	**Other considerations**	**Conclusion**
PFOA 13 studies, all antibodies (n= 4 830) in SR by Crawford 2023[120]	Not serious	**Serious**: -1	Not serious	Not serious	Small	Plausible: +1	No Publication bias Residual confounding: not applicable	**Low**
PFOS 13 studies, all antibodies (n= 4 830)	Not serious	**Serious:** -1	Not serious	Not serious	Small	Plausible: +1	No Publication bias Residual confounding: not applicable	**Low**
PFHxS 10 studies, all antibodies (n=3165)	**Serious**: -1	Not serious	Not serious	Not serious	Small	Plausible: +1	No Publication bias Residual confounding: not applicable	**Low**
PFNA 10 studies, all antibodies (n= 3 165))	**Serious**: -1	**Serious:** -1	Not serious	**Serious**: -1	No significant effect	NA	No Publication bias Residual confounding: not applicable	**Very low**
PFDA 7 studies, all antibodies (n=1850)	Not serious	**Serious**: -1	Not serious	Serious: -1	No significant effect	NA	No Publication bias Residual confounding: not applicable	**Very low**

Initial rating for all PFAS is low, following GRADE framework

4.9 Infections during infancy and early childhood

4.9.1 Definition of the outcome

All infectious diseases during infancy were considered, ranging from gastrointestinal infections to respiratory infections. Symptoms of infectious disease such as fever were not specifically targeted, though they are sometimes mentioned in studies.[127, 128] Both incidence of infectious disease as expressions of severity of disease (such as number of episodes, rate, hospitalisation rates) were considered.

4.9.2 Key points

- Based on a recent good quality SR (Rosen 2025)[18] meta-analysing 14 studies on infection risk and rate in children, we concluded there is very low certainty in an association of PFAS and increased risk for infection in children
- Numerous individual PFAS congeners were evaluated for each infection type, and per exposure increment metric, and most analyses did not demonstrate statistically significant associations
- Statistical significant results were noted for PFNA (n=4 studies) for lower respiratory tract infection rate expressed in log increase; PFDA (n=3) for overall infection rate in absolute scale; PFHxS (n=5) for overall infection rate in absolute scale, PFOSA (n=2) for lower respiratory tract infection rate in log scale, PFUnDA (n= 4) for overall infection rate expressed in log increase

4.9.3 Results of systematic reviews

Three recent SRs were identified, of which two were of good quality,[18, 129] and one of lower quality[121](as rated with the AMSTAR 2 criteria see supplement 3.1.9).

Lyrou et al. focused on the incidence of respiratory infections in infants and children. In contrast, Rosen and colleagues adopted a broader scope by examining infectious diseases across all age groups, although most of the included studies involved children. All studies included in Lyrou were also included in Rosen, and the SR by Rosen additionally incorporated more recent studies.

Lyrou et al included six prospective cohort studies focusing on mother-child pairs (ranging from 235 pairs in a Chinese study to 1 558 in a Japanese study). Follow-up periods ranged from infancy to mid-childhood, extending up to 10 years in some. Each study was systematically reviewed, but no meta-analysis was performed as the included studies exhibit heterogeneity in study design, exposure assessments methods, outcome definitions. While several studies reported associations between higher prenatal PFAS exposure, particularly to PFHxS and PFOS, and increased risk of respiratory infections in early childhood, findings were not entirely consistent across PFAS compounds or age group.

The SR and meta-analysis by Rosen was requested by 3M, but the company was not involved in the protocol. Although the target population included humans of all ages, Rosen identified 18 studies that reported on the outcome in children. Exposure was assessed during gestation in the majority of studies, except Impinen 2019, Huang 2020 and Huang 2023 in cord blood and Timmermann 2020 and Wiener and Waters 2019 in the child. Rosen meta-analyzed log and absolute exposure results separately and re-expressed as per log2 and per IQR increase. However not all studies provided data that could be pooled. For studies that could not be included in the meta-analysis, a combined p-value approach was applied to synthesize their statistical evidence. The meta-analytic results restricted to 14 studies of children (n ~13800) did not show a clear consistent association between one of the twelve PFAS under study and risk or rate of low respiratory tract infection, upper respiratory tract

infection, gastrointestinal infection, otitis media, nor on respiratory tract infections not otherwise specified. Depending on whether expressed on either the log scale or the absolute scale, some compounds showed a significant association when the effect estimate was expressed as an event rate (rather than a risk) (PFNA 4 studies β=0.1233, 95%CI 0.0187-0.228 for lower respiratory tract infection rate expressed in log increase; PFDA 3 studies β=0.8321, 95% CI 0.43-1.2332 for overall infection rate in absolute scale; PFHxS in 5 studies β=0.1885, 95%CI 0.0408-0.3363 for overall infection rate in absolute scale, PFOSA in 2 studies β=0.1438, 95%CI 0.0861-0.2014 for lower respiratory tract infection rate in log scale, PFUnDA in 4 studies β=0.1606, 95%CI 0.0395-0.2816 for overall infection rate expressed in log increase). The leave-one-out analysis showed that each of the significant results depended on the findings of a single study (the specific critical study varied) which, when excluded, meant loss of statistical significance. This pattern shows that the findings were not robust.

Table 25 – Overview of systematic reviews and meta-analyses on infection risk

Systematic review	Included primary studies on infants/children	Result	Remark	Quality appraisal
Lyrou 2025[129]	• Manzano-Salgado 2019 (Spain): 1 214 mother child pairs • Dalsager 2016 (Denmark): n= 359 mother-child pairs • Impinen 2018 (Norway): 641 infants • Impinen 2019 (Norway): 792 participants • Wang 2022 (China): 235 mother child pairs • Goudarzi 2017 (Japan): 1 558 mother child pairs	Narrative reporting, no meta-analysis. While several studies report associations between higher prenatal PFAS exposure, particularly to PFHxS and PFOS, and increased risk of respiratory infections in early childhood, findings are not entirely consistent across compounds or age group. Evidence remains limited by heterogeneity in study design, exposure assessment, and outcome definitions	Limitation of the primary studies: • Self-reported outcomes • Only a few controlled for co-exposers and confounders Older studies not taken into account: Fei 2010 (Denmark, n= 1400) Some studies not identified? Philippat 2023 (France, n=404) Svelsted 2023 (Denmark, n=634)	no critical limitations
Rosen 2025[18]	<u>18 Studies on children <7 years</u> • Huang 2020 (China) • Huang 2023 (China) • Impinen 2018 • Philippat 2023 (France) • Sevelsted 2023 (Denmark) • Timmermann 2020 • Wang 2022 (China) • Fei 2010 • Manzano-Salgado 2019 (Spain) MoBa study (Norway): • Granum 2013 • Impinen 2019 Hokkaida study (Japan): • Ait Bamai 2020 • Goudarzi 2017 (HR) • Okada 2012	identified moderate evidence of positive associations that were of variable size but usually small; the certainty of evidence was, however, generally low or very low and diminished by the possible influences of multiple testing and covariance among results not accounted for in the analyses most of the positive findings were between PFAS and event rate, rather than initial disease occurrence. This suggests that PFAS exposure may influence the frequency of infections rather than	Used GRADE methodology largest dataset and stratification by risk, event rate, and exposure scale re-expression OR as RR, and pooled log and absolute exposure results separately, as they are not directly comparable. Specific studies on infants < 2y: Impinen 2019: number of common cold episodes by age 2 Manzano Salgado 2019: number of LRTI at 1.5y	no critical limitations

Systematic review	Included primary studies on infants/children	Result	Remark	Quality appraisal
	NHANES (USA) • Wiener and Waters 2019 • Zhang 2022 Odense child cohort (Denmark) • Dalsager 2016 • Dalsager 2021	the likelihood of an initial occurrence.	Philippat 2023: bronchiolitis/bronchitis by age 2 Wang 2022: any occurrence and number of common cold, bronchitis, pneumonia, diarrhoea 3M sponsored study	
Antoniou and Dekant 2024[121]	• Ai Bamal 2020 (Japan): Rhinitis, Chicken pox, Otitis media, Pneumonia at 7y • Dalsager 2016 (Denmark): Fever cough diarrhea at 1y • Dalsager 2021 (Denmark): hospitalization , respiratory infection, gastrointestinal at 4y • Fei 2010 (Denmark): hospitalisation at 9y • Goudarzi 2017 (Japan): any infection at 4y • Impinen 2018 (Norway): cold, atopic dermatitis at 2y • Impinen 2019 (Norway): cold, pneumonia, stretococ, pseudocroup, otitis media at 3y • Okada 2012 (Japan): otitis media at 1.5y • Zhang 2022 (USA): cold at 7y • Timmermann 2020: measles, fever, coughing diarrhea at 2y • Stein(USA) at 14.5y 6 studies on adults	the results of this meta-analysis on the epidemiologic evidence do not suggest a strong association between PFAS and immune conditions or infectious diseases in humans. Although “suggestive evidence” for PFOA, PFOS, PFHxS, and PFNA in relation to infections (based on evidence from 1 study) , they lacked consistency across studies.	Used GRADE methodology 3M sponsored study	critical limitations

4.9.4 Certainty of evidence with GRADE

Rosen and colleagues assessed the strength of evidence for each PFAS by evaluating associations with risk, event rates, and a combined rate-risk metric for each infection outcome individually, as well as for an overall composite outcome (all infectious disease risks and rates). They did not rate indirectness, or residual confounding, arguing that confounding had already been addressed within their risk-of-bias assessment, nor did they assess publication bias because fewer than ten studies were available for most exposure–outcome combinations.

They conducted a GRADE assessment beginning from a low certainty rating, and a sensitivity analysis beginning from a moderate rating; both approaches ultimately resulted in a conclusion of very low certainty with a few outcomes reaching low certainty. Oftentimes risk of bias and imprecision led to downgrading.[18]

Inconsistency

Rosen did not report the individual effect measures and associated 95%CI per study to be able to rate inconsistency. However they reported effect direction plots per exposure-outcome combination in supplements and concluded: *albatross plots showed that a small positive association between PFAS exposure and infectious disease risk and rate was more frequently reported than not.*

Risk of bias

Rosen reported an overall low risk of bias as measured with ROBINS-E for most the studies on children, except for the Japanese studies, Fei 2010, Granum 2013, Huang 2023, Philippat 2023 where a high risk of bias due to confounding was identified. Rosen downgraded for risk of bias when considering all relevant studies (also including adults). In our approach (see methods 3.1.5.1), downgrading was applied only when more than half of the studies showed a probably high risk of bias in at least two domains, which was not the case; therefore, no downgrading was applied.

Imprecision

The pooled effect measures were non-significant for the majority of exposure–outcome combinations in children. For example for PFOA there were 19 exposure-outcome combination as well as for PFOS, and none showed a significant association. For PFNA, PFDA, PFHxS and PFUnDA there were significant associations, but always in one particular exposure-outcome combination. Therefore, we rated down for imprecision.

Indirectness

Rosen and colleagues adopted a broader scope by examining infectious diseases across all age groups, although most of the included studies involved children. Moreover in their meta-analysis they performed a sensitive analysis on the 14 studies involving children, and we thus focused on these effect estimates.

Magnitude of effect

Rosen reported for some exposure-outcome combinations an upgrade for magnitude of effect applying a dedicated methodology.[130] However we did not applied this particular methodology.

Dose-response analysis

Rosen did not perform dose response analyses. However they state that the meta-analysis results using an absolute exposure scale might be an indication for dose-response.

The SRs by Rosen reported that there were not sufficient studies to statistically assess publication bias, but that because positive and negative results were reported at the same frequency publication bias was not of particular concern.

Table 26 – GRADE assessment on infections in children

GRADE assessment								
No of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Magnitude of effect**	**Dose-response**	**Other considerations**	**Conclusion**
14 (n= 13 800 (Rosen et al 2025)	Not Serious	undetermined*	Not serious	**Serious** imprecision for most analyses**	Rosen et al. indicated generally low magnitude of effect	Indications but no analysis	No indication of publication bias not assessed Residual confounding: not applicable	**very low**

**the individual effect estimates per study were not shown in Rosen; **Rosen pooled the data per individual PFAS and per infection outcome (risk, rate or a composite outcome) resulting in many different exposure-outcome combinations of which the vast majority were non-significant*

4.10 Acute lymphoblastic leukemia in children

4.10.1 Definition of the outcome

Acute lymphoblastic leukemia (ALL) in children is rare, but it is the most common childhood cancer, representing around 25% of all cancers in children under 15 year.[131] ALL is a complex disease involving genes, biology, and environmental factors.

4.10.2 Key points

- Two nested case control studies were identified (n=1044), and both reported a signal of an association with MeFOSAA (PFOS precursor)
- Based on the available evidence the confidence in an association with MeFOSAA is very low based on the GRADE assessment because 1 study had a high risk of bias, and other GRADE domains were difficult to assess.
- Overall the evidence basis for this outcome is small and this concerning signal should be further examined in future research.

4.10.3 Results from primary studies

No systematic review has been identified for acute lymphoblastic leukemia (ALL) in children. The search for primary studies on 21 April 2026 identified 2 studies from two different research groups (see supplement 1.2.5 and 2.5).[132, 133] A Californian research group and a Finnish research group identified a (borderline) significant association between ALL and the MeFOSAA levels in archived neonatal blood or maternal blood, respectively. There was no association identified with other PFAS compounds, nor the mixture. MeFOSAA is a long-chain PFAS which can metabolize into PFOS under certain conditions. The Californian study also collected maternal blood in the second trimester, but did not identify an association with MeFOSAA, nor any other PFAS compound in this matrix.

Table 27 – Overview of primary studies on PFAS and acute lymphoblastic leukaemia in children

Primary studies	Study details	Result	comments
Morimoto 2025[133]	Case (n=122) matched control (n=122) in the Californian Childhood Cancer Record Linkage Project **Healthy controls** were matched to cancer cases by birth records, ensuring similar distributions of birth year, sex, and race/ethnicity **Exposure**: archived neonatal blood samples and prenatal serum (2nd trimester) with untargeted LC-HRMS **Outcome**: diagnosed with ALL at ages 0–14 years **Analysis**: conditional logistic regression Continuous log 10 increase Mixture: Quantile G-computation (qgcomp)	Association between MeFOSAA levels at birth (not prenatal maternal samples) and increased ALL risk (OR: 2.04 per log 10 increase, 95% CI: 0.97–4.29, p=0.06); after adjusting for all other PFAS (OR: 2.88, 95% CI: 1.12–7.38) gcomp model represent the estimated change in odds of the outcome per one-quartile increase in the joint exposure mixture. OR: 1.18, 95% CI: 0.75–1.89	Analysis with adjusting for all other PFAS only moderate correlation between maternal PFAS levels during early pregnancy and PFAS levels in newborns, suggesting that PFAS levels between mother and child, especially across different periods of embryogenesis, may largely be derived from different sources. Untargeted PFAS analysis so no exact concentrations
Jones 2024[132]	Nested Case (n=400) control (n=400) in the Finnish Maternity Cohort. Controls matched on sample year, mother's age, gestational age, birth order, and child's sex. **Measure**: 19 PFAS in maternal serum (collected in timeframe 1986-2010) at around 10 weeks gestation Outcome: acute lymphoblastic leukemia (ALL) before age 15 **Analysis**: Continuous log 2 increase Categorical in quartiles	Statistical association between MeFOSAA and ALL in children in Finland continuous (per each doubling in levels: adjusted for smoking: aOR (log2) 1.18 (95% CI 1.04 to 1.34) Adjusted for smoking and other PFAS: aOR (log2): 1.22, 95% CI 1.07 to 1.39) The categorical analysis suggests dose-response relationship but only the highest Q4 (>0.94ng/ml) shows significant association: aOR=2.52 (1.33-4.78) Sensitivity analysis by sample year (1986-1995 with median conc PFOS 17.9 ng/ml): aOR 4.01 (1.62-9.93) aOR per log 2 increase PFOA: 1.11 (95%CI 0.85-1.45) PFOS: 0.96 (95%CI 0.73 – 1.26) PFNA: 1.02 (95%CI 0.83-1.24)	Analysis that adjusts for correlated PFAS; the correlation between PFOS and PFOA is high (Spearman ρ 0.54)

LC-HRMS : Liquid Chromatography–High-Resolution Mass Spectrometry; ALL acute lymphoblastic leukaemia; aOR adjusted odds ratio

4.10.4 Certainty of evidence with GRADE

Inconsistency

Given the very limited evidence base—only two studies, one of which had a clear high risk of confounding bias—it was difficult to reliably assess inconsistency.

There is some consistency in direction of a harmful effect for MeFOSAA, therefore no rating down for inconsistency for this particular compound. None of the other studied PFAS, nor the PFAS mixture did show consistent pattern.

Risk of bias

The study by Morimoto shows probably high risk of bias for confounding and selection bias. This warranted a downgrading for risk of bias.

Imprecision

As we did not perform a pooling there is no single risk estimate to judge imprecision. The study of Morimoto was rather imprecise (wide confidence intervals including the null effect).

Indirectness

The studies focused on ALL diagnosis before 15 years which is in concordance with the PECO focussing on concerning health outcomes. We did not rate down the certainty of evidence for indirectness.

Dose-response analysis

The categorical analysis in Jones 2024 suggests dose-response relationship but only the highest Q4.

The magnitude of effect.

There was no pooled estimate. The rigorous observational study by Jones 2024 with low risk of confounding did not indicate a large effect (aOR<2).

Table 28 – GRADE assessment for Acute Lymphoblastic Leukemia

GRADE assessment								
No of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Magnitude of effect**	**Dose-response**	**Other considerations**	**Conclusion**
2 (n= 1 044)	**Serious**	Not serious	Not serious	Not assessed	Not assessed	undetermined	publication bias not assessed Residual confounding: not assessed	**MeFOSAA: very low**

5 EXPOSURE THROUGH BREASTFEEDING

PFAS can be present in breast milk (also called 'human milk'), and can be transferred from the mother to infants through breastfeeding. The PFAS concentration in colostrum and breast milk are much lower, approximately 0.9 to 2 % and 1.8 to 9 % of the levels in the mother's blood for PFOS and PFOA respectively.[134, 135]

This section focuses on adverse health effects of breastfeeding infants by PFAS exposed women. What does literature tell us, and what are the current recommendations regarding breastfeeding in highly exposed women?

5.1 Key points

- There is no conclusive evidence from systematic reviews on the detrimental health effects in infants through breastfeeding.
- It is difficult to differentiate between in utero exposure and exposure through breastfeeding, and to determine the relative exposure from breastfeeding versus prenatal exposure
- The available high quality systematic review dating from 2023 included 1 human study and 9 animal studies and concluded "*direct relevance to human health is uncertain, and it is possible that many adverse health effects of exposure through breastfeeding have not yet been studied*".
- The level of uncertainty is reflected in the available international guidance stating the benefits of breastfeeding outweigh risks, given the limited evidence of harm from breast milk–specific exposure.
- Research on breast milk is ongoing, but it remains largely focused on monitoring contaminant levels.

5.2 Literature review on adverse health effects

5.2.1 Results of systematic reviews

The umbrella search identified 7 references relevant on breast milk/breastfeeding and two additional SRs were identified subsequently (list of identified SRs in supplement 2.1). Only one SR addressed health outcomes, but it did not identify primary studies on our selected *concerning* health outcomes.[136]

Most SRs report on biomonitoring studies that measured PFAS concentrations in breast milk, some estimated an infant's daily intake, but most did not link further with possible health outcomes in children.[137-142] The breast milk concentrations are in the range of pg/ml and, depending on the study, the levels of PFOS and PFOA measured in breast milk were approximately 0.9 to 2 % and 1.8 to 9 % of the levels in the mother's blood, respectively.[135] PFAS has also been detected in donor human milk.[143] Biomonitoring studies suggested a decline in the concentrations of legacy PFAS in breast milk (e.g., PFOS, PFOA), while at the same time detecting emerging PFAS in recent years.[139] This indicates a shift in exposure patterns due to the replacement of legacy PFAS.[139]

The US Agency for Toxic Substances and Disease Registry (ATSDR) performed a SR with the intend to inform guidelines for breastfeeding mothers who have been exposed to PFAS, and thus addressed health outcomes.[136] Based on evidence gathering till February 2018, the SR reported that the direct evidence of adverse health effects due to PFAS exposure specifically through breastmilk is primarily limited to animal studies.[136] Animal studies provided evidence of associations between exposure to PFOA through breastfeeding and reduced early life body weight gain, mammary gland development, and thyroid hormone levels. Only one epidemiological study in 850 mother-infants pairs in Norway

measured associations with concentrations in breastmilk with health outcome, and did not find an association with developmental delay and behaviour problems assessed via self-reported questionnaires at 6 months, 12 and 24 months.[144] Two other cohort studies assessed PFAS exposure through maternal serum short after delivery and infant's serum, and were included for narrative study. However conflating in utero and breastfeeding exposure is less informative for parents deciding whether or not to breastfeed infants. Research is needed to evaluate the relative exposure from breastfeeding versus prenatal exposure.[134] Nevertheless most research on adverse effects linked to early life exposure comes from maternal prenatal exposure assessment (see list of identified and excluded SRs in supplement).

Maternal PFAS exposure has also been examined in relation to breastfeeding duration. A SR by Timmermann et al. assessed this association and found that five of the six included studies reported shorter overall breastfeeding duration among mothers with higher PFAS concentrations.[145] In contrast, the single U.S. study reported an inverse association, suggesting longer breastfeeding duration with higher PFAS exposure. The SR also reported a possible pathophysiological explanation linking PFAS exposure to insufficient mammary gland development in mouse models, though extrapolation to humans remains hypothetical.

Table 29 – Identified systematic reviews on PFAS in breast milk and health outcomes

Systematic review	Included primary studies	Conclusion of SR	Quality appraisal (AMSTAR)
Hoadley 2023[136] ***ATSDR***	3 human cohort studies • Forns 2015 (in breast milk) • Grandjean 2017 (exposure measured postnatal in maternal and children's serum) • Oulhote 2016 (exposure measured prenatal and children age 5) 34 animal studies	*Explores whether exposure to PFAS through breastfeeding is associated with adverse health outcomes among infants and children using evidence from human and animal studies* *Forns et al. (2015) was the only study of the 3 that measured the association between health outcomes (i.e. developmental delay and behavioural problems) and concentration of PFAS in breast milk.* *Direct relevance of any of these outcomes to human health is uncertain, and it is possible that many adverse health effects of exposure through breastfeeding have not yet been studied*	no critical limitations

5.2.2 Overview of recent primary studies

Because the most recent good quality SR on health outcomes by Hoadley was based on a literature search conducted in 2018, we performed an updated literature search on 2 April 2026 to identify primary studies reporting PFAS exposure through breastfeeding and health outcomes (search strategy provided in the Supplement 1.2.6). This search identified 155 references of which 14 were selected for full text review and 9 were selected as they reported on PFAS exposure through breastfeeding and health outcomes. Our aim was to provide an overview of the different health topics. Because these outcomes were not part of our selected *concerning health outcomes*, we did not conduct a detailed analysis or assess the quality of evidence for them (the overview is in supplement 5.1).

- Several studies were on influence of PFAS on gut microbiome.[146-149] One study stating PFAS in infant feeding (breast milk or formula) negatively affects microbiome diversity in preterm infants,[148] and another stating PFAS in breast milk has a positive effect on microbiome diversity.[149]
- Three Dutch studies in the Sophia Pluto study cohort compared 'exclusively breastfed children' to 'exclusively formula fed'.[150-152] One did not find negative effects of PFAS exposure via breastfeeding on metabolic health and insulin sensitivity at 2 years.[152] Higher PFAS levels at 3 months and 2 years were associated with reduced overall growth,[151] and rapid fat mass

percentage gain,[150] though in contrast "exclusive breastfeeding" was positively associated with growth and a higher fat-free mass at the age of 2 years. The authors concluded all these findings warrant further research.

- A Norwegian study reported that PFOS in breast milk was associated with increased risk of ADHD.[153] This finding was not reported in other studies of PFAS exposure (not limited to breast milk).[154,155]
- There were no associations for PFAS exposure through breast milk and cryptorchidism (i.e. testicles fail to descend into the scrotum before birth).[113]

5.3 International/national guidance and ongoing research

In our grey literature search we identified several guidance/statements on breastfeeding.[1, 156-159] Overview of identified guidance is presented in supplement 5.2. Current guidance in Australia,[156] the USA,[157],[158],[1, 160] Germany,[159], Canada[161], as well as guidance in Belgium,[162, 163] indicates that breastfeeding should continue even when there is a risk of elevated PFAS exposure. None of the reviewed recommendations advise stopping breastfeeding or reducing duration, as available evidence does not show that potential harms outweigh its well-established benefits.

The European Partnership for the Assessment of Risks from Chemicals (PARC) initiative was launched in 2022 and aims to improve knowledge about chemical substances.[x] One of its objectives is to implement a longitudinal human biomonitoring (HBM) survey to investigate exposure to PFAS in the most vulnerable population: pregnant women and their newborns.[164] The study will follow participants across three key time points, collecting various biological samples – with a strong focus on breast milk – to detect both known and emerging PFAS. The Dutch RIVM is participating and is for example performing a monitoring in breast milk and mother serum sampled from the COVID MILK-POWER MILK study (1650 women) (results expected in 2026).[165] Belgium did not participate to this particular breast milk study. In the past, there has been monitoring of PFAS in breast milk in Belgium, as part of the WHO coordinated study in 2006,[166] as well as a study in 40 samples in rural Flanders in 2010.[167] The conclusion was that the level of PFOS and PFOA was lower or comparable to the study in 2006, and that concentrations were significantly higher in milk of primiparous participants.

Many contaminated PFAS hotspots (e.g. Ronneby in Sweden, Veneto in Italy,..) do not have published breast milk biomonitoring. The recent PFAS study conducted in the 3M area near Antwerp also did not analyse breast milk directly, but it did identify breastfeeding as one of the factors associated with higher PFAS concentrations in children.[168]

The Flemish biomonitoring study in the surroundings of the 3 M factory, indicated that breastfeeding was one of the factors associated with higher PFAS concentrations in children.[168] This mother-child study in 135 mothers and 207 children showed correlation between PFOS blood concentration in mothers and children as measured in serum, and correlations appear to increase with the child's age. Although this result suggests that the shared environment (i.e. diet, location, etc.) may be a more significant contributor than maternal transfer to the child's exposure, the relatively small number of children in these analyses limits the ability to draw robust conclusions. It should also be noted that longer periods of breastfeeding were also a determinant of higher PFAS concentrations in the child, but again with the caveat that the sample size was small.

[x] PARC is a 7 year partnership in 28 countries funded by Horizon Europe and builds on lessons and knowledge from the "Human biomonitoring for Europe" (HBM4EU), which was funded by Horizon 2020

Most existing and planned research is based on biomonitoring studies that quantify PFAS concentrations in breast milk and estimate infants' daily intake. However, there remains a significant knowledge gap regarding the potential adverse health effects associated with PFAS transfer to infants through breastfeeding.[138]

6 HEALTH-BASED GUIDANCE VALUES FOR PFAS

There are no clear thresholds for defining a **blood concentration** that is harmful to health **at the individual level**.[169] However, there are health-based **guidance values** which are population-level tools for regulatory and public-health decision making, and not designed to predict possible adverse health effects in individuals. As mentioned in the KCE report 403 on PFAS, the positive predictive value and the negative predictive value of health-based guidance values at the individual level are unknown.[2]

6.1 Available health-based guidance values in blood

A number of countries and authorities have published or proposed guidance values for PFAS in recent years (see Table 30). They vary considerably, depending on the PFAS included and methodology used (i.e. the German Human Biomonitoring for PFOA and PFOS, the NASEM for the sum of 7 PFAS, the European Food Safety Authority for the sum of 4 PFAS).[1, 122, 170, 171] These inconsistencies challenge effective risk management and public health communication.[172, 173]

Some recent biomonitoring studies in Flanders, Wallonia, and the Netherlands used these guidance values to interpret their results (Table 31).[168, 174-177] The proportion of exceedance depends on the guidance value used. A large proportion of the adults (61% in the Flanders 3M study, and 71% in the Netherlands background exposure study [175] exceeded the EFSA blood level of 6.9 ng/ml for the sum of 4 PFAS (PFOS, PFHxS, PFOA, PFNA). For children this was 24% in the Flanders 3M study,[168] and 27% in the Netherlands. The Walloon studies also compared the biomonitoring results to the NASEM value, and concluded that in both the reference study on background level, as in the studies on excess exposure, the healthy cutoff of less than 2 ng for the sum of 7 PFAS was exceeded in almost all participants (94% in the Walloon reference population,[177] and 99.6% in Chièvres[176]). Important to note is that some studies report on linear isoforms, while others report on the sum for linear and branched isomers. This distinction matters because differences in reporting formats across studies or regions can lead to misleading comparisons.

Table 30 – Overview of health-based guidance values for PFAS in blood

Author	Health based guidance value	Methodology
European Food Safety Authority (EFSA)[122]	Sum of 4 PFAS: PFOS, PFHxS, PFOA and PFNA in serum • 6.9 ng/ml in adults (including breastfeeding women) • 17.5 ng/ml in children	This value is based on extrapolation of a cross sectional study in the late '90 in 101 children at 1 year of age which had a lower antibody titer against diphtheria, Haemophilus influenza type b, and tetanus after vaccination, when PFOA concentration was higher (this effect was not seen for PFOS).[178]* Using benchmark dose modelling the serum concentration in infants for a 10% reduction in diphtheria antibody titers was defined for the four PFAS: 17.5 ng/ml Using PBPK modelling this serum level in children was estimated to correspond to a milk level of 0.133 ng/ml, a maternal exposure of 0.63ng/kg bodyweight per day and a tolerable weekly intake of 4.4 ng/kg bodyweight per week. Similar potency was assumed for the 4 PFAS
German Human Biomonitoring Commission[170, 171]	HBM-I (no risk for health expected) • PFOA under 2 ng/ml • PFOS under 5 ng/ml HBM-II (increased risk for adverse health effects) • PFOA above 10 ng/ml (above 5 ng/ml for women of childbearing age) • PFOS above 20 ng/ml (above 10 ng/ml in women of childbearing age)	Predominantly based on human studies showing relevant and statistically significant associations between PFOA and PFOS 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 Reduced immune response is the most sensitive effect.
US, NASEM[1]	Sum of 7 PFAS (PFOS sum of linear and branched isomer, PFOA sum of linear and branched isomer PFHxS, PFDA, PFUnDA, MeFOSAA, PFNA) • Healthy cutoff: Under 2 ng/ml for sum of 7 PFAS • Grey zone: between 2 and 20 ng/ml • Unhealthy cutoff: above 20ng/ml	Based on German HBM-I and HBM-II values

*HBM: human biomonitoring; PBPK: physiological based pharmacokinetic modelling *The EFSA values of 2018 were based on increase of cholesterol and decrease of antibody response after vaccination.*

Table 31 – Biomonitoring studies that use health-based thresholds

Study	Details	PFAS serum concentrations	Comparison to health based guidance values
Flemish 3M study 2025[168]	8 568 residents living in the surrounding 5km of 3M facility in Zwijndrecht (of which 475 children < 12y) 13 PFAS in serum collected in 2023-2024	Adults PFOA* median 1.57 ng/ml PFOS* median 4.9 ng/ml Children (<12y) PFOA* median 1.21 ng/ml PFOS* median 2.07 ng/ml	The EFSA value of 6.9 ng/ml was exceeded in 48% of adults and 21% of children. When both branched and linear isomers were included, exceedance increased to 60.9% in adults and 24% in children. The German HBM-I value was exceeded in 31.4% for PFOA* and 49.1% for PFOS*.
Dutch RIVM study 2025[175]	1487 individuals from the PIENTER-3 cohort (of which 233 children 4-17y) 29 PFAS in serum collected in 2016-2017	Adults PFOA median 1.8 ng/ml PFOS median 6.3 ng/ml Children (4-17y) PFOA median 1.5 ng/ml PFOS median 3.2 ng/ml	The EFSA value of 6.9 ng/ml was exceeded in 71% of the adult population and in 27% of the children.
Walloon study 2025 BMH-Wal 3[174, 177]	302 adults 40-59 year in Wallonia 7 PFAS in serum collected in 2023 (but only 3 detected)	Adults PFOA median 1.10ng/ml PFOS median 2.51ng/ml	The German HBM-I value was exceeded in 14.9% for PFOS and in 11.3 % for PFOA of the participants (only the linear isomers) The NASEM value of 2ng/ml for the sum of 7 PFAS was exceeded in 94% of adults, and 0.7% exceeded the 20ng/ml threshold.
Walloon contamination Chièvres 2025 BMH-PFAS[176]	1 031 residents in Chièvres with PFAS serum measurements (of which 59 younger than 12y) 19 PFAS in serum in 2024	Figure with geometric mean per age group: PFOA: between 1 and 4 ng/ml PFOS: between 5 and 11 ng/ml With higher exposure in older age groups	The German HBM-I value was exceeded in 42.5% for PFOS and 52.3% PFOA (only the linear isomers) The NASEM value of 20 ng/ml was exceeded in 46.4% of participants, 53.2% was in the grey zone (between 2 and 20 ng/ml). Only 0.4% did not exceed the healthy threshold of 2ng/ml.

*PIENTER cohort are national sero-epidemiological studies executed by the Dutch Rijksinstituut voor Volksgezondheid en Milieu (RIVM); BMH-Wal 3 is the third round of human biomonitoring program in Wallonia; BMH-PFAS is a dedicated human biomonitoring in areas where an excessive level of environmental pollution is expected (Chièvres, Ronquières, Nandrin and Florennes) EFSA: European Food Safety Authority; *sum of linear and branched isomers*

Since 2025, EFSA is reviewing the health-based guidance values for trifluoroacetic acid (TFA) together with the European Member States and the European Chemicals Agency (ECHA), which is responsible for classifying the chemical properties of TFA. The results of the review are expected by the end of July 2026.[179]

6.2 A WHO-initiative

Since 2023, the WHO has been running an initiative to develop **harmonised health-based guidance** values for **ingested PFAS (food and drinking water)**.[180] These can be adopted and utilized by national and regional authorities. However, it is not clear whether these guidance values can and will be used to interpret PFAS blood levels. This initiative is ongoing therefore no specific guidance is available yet.

In the first phase (2024–2025), the WHO initiative focused on creating a methodology and conducting a landscape review[y] to identify and prioritize the most important PFAS and associated health effects.[26, 181, 182] This work led to the selection of 18 PFAS and 6 key health outcomes — cancer, developmental, hepatic, immune, metabolic, and reproductive effects.[180]

These priorities will guide the next phase (2025–2027), during which the WHO will carry out systematic evidence reviews and conduct risk assessments for individual PFAS and/or PFAS mixtures. The overall objective is to establish a range of health-based guidance values for PFAS.

Table 32 – WHO initiative - Methodological considerations for systematic evidence collection and evaluation.[26]

Populations: humans worldwide, but also laboratory animals, cell lines,…
Exposure: PFAS exposure to the 18 selected PFAS: PFOS, PFUnDA, PFHpA, PFOA, PFHpS, PFBA, PFTrDA, PFHxA, PFTeDA, PFBS, PFHxS, PFPA, PFDoA, PFNA, PFDA, PFDS, HFPO-DA, TFA
Outcomes: health outcomes — cancer, developmental, hepatic, immune, metabolic, and reproductive effects
Comparator: for epidemiological data it is low exposure, for animal data it is a negative control group
Studies: only English primary research studies in timeframe 1950-2025

7 MEDICAL INTERVENTIONS

Based on a rapid grey-literature review, including a search in the clinical trials.gov registry, we reached the same conclusion as the previous KCE report: there are currently no approved interventions to reduce high PFAS concentrations in humans.[2] At the moment, interventions that reduce blood PFAS are of uncertain benefit and may cause harm.[183] Research is ongoing for phlebotomy,[184, 185] cholesterol lowering agents (e.g. colestyramine,[186] colesevelam[187z]), and an oat β-glucan intervention.[188] Other studies also suggested the protective effects of folate or folic acid, though the physiological pathway is not clear.[189]

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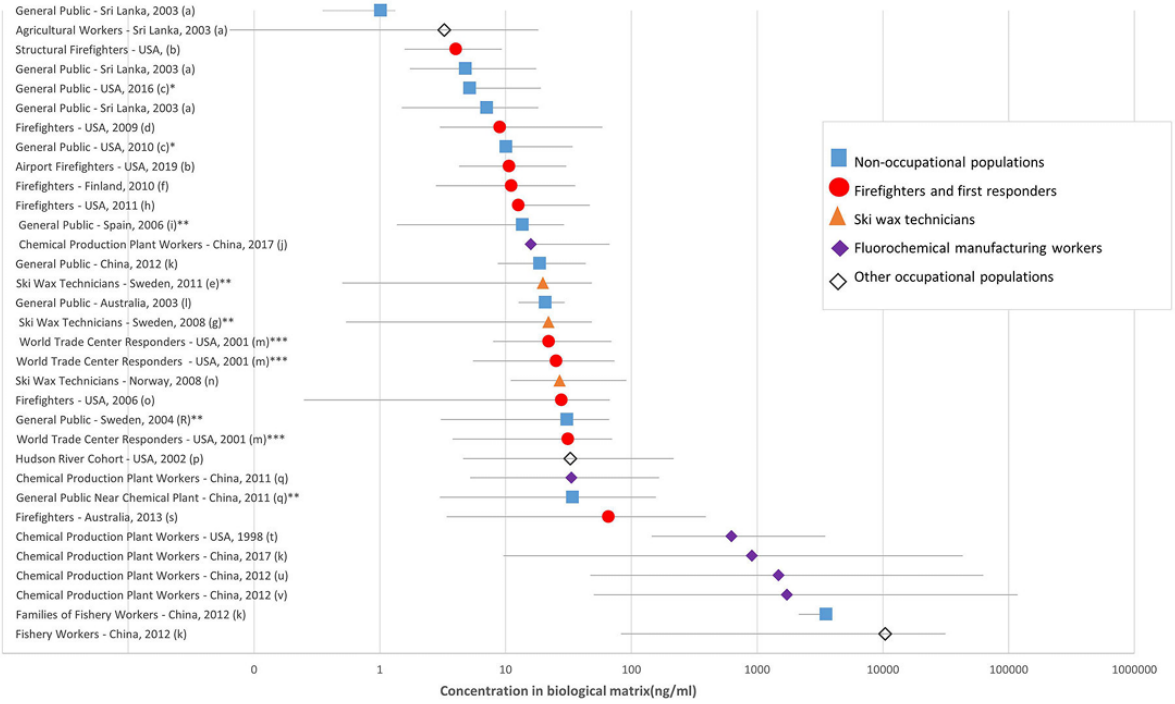
y The landscape review is planned to be published as a WHO report in 2026

z US PAVERS study - Use of Bile Acid Binding Resins to Decrease PFAS Levels Via Colesevalem in Veterans Study; US ENGINE study on feasibility and acceptability of colesevelam in male firefighters

8 OCCUPATIONAL EXPOSURE

Workers might be exposed to PFAS in ways that are different than the general public, such as by contaminated air and/or dermal contact, and these exposures can occur at much higher concentrations. The occupations with the highest exposure possibilities are chemical manufacturing workers (e.g. PFAS production, chrome plating facilities), firefighters due to the presence of PFAS in some firefighting foams, ski wax technicians and textile manufacturing.[190-193]

Figure 10 – Overview of PFOA in serum, plasma, or whole blood by population as copied from the review by Christensen and Calkins[192]



*Upper limit based on 95th percentile
**Whole blood sample. Serum concentration multipled by 1.8 for comparison to serum and plasma
***Plasma sample
(a) Guruge et al., 2005; (b) Leary et al., 2019; (c) CDC, 2019; (d) Shaw et al., 2013; (e) Nilsson et al., 2013; (f) Laitinen et al., 2014; (g) Nilsson et al., 2010; (h) Dobraca et al., 2015; (i) Ericson et al., 2007; (j) Lu et al., 2019 (k) Zhou et al., 2014; (l) Karrman et al., 2006a; (m) Tao et al., 2008; (n) Freberg et al., 2010; (o) Jin et al., 2011; (p) Tanner et al., 2018; (q) Wang et al., 2012; (r) Karrman et al., 2006b; (s) Rotander et al., 2015; (t) Olsen et al., 2007; (u) Gao et al. 2016; (v) Fu et al., 2016

The highest blood concentrations were reported in 39 Chinese fishery employees with median levels of PFOS of 7 840 ng/ml in 2014.[194] In Europe the highest internal exposure (as measured in the blood) has been reported in chemical factory workers in Italy and the Netherlands, specifically for PFOA (median 5 710 ng/ml and 2 200 ng/ml respectively). The mean blood serum concentration in workers of 3M factory near Antwerp has been reported to be 1 930 ng/ml for PFOS and 1 160 ng/ml for PFOA in 1995,[195] and decreased to 800 ng/ml for PFOS and 840 ng/ml for PFOA in 2000[aa].[196, 197] As part of the HBM4EU initiative, PFAS concentrations in 172 individuals from 4 countries including Belgium, were performed in 2018-2019. Although the concentrations were lower than those reported in fluorochemical production workers, elevated PFOS and PFHpS levels were observed among 9 electroplaters and 6 welders from the Belgian cohort. Median PFOS values were 8.81 ng/ml for the electroplaters and 267 ng/ml for the welders. These elevated levels were largely driven by one

[aa] For 2000 also the median concentrations were available of 3M workers near Antwerp: 550 ng/ml for PFOS and 650 ng/ml for PFOA.

company, suggesting a company-specific exposure scenario and possible bystander exposure among welders.[190]

Also workers handling PFAS-containing byproducts, such as those in laboratories, waste management, or soil-related jobs (farmers, construction, and road workers) have been cited to have elevated exposure risk.[198] Specifically for the US, the serum levels of PFAS were analyzed for 21 industries and 22 occupation groups, in the context of the NHANES 2005-2014 study. Especially construction (geometric mean PFOS of 12.61 ng/ml), utilities (PFOS = 12.46 ng/ml), and installation/repair (PFOS = 12.75 ng/ml) sectors showed elevated serum PFAS, with a general decreasing trend in concentrations over the years.[199]

There is still no comprehensive overview of which occupational groups face an elevated risk of increased exposure to the various PFAS compounds. Several initiatives are mapping and inventorying PFAS exposure in industrial settings.[200] For example a 2023 Belgian report, commissioned by the federal public service stated that medical devices, technical textile and heating, ventilation, air conditioning and refrigeration, used more than 75% of estimated PFAS volume in Belgium.[201]

However, the focus of this research is to answer the question whether there should be PFAS testing to guide medical management in occupational exposure. What does literature tell us on adverse health effects of occupational exposure to PFAS, and what is the available guidance?

8.1 Key points

- The evidence base on adverse health effects in occupational cohorts remains sparse. Only a limited number of systematic reviews have included subgroup analyses focused specifically on occupational populations, and the findings from these analyses have been inconsistent (see SR by Hussey on cholesterol).
- In the current regulatory framework on occupational health, biomonitoring for PFAS is not explicitly mandated. However, employers are required to provide (regular) health assessment/surveillance but the decision to perform biomonitoring for occupational exposure is very much dependent on the risk assessment of the employer.
- Several scientific bodies conclude biomonitoring is the more appropriate approach for PFAS exposure assessment.
- There are no generally accepted or legally binding biological limit values for PFAS (except for PFOS and PFOA in Germany) available, making interpretation and management complex.
- Few initiatives make PFAS biomonitoring available to workers, generally intended to support exposure assessment rather than to guide subsequent medical decision making.
- The available guidance on post-test clinical follow-up remains limited.

8.2 Literature review on adverse health effects

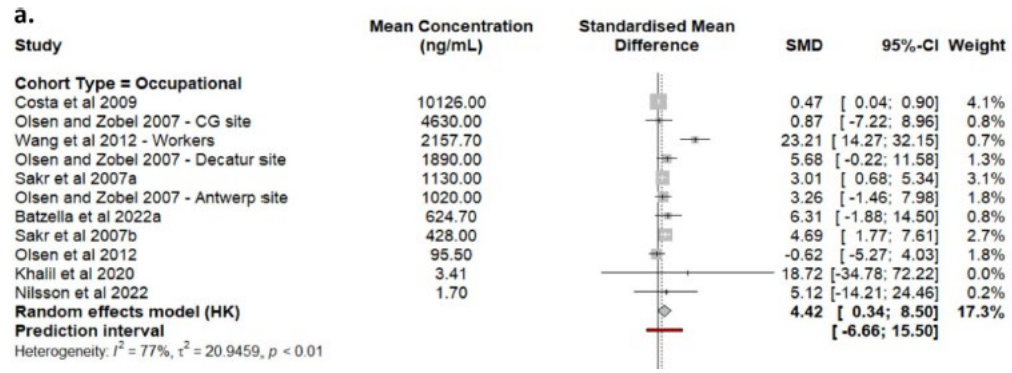
8.2.1 Results of systematic reviews

The search identified 130 references, of which 29 were selected for full text analysis (search string, flowchart and list of excluded SRs in supplement). The focus was on SRs assessing health outcomes (see PECO Table 5). However, most available SRs dedicated to occupational exposure focused on quantification of the exposure in different settings and did not discuss health effects.[192, 193, 202] Conclusion of these SRs was that more research is needed, both on the analytical methods to fully capture the potential range of different PFAS present across different workers and workplace, as well as further research on estimating health risks.

There were no dedicated SRs examining health outcomes specifically in occupational cohorts. As shown in Table 33, five SRs reported on a dedicated sub-analysis of occupationally exposed groups. This was the case for the SR on dyslipidemia,[203] as well as for the series of cancer-risk studies conducted by the same group of authors.[204-207]

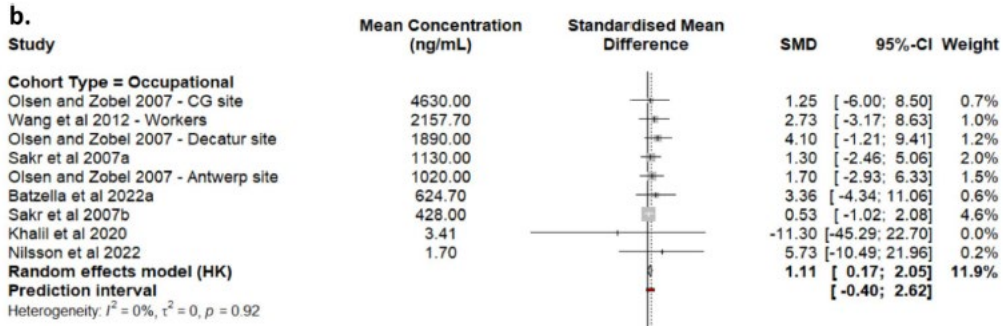
The SR by Hussey analysed dyslipidaemia, and performed a separate meta-analysis for occupational cohorts.[203] The SR was of good quality as rated with AMSTAR (see supplement 3.1.11). Because for the meta-analysis the study estimates were transformed into the same scale (difference in serum lipid levels per 1 interquartile range change in blood PFAS concentration), a large set of studies was excluded. In total 10 studies on occupational exposure were included (6 cross-sectional and 4 longitudinal). All studies adjusted for age and BMI (except one), and often also for smoking and alcohol consumption. Significant subgroup-specific pooled effects were observed for PFOA on total cholesterol within occupational studies (SMD = 4.42; 95% CI: 0.34–8.50) with a high heterogeneity (I^2=77%), and on LDL cholesterol (SMD = 1.11; 95% CI: 0.17–2.05) (see Figure 11 and Figure 12). Effect sizes as well as heterogeneity were high. When only the longitudinal studies were considered the associations were not significant. The strong association between PFOA and total cholesterol in the pooled estimate of 10 studies in workers is thus difficult to interpret. No significant association of PFOA with HDL-cholesterol nor triglycerides was reported. There were no significant pooled effects for PFOS in the occupational cohorts. The authors of the study concluded based on both occupational and non-occupational cohorts, that the results appeared to be inconsistent and inconclusive.[203]

Figure 11 – Meta-analysis of PFOA association with total cholesterol in occupational cohorts, as reported by Hussey[203]



Standardised mean differences (SMD) are expressed in terms of mg/dL change in total cholesterol per IQR change (in ng/mL) in PFOA

Figure 12 – Meta-analysis of PFOA association with LDL-cholesterol in occupational cohorts, as reported by Hussey[203]



Standardised mean differences (SMD) are expressed in terms of mg/dL change in LDL lipid per IQR change (in ng/mL) in PFOA

A group of authors published SRs including meta-analyses on cancer risk (hematological cancer[204], breast and female genital cancers[205], lung, head and neck, and thyroid cancer,[206] kidney, liver, and testicular cancers[207]) and reported on occupational studies separately. None of the analyses reported a significant association with cancer risk in the occupational studies. Cancer risk was assessed based on incidence or mortality outcomes. Most studies focused on PFOA exposure and mortality. However exposure was not always measured in plasma/serum. Some used estimates via modelled approaches i.e. statistical approaches based on actual serum measurements performed on a limited proportion of study participants together with other exposure-related variables (e.g., residence in a contaminated area, type of job), which increases the heterogeneity.[208] Across meta-analyses, different effect measures (e.g. ORs, HRs) were pooled as relative risks, and in some cases incidence and mortality outcomes were combined. Effect estimates were not harmonised to a common exposure scale; instead, the highest estimates reported in the primary studies were used. These methodological choices complicate interpretation. Authors concluded that the number of studies was limited, and further prospective studies with appropriate account of co-exposure with other carcinogens are needed.[206]

Table 33 – Systematic Reviews on occupational exposure to PFAS

Author and title	Study info – included primary studies	Results as reported in review	Quality appraisal (AMSTAR)
Hussey et al 2025 - The relationship between PFAS exposure and dyslipidemia: an updated review, meta-analysis, and evaluation of bias.[203]	Separate analysis for occupational cohorts. Included studies: Cross sectional • Batzella 2022 (Italy, 232 male former workers of Rimar Meteni plant) • Khalil 2020 (USA, 87 firefighters) • Wang 2012 (China, , 55 workers from fluorochemical plant) • Gilliland and Mandel 1996 (USA, 115 workers 3M) • Olsen and Zobel 2007 (506 workers 3M Cottage Grove, Decatur, Antwerp) • Sakr 2007 (USA, 1019 adult workers DuPont) longitudinal • Costa 2009 (Italy, 56 workers Miteni plant) • Nilsson 2022 (Australia, 130 firefighters) • Olsen 2012 (USA 179 workers 3M) • Sakr 2007 (USA 454 workers from DuPont)	*Change in lipids (mg/dl) per 1 IQR increase in PFOA or PFOS (ng/ml)* *PFOA* ***Total cholesterol*** *9 studies SMD = 4.42; 95% CI: 0.34–8.50) with a high heterogeneity I^2=77%,* ***LDL*** *7 studies SMD = 1.11; 95% CI: 0.17–2.05, I^2=0%* ***HDL*** *11 studies SMD = − 0.22 (95% CI: −0.65,0.20)* ***Triglycerides*** *7 studies SMD = 0.96 (95% CI: −0.16, 2.07)* *PFOS* ***Total cholesterol*** *4 studies SMD = 2.81 (95% CI: −3.56, 9.19), I^2=38%* ***LDL*** *3 studies SMD = 1.66 (95% CI: −10.68, 14.00), I^2=68%* ***HDL*** *4 studies SMD = 0.23 (95% CI: −0.64, 1.11)* ***Triglycerides*** *2 studies SMD = 2.49 (95% CI: −3.92, 8.91)*	No critical limitation Funding by Mitsubishi Corporation

Author and title	Study info – included primary studies	Results as reported in review	Quality appraisal (AMSTAR)
Sassano 2025 - Exposure to per- and poly-fluoroalkyl substances and hematological cancer: A systematic review and meta-analysis[204]	Separate analysis for occupational cohorts Included 6 studies on occupational exposure: PFAS Measured in blood • Gilliland 1993 (USA), PFOA mortality • Leonard 2008 (USA) PFOA mortality • Lundin 2009 (USA), PFOA mortality • Alexander 2024 (USA), PFOS mortality and incidence modelled serum levels • Girardi 2019 (Italy), multiple PFAS mortality • Steenland 2012 (USA, update of Leonard),PFOA mortality	*Pooled Relative Risk in occupational cohort* • *total haematological cancer* *For 5 occupational studies RR=1.24 (95%CI: 0.96-1.60)* • *leukemia* *1 study RR=1.05 (95%CI: 0.63-1.76)* • *Lymphoma* *2 studies RR=1.79 (95%CI: 0.51-6.32)* • *Non Hodgkin lymphoma* *2 studies RR=1.74 (95%CI: 0.43-7.03)* all relative measures of associations other than RR such as HR, OR, were considered as valid proxies of RR. The most adjusted estimate was chosen, and the estimate relative to the highest level of exposure.	Critical limitation
Seyyedsalehi 2024 - Per- And Poly-Fluoroalkyl Substances (PFAS) Exposure and Risk of Breast, and Female Genital Cancers: A Systematic Review and Meta-Analysis[205]	Separate analysis for occupational cohorts **Breast and female genital cancer** mortality • Gilliland 1993 (USA) – exposure via job history • Alexander 2003 (USA) serum sample • Leonard 2008 (USA) serum sample • Steenland 2012 (USA) serum sample (update of Leonard) • Raleigh 2014 (USA) work records Cancer incidence: • Barry 2013 (USA) serum sample • Feng 2022 (China) serum sample	*Pooled Relative Risk in occupational cohort* *Breast cancer incidence* *4 comparisons RR= 1.09 (95%CI 0.89-1.32)* *Breast cancer mortality* *6 comparisons RR= 1.00 (0.69-1.43)* *No occupational cohorts on female genital cancers*	Critical limitation
Sassano 2025 - Exposure to per- and poly-fluoroalkyl substances and	**Lung cancer** Mortality	*Pooled relative risk for occupational cohorts*	No critical limitation, but none of the

Author and title	Study info – included primary studies	Results as reported in review	Quality appraisal (AMSTAR)
lung, head and neck, and thyroid cancer: A systematic review and meta-analysis[206]	• Gilliland 1993 (USA) – work history PFOA • Alexander 2003 (USA)- work history PFOS • Lundin 2009 (USA) -work history PFOA • Leonard 2008 (USA) – work history PFOA • Steenland 2012 (USA) serum PFOA • Girardi 2019 (Italy) – estimated serum levels several PFAS <u>Incidence</u> • Barry 2013 (USA) – estimate serum level PFOA • Olsen 2004 (USA) – work history PFOS **Thyroid cancer** <u>Mortality</u> • Leonard 2008 (USA) – work history PFOA <u>Incidence</u> • Barry 2013 (USA) – estimate/modelled serum level PFOA	*Lung cancer (mortality + incidence)* *6 studies RR=1.02 (95%CI 0.74 -1.42)* *There were no results coming solely from occupational studies on thyroid cancer*	occupational studies on lung cancer, thyroid cancer used PFAS serum levels
Seyyedsalehi and Boffeta 2023 - Per- and Poly-fluoroalkyl Substances (PFAS) Exposure and Risk of Kidney, Liver, and Testicular Cancers: A Systematic Review and Meta-Analysis[207]	**Kidney cancer** • Leonard 2008 PFOA • Steenland 2012 PFOA • Raleigh 2014 PFOA **Liver cancer** • Alexander 2003 PFOS • Leonard 2008 PFOA • Steenland 2012 PFOA • Raleigh 2014 PFOA **Testis cancer** • Gilliland 1993 PFOA • Leonard 2008 PFOA • Steenland 2012 PFOA • Raleigh 2014 PFOA	*Pooled relative risk for occupational cohorts* *Kidney* *3 studies RR=1.15 (95%CI: 0.60-2.20)* *Liver* *5 studies RR=1.31 (95%CI: 0.90-1.90)* *Testicular* *3 studies RR=1.80 (95%CI: 0.53-6.14)*	Critical limitations

8.3 Grey literature search for guidance

In this section, the focus is on identifying guidance for medical management of individuals with occupational PFAS exposure.

8.3.1 Regulatory framework

In Belgium the legislation *Codex on Health and Safety at Work on chemical agents*[bb] requires **all sectors/each employer** to conduct risk analyses for exposure to chemical agents and to implement appropriate preventive measures or health surveillance when the assessed level of risk justifies it. Health surveillance which may include biomonitoring, is therefore not mandatory but risk-based. Mandatory health surveillance applies to substances that have a specific binding biological limit value (e.g. lead). At present no PFAS groups or compounds have such a binding biological limit value included in legislation.

Occupational exposure limits (OELs) primarily address inhalation exposure and are typically expressed as airborne concentrations; for some substances, additional skin notations indicate relevant dermal absorption. Several countries have OELs[cc] for PFAS.[5] In Belgium, there is an OEL for ammonium perfluorooctanoate (APFO) of 0.01 mg/m³ specified as an 8-hour time-weighted average. No short-term exposure limit is defined. It carries a skin notation (D), indicating that significant uptake may occur via dermal contact in addition to inhalation, and that risk management measures should therefore address both exposure routes. Specifically when a substance is categorised as carcinogenic[dd], mutagenic, reprotoxic, or endocrine-disrupting under the EU CLP Regulation (EC No1272/2008),[8] the legislation is a little stricter with the need to perform annual risk analyses, regular health assessments, and with more focus on preventive measures (limit exposure, e.g. work in closed systems, protective clothing etc).[ee] Some PFAS are classified as reprotoxic (1B) (e.g. PFOS, PFOA, PFHpA) under the EU CLP Regulation, and thus implies that workers must undergo a health assessment prior to exposure and periodic follow-up assessment thereafter, though does not specify biomonitoring is needed.

As biomonitoring (in blood, urine) can be an intrusive method, air monitoring and associated OELs might be preferred as they also fit better with the policy to prevent exposure.[210] However, multiple scientific and regulatory bodies—including ECHA's RAC, the German Human Biomonitoring Commission, and the HBM4EU consortium—conclude that biomonitoring is more appropriate for PFAS exposure assessment than air-based occupational exposure limits when substances are known to bioaccumulate.[210]

At present, no Biological Exposure Index (BEI) has been established for PFAS, including perfluorooctanoic acid (PFOA) or perfluorooctane sulfonic acid (PFOS). In particular, the American Conference of Governmental Industrial Hygienists (ACGIH) has not adopted BEIs for PFOA, PFOS or PFAS as a class, although these substances have been discussed within ACGIH scientific activities; this reflects the very long biological half-lives of PFAS and the substantial contribution of non-occupational background exposure, which limit the applicability of classical BEI concepts. Similarly, no EU biological limit values (BLVs or BGVs) have been established for PFAS under the

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bb Title 1 on chemical agents in Book VI of the Codex on Health and Safety at Work.

cc German Federal Institute for Occupational Safety and Health (BAuA) has defined a mandatory OEL in air for PFOS: 0.01 mg/m³ over 8h[209].

dd The International Agency for Research on Cancer (IARC) has categorized PFOA "carcinogenic to humans" (group 1) and PFOS "probably carcinogenic to humans" (group 2A), primarily based on evidence in experimental animals and mechanistic evidence in humans

ee Title 2 on Carcinogenic, mutagenic and reprotoxic substances, and substances with endocrine-disrupting properties in Book VI of the Codex on Health and Safety at Work

occupational chemical agents framework. An exception is the German Federal Institute for Occupational Safety and Health that had set a legally binding biological limit value (BLV) for PFOS (15 mg/l in serum) and PFOA (5 mg/l in serum) in 2023.[211]

The absence of enforceable occupational limits (OELs or BEIs) makes management more complex for interpretation as it is risk-based. The final responsibility for implementing measures to protect the workers, including biomonitoring and health surveillance, remains with the employer. Implementation is controlled by government inspectors (in Belgium the FPS Employment, Labor and Social Dialogue). External and internal prevention services provide guidance and can be involved in risk analyses and health surveillance.

8.3.2 Guidance for biomonitoring and medical management

In general, independent of PFAS, the role of biomonitoring in occupational health is gaining increasing prominence as researchers have described biomonitoring as an underused tool for exposure assessment in occupational settings.[212] The European Agency for Safety and Health at Work (EU-OSHA) published a general guidance document on biomonitoring in 2025.[213] It was not specifically targeted to PFAS, but it enlists advantages of performing biomonitoring (e.g. implementing biomonitoring can help in the assessment of health risks, and assess whether protection measures reduce exposure). To address the importance of biomonitoring and enhance harmonization, a guidance document on occupational biomonitoring levels was published in the framework of the OECD.[214] Similarly a Dutch initiative developed a framework to assess the need for biological limit values.[210]

Specific for PFAS, multiple scientific and regulatory bodies—including ECHA's RAC, the German Human Biomonitoring Commission, and the HBM4EU consortium—conclude that biomonitoring is more appropriate for PFAS exposure assessment than air-based occupational exposure limits. In the absence of legally binding occupational biological limit values, the existing health-based **guidance values** are often cited in occupational settings (such as the German HBM-I and HBM-II values for PFOS and PFOA, NASEM see section 6.1). These health-based guidance values provide benchmark values, are public-health reference values and are designed to help interpret exposure, possible trigger further exposure assessment. They do not predict health effects. Moreover, health based guidance values are not occupational BEIs, and they are therefore not intended for compliance assessment against workplace exposure limits.

Table 34 gives an overview of identified guidance on medical management. Most of the time it is limited to guidance on PFAS testing or not (biomonitoring).

In terms of explicit guidance on medical management for PFAS, most guidance is available from the US (US Department of Defence for firefighters, veterans, the NASEM guidance which was also targeted to occupational exposure),[1, 158, 215] as well as some general guidance from Australia,[156] and a Belgian FEDRIS guidance specifically for occupational exposure.[197]

Guidance in the United States is not fully harmonized. On one hand, the 2022 NASEM recommendations state that PFAS blood testing should be available in addition to specific medical follow-up.[1] On the other hand, the 2024 recommendations from the Agency for Toxic Substances and Disease Registry (ATSDR) emphasize adherence to standard clinical practice while prioritizing exposure reduction.[158] With regard to occupational exposure, current initiatives remain situated within a research context, with early efforts focusing on the introduction of PFAS blood testing among firefighters, but with no specific medical follow-up.[216] A Dutch literature study of the Dutch institute of Public Safety concluded in 2024 that exposure in firefighters is not particularly higher than reference populations. For this reason they did not recommend large scale biomonitoring studies among fire service personnel.[217]

In 2022, a study by the Belgian FEDRIS Commission on Chemical and Toxic Agents was performed aiming to investigate whether there are arguments to support extended health surveillance of workers whose intensive occupational exposure to PFOS and PFOA ceased in the early 2000's (phase-out).[197]

The authors reported on the available epidemiological studies on occupational exposure of chemical manufacturing workers of 4 companies and 7 sites in the US and EU. During exposure episodes workers were subjected to health surveillance and biomonitoring of PFAS of which results were published.[218] However some researchers suggested not all available data had been published.[219]

The FEDRIS analysis concluded that up to 2022 the evidence available of an increased risk of specific diseases that justify a prolonged health surveillance programme, was inadequate. Therefore, FEDRIS commission on chemical and Toxic Agents recommended a longitudinal epidemiological study on workers.[197] However, as of May 2026, there is no such longitudinal epidemiological study on workers launched.

Table 34 – Overview of guidances on occupational PFAS exposure and medical management

Author/institution	Guidance
European Agency for Safety and Health at Work[213]	General guidance on biological monitoring at work. Not specifically targeted to PFAS *Any individuals who are potentially exposed to substances that may be hazardous to health can be considered for biological monitoring*
US Department of Defence 2024[216]	Blood testing is offered to all Department of Defence **firefighters** during their annual occupational medicine examination, and to newly hired in order to establish a baseline PFAS level. This testing is not part of the occupational medical qualification or medical surveillance program, rather it is a congressionally mandated offer to assess PFAS exposure of DoD firefighters. The target PFAS analytes includes 15 PFAS, and must be sent to a CLIA-certified lab. The results of the analyses must be included in the firefighter's medical record. There are no established health-based reference levels. There is insufficient evidence at this time to deviate from established standards of medical care.
US Department of Veterans Affairs[215]	Although PFAS testing is not currently available at Veteran Affairs medical centers, the department is evaluating blood testing in accordance with new Federal research. Although some studies have reported possible health outcomes, the overall scientific and medical evidence is currently inconclusive. However, Veterans may file a claim for disability compensation for health problems they believe are related to exposure to chemicals during military service. VA decides these claims on a case-by-case basis.
Belgian FEDRIS commission on Chemical and Toxic Agents 2022[197]	No consistent evidence was available that there was an increased risk of specific diseases that justify a prolonged health surveillance programme. However, a longitudinal epidemiological study on workers was recommended.
US National Academies of Sciences, Engineering, and Medicine (NASEM) 2022[1]	If patients may be exposed occupationally, such as by working with fluorochemicals or as a firefighter, clinicians should consult with occupational health and safety professionals knowledgeable about the workplace practices to determine the most feasible ways to reduce that exposure. All other recommendation from NASEM to the general public are also relevant for occupational exposure: • Communication (acknowledge and address uncertainty). Make blood test available, and offer additional medical screening for those with elevated levels (lipid panels, liver function tests, serum creatinine, urinalysis, thyroid test, screen regularly for testicular cancer, breast cancer, ulcerative colitis, blood pressure during pregnancy).

Author/institution	Guidance
Agency for Toxic Substances and Disease Registry (ATSDR) Clinical Evaluation and Management: PFAS Information for Clinicians - 2024[158]	Blood testing? Clinicians need to decide with their patients weighing of benefits and risks ATSDR has not developed health-based screening based on PFAS blood levels and encourages clinicians to follow usual standards of care for health concerns
Australian Government Department of Health and Aged care [156]	For all exposure, not specific for occupational exposure • blood testing has no current value in informing clinical management including diagnosis, treatment, or prognosis in terms of increased risk of particular conditions over time • the monitoring of pooled community blood samples over time can help determine the success of exposure reduction measures. • exposure reduction is the key measure to reduce any possible risks posed by PFAS
Dutch institute of Public Safety - Dutch Academy for Crisis Management and Fire Services[217]	studies show that firefighters do not have higher blood PFAS concentrations than reference populations. For this reason, it does not seem necessary at this moment to conduct large-scale studies on PFAS concentrations in blood among fire service personnel.

A position paper issued in January 2026 by Public Services International - a global trade union federation representing public-sector workers, including firefighters and waste-management personnel – represents an important stakeholder voice.[198] In terms of medical management the following actions were advocated for:

- "Ensure access to free, voluntary, and confidential blood and/or hair testing for exposed workers to assess PFAS concentrations."
- "Establish specific health surveillance protocols for workers exposed to PFAS."
- "Develop and provide scientifically validated, safe medical treatments and measures to reduce or remove PFAS contamination from the body (e.g. blood filtration for firefighters and waste workers), made available free of charge to affected workers."

8.3.3 Ongoing research/initiatives

On European level, ECHA's Committee for Risk Assessment (RAC) and Committee for Socio-Economic Analysis (SEAC) are engaged in evaluating PFAS hazards as part of the EU-wide PFAS restriction proposal, but no OEL or biological limit value as regulatory endpoint.

The EU research initiative PARC has work packages relevant for PFAS in occupational settings (work package on human biomonitoring cohorts, work package on innovation in regulatory risk assessment), including the PARC Waste Management Study.[220]

In France, in April 2024 the Interministerial action plan on PFAS was launched.[221] Of particular relevance for occupational exposure are action 19 "*assess the advisability and feasibility of setting up medical monitoring and care for potentially overexposed populations*" and action 20 "*consider the work-related health issues for professions likely to be particularly exposed*".

Also in France, the Haute Authorité de Santé (HAS) and Société Française de Santé au Travail are developing occupational medicine guidelines for the surveillance of workers of reproductive age and pregnant women exposed to reprotoxic molecules, with an expected release by the end of 2026.[222]

In the USA - The National Institute for Occupational Safety and Health (NIOSH) is engaged in PFAS research since 2004.[223] NIOSHTIC-2 is a database of occupational safety and health publications funded in whole or in part by NIOSH. This research informs the work on thresholds of the American Conference of Governmental Industrial Hygienists.

From the perspective of the workers, there is the 2026 published position paper from the global union federation of workers in public services (incl. firefighters).[198] It states that "*Comprehensive analyses and systematically collected data on workplace exposure and health outcomes are still largely lacking*." And they therefore recommend to focus on research data and knowledge development on health consequences.

9 DISCUSSION

This report builds further on the results published in July 2025, and focused on individuals with occupational exposure, pregnant women and breastfeeding women. This report investigated the relevancy of testing for PFAS contamination in blood to inform medical management. To decide if such testing is appropriate, we focused on four criteria of the UK screening framework (see section 2.1).

We particularly reviewed the human epidemiological evidence on PFAS effect on *concerning* health outcomes for pregnant women, breastfeeding women and young children. Heterogeneity of methods and results across studies and across PFAS make evidence synthesis and meta-analysis challenging. The epidemiological literature on PFAS is both dense and heterogeneous, and we carried out an umbrella review. To provide the most comprehensive overview of the human epidemiological literature, we supplemented the umbrella review with primary studies when no good quality recent systematic review was available. We additionally performed a grading of the certainty of evidence to be able to interpret and draw conclusions.[224]

We also reviewed guidance on breastfeeding. In addition we looked at occupational exposure by reviewing available literature and available clinical guidance.

9.1 Summary of main findings

Similar to the results in July 2025, the currently available evidence does not support an affirmative conclusion for any of the four criteria used to evaluate the clinical utility of PFAS testing, i.e. whether it can inform and possibly change standard medical practice.

The bulk of our research was on identifying and assessing the effect of PFAS on concerning health outcomes with the aim to inform health professionals so that they are in a position to advise their patients and ensure their medical follow-up. Our analysis of the available epidemiological evidence in pregnant, breastfeeding women and young children, revealed that the evidence was of low to very low certainty for most of them, with a few exceptions (see Table 35 for an overview). Consequently, based on the evidence available to date, it is just as difficult to state with certainty that PFAS trigger the concerning outcomes studied as it is to state that they do not.

The three other criteria are not fulfilled neither. First, there is no clear threshold to judge health risk at the individual level.[169] The available health-based guidance values are there to identify a PFAS contamination at the population level or to regulate dietary exposure (EFSA), not to predict deleterious health effects in screened individuals. Moreover, most health based guidance values are only set for a limited number of PFAS, and do not take into account mixture effects. These limitations have motivated the recent WHO initiative to develop harmonized health-based guidance values for ingested PFAS (e.g. food and drinking water), though it is not clear whether these values can and will be used for interpreting PFAS blood levels. Second, outside of research settings, no medical interventions are currently available to actively reduce PFAS concentrations in blood. The only effective approach is to minimize or eliminate further exposure. Third, as mentioned in the previous report, there is currently no standard method for measuring PFAS in the blood in clinical practice and no consensus on which PFAS should be measured in blood. Research is ongoing, but analytical and technical parameters

need clarification and standardisation in order to develop a fully valid PFAS blood test for use in routine clinical practice.

9.2 Implications of our findings for clinical management

All these elements suggest that testing for blood PFAS contamination to inform clinical management cannot be recommended at the moment. Similar to other recent recommendations (Australia),[183] our results indicate that PFAS blood testing does not alter clinical management, indicating no clinical utility.

Routine clinical management, with follow-up and preventive care pathways (e.g. antenatal care) are already well established. Specifically for pregnant women, routine clinical care guidelines recommend already that pregnant women should receive regular follow-up by a general practitioner, gynaecologist, or midwife.[225, 226] This includes monitoring of foetal development, and maternal health indicators such as blood pressure, the risk of preeclampsia as well as gestational diabetes.

As regards the lowering of immune response to some vaccines by some PFAS, the current evidence base is too thin to recommend a change in vaccination practice. A central limitation is the uncertain clinical significance of these observed antibody reductions. A statistically significant decrease in antibody titer does not necessarily mean loss of clinical protection, especially if antibody levels remain above accepted protective thresholds. However, even small downward shifts in antibody distributions could matter at the population level, particularly for children with lower baseline responses, incomplete vaccination, waning immunity, or higher exposure burdens. However, such impact is still to be demonstrated.[120]

With respect to breastfeeding specifically, our analysis showed that current evidence is insufficient to support recommending avoidance in cases of elevated maternal blood PFAS concentrations (see chapter 5).

A context where PFAS blood testing can be recommended is within research or population-level biomonitoring contexts. PFAS blood measurements can inform public health policy and support the development of exposure-reduction strategies. There are several initiatives and legislation aiming to reduce exposure (EU REACH,[9] EU POP,[7] EU Drinking Water directive[ff],[10] on food contaminant,[227] the request for an EU-wide restriction on the industrial production[gg]). Individual-level exposure-reduction strategies have also been proposed, and clinicians may advise patients on practical measures to minimize their personal exposure. To ensure completeness, we therefore direct readers to existing guidance on exposure-reduction measures. In Belgium, the Federal Public Service for Health, Food Chain Safety and Environment refers to preventive advice and actions issued by the regional authorities (Flanders, Walloon Region, and Brussels-Capital Region).[228]

[ff] Since 2026, the new EU Drinking Water Directive set stricter threshold (limit of 100 ng/l for sum of 20 specific PFAS and 500 ng/l for PFAS total

[gg] In March 2026 the European Chemicals Agency (ECHA) followed Sweden Denmark, Germany, Norway and the Netherlands in their request for an EU-wide restriction. ECHA's final advice to the European Commission is expected by the end of 2026

9.3 How to interpret the evidence of PFAS on concerning health outcomes

9.3.1 Framework for rating the evidence.

We applied the GRADE framework in assessing the associations between PFAS and health effects. GRADE evaluates the certainty of evidence and is developed for clinical medicine and public health. However in toxicology hazard assessments and environmental health, there are also other frameworks available, such as the OHAT framework.[229]

The main differences between the OHAT framework and GRADE lie in the fact that the OHAT framework takes into account human epidemiological studies, animal toxicological studies and mechanistic data.[230] In contrast to GRADE where the initial rating is based solely on study design, the OHAT methodology takes into account more study design features (controlled exposure or observational, exposure prior to outcome, individual outcome data, and comparison group used). Unlike the GRADE system, upgrades may additionally be given for consistency across different study designs, species, or dissimilar populations, and for "other" reasons.[229]

OHAT translates the certainty of evidence further into level of evidence (high, moderate, low, inadequate, evidence of no health effect). If the confidence rating is "very low," the level of evidence is automatically classified as "inadequate".[136] This reflects the idea that when evidence is extremely uncertain, it cannot be used to draw conclusions about a health effect. Evidence of "no health effect" can only be assigned when confidence is high. This acknowledges that it is inherently difficult to prove the absence of an effect.

Because our objective was to inform clinical practice rather than to establish toxicological hazard classifications, we focused exclusively on human observational evidence and did not incorporate animal or mechanistic data. Under these conditions, GRADE represents the most appropriate and methodologically aligned framework for evaluating the evidence. However, this approach may have resulted in lower certainty ratings, because animal and mechanistic studies were not considered, and because in GRADE observational studies are considered as low quality from the start. Variants of the GRADE framework exist, where even observational studies can be rated high quality at the start of the evaluation. This is for example the case for prognosis studies, because such studies assess the mere association between a predictor and an health outcome, without an assumption of causality between the two. [224, 231]

9.3.2 Accounting for confounding

Confounding is one of the central challenges in observational studies. This inherent limitation is why the GRADE framework begins by rating the certainty of evidence from observational studies as low.

Most included SRs and primary studies relied on risk estimates that were adjusted for important confounding factors such as age, pre-pregnancy BMI, parity in studies of gestational diabetes,[16] as well as for smoking in studies on birth weight.[17, 98] Comorbidities were seldom considered, though they can for example have an effect on kidney function and therefore influence PFAS concentration, as well as affect foetal development or birth outcomes. More information on confounding by physiologic changes in pregnancy (renal function, plasma expansion) can be found in section 4.6.9.

Confounding due to co-exposure to other pollutants is an inherent limitation of observational environmental epidemiology. Although we explicitly acknowledged this issue, we did not consider it a basis for rating studies as having a high risk of bias, because doing so would imply that all studies in this field are uniformly high risk, which would eliminate meaningful differentiation in study quality. Conversely, we assume that if we would have adjusted for other pollutants, possibly the strength of an association between PFAS and health outcomes would attenuate. Therefore, in the GRADE assessment we did not upgrade the certainty for residual confounding.

9.3.3 Challenging aspects in GRADE

A challenging aspect in applying the GRADE framework in our study was that we did not had a single pooled estimate per health outcome as was for example the case for birth weight. More specifically, this complicated the assessment of imprecision, the magnitude of effect or dose-response effect. For certain health outcomes we combined the information from a good quality systematic review with data from more recent primary studies (gestational diabetes, prematurity). Consequently, we integrated evidence from both pooled and non-pooled sources, with explicit documentation of the rationale for each judgement. For some outcomes no sufficiently rigorous or up-to-date systematic review was available, requiring reliance on primary studies (preeclampsia, miscarriage, acute lymphoblastic leukaemia, congenital heart disease). However pooling data from those primary studies was not opportune due to the substantial heterogeneity, and the limited interpretability of any pooled estimate in the absence of a valid transformation to a common metric. For example some SRs pooled different effect measures, often the OR, RR, HR estimate with the largest effect in the primary study was selected.[62] In such case, the meaning of the pooled OR is unclear, and it could only serve as an indication of a significant association, not for a numerical estimation of the risk increase.

Throughout the report we had to rely on different tools to assess risk of bias. Because this work was based on an umbrella review, we drew on the risk-of-bias assessments reported in the included SRs, which most often classified all included primary studies as being at low risk of bias using the Newcastle Ottawa Scale (Quan 2026 on gestational diabetes, Yang 2022 on prematurity, Fu 2025 on birth weight). The NOS tool tends to yield high scores and might underestimate risk of bias (the scoring implies all items as equally important, it lacks detailed signalling questions or standard algorithms, does not distinguish between bias and reporting quality[23]). For analyses conducted at the primary-study level, we performed the risk-of-bias assessment ourselves with the OHAT risk of bias tool, recommended in the WHO initiative for studies on exposure. Consequently, the risk-of-bias appraisal was not applied uniformly across all included studies. Moreover, when comparing and selecting the most appropriate SR (recent good quality) for each health outcome, the AMSTAR assessment was used. However, we did not disregard or considered SR as low quality when NOS was applied as risk of bias tool. In general, using different risk-of-bias tools can lead to different risk-of-bias ratings, which in turn may affect the overall GRADE assessment. However, in this report this is likely minimal: most health outcomes were already rated as low or very low certainty, and few were downgraded for risk of bias. Applying a more stringent risk-of-bias assessment would therefore not have changed the final GRADE conclusions.

9.3.4 Interpreting certainty rating

As shown in table 35, the vast majority of evidence is of low/very low certainty, making it not possible to conclude or refute on the effect of PFAS on the concerning health outcomes. For two outcomes there is a larger evidence basis with moderate certainty ratings indicating moderate confidence that the true effect is likely close but may differ: this is the case for PFOA and gestational diabetes, and for PFOS, PFOA, PFNA and reduced birth weight. Both were based on high quality SRs pooling the evidence on an uniform scale, making quantification possible. However, a recent publication of a large U.S. cohort study suggesting no association with gestational diabetes—and even indicating potential protective effects,[56] was not included in the pooled analysis. These findings complicate the overall interpretation of the evidence and highlight the need for careful evaluation of the totality of data.

Specifically for birth weight, PFOS, which was the most studied PFAS (53 studies included in the review by Wright et al. 2025[17]) yielded a 30 g decrement (95%CI: -41.6, -18.9) per 2.7 increase (ln-unit) in PFOS. The decrement linked to PFOA and PFNA was in the same range. However the clinical implication of the decrease in birthweight is not clear as the certainty level on the more clinical relevant outcomes “low birth weight (< 2500g)” and “small for gestational age” were generally very low. Although these results constitute a warning signal of PFAS toxicity during pregnancy, their validity must be tested along two lines of questioning: the role of physiological changes in pregnancy as a confounding factor and the statistical limitations encountered in the studies (see chapter 4.6).

Table 35 – Overview GRADE table certainty of evidence for concerning health outcomes

Evidence base of human epidemiological studies	Downgrading	Upgrading	Certainty of evidence$
	Risk of bias, inconsistency, indirectness, imprecision, publication bias	*Dose-response, magnitude of effect, residual confounding*	*Start point of observational studies is low*
Preeclampsia			
15 studies (n=22 963) *No pooling*	Downgrading for inconsistency	No upgrading	**Very low**
Gestational Diabetes mellitus			
21 studies (pooled estimate from SR Quan 2026)[16] *(n= 16 212 women)*	• PFOA: consistency across analyses • PFNA and PFDA show significant association in ln increase • Other PFAS: downgrading for imprecision	Upgrading for PFOA as there is a linear dose response reported	• PFOA: **moderate** • PFNA and PFDA: **low** • PFOS and other studied PFAS: **very low**
1 cohort study[a] (Starling 2026)[56] *(n= 5229 women)*	Due to the reported protective effects, a general downgrading for inconsistency was considered because in contrast to the findings of the SR. However, because the study had a probably high risk of bias—particularly for confounding and detection—no downgrading was ultimately applied.		
Miscarriage			
13 studies[b] (n=9429) *No pooling*	Downgrading for inconsistency and risk of bias	No upgrading	**Very low**
Prematurity			
14 studies (pooled estimate from SR Yang 2022)[62] (n= 21 935) *+ 6 studies (n= 5260)*	Downgrading for inconsistency	No upgrading	PFOS: **very low** PFOA: **very low**

Evidence base of human epidemiological studies	**Downgrading**	**Upgrading**	**Certainty of evidence$**
	Risk of bias, inconsistency, indirectness, imprecision, publication bias	***Dose-response, magnitude of effect, residual confounding***	***Start point of observational studies is low***
Birth weight			
53 studies on PFOS (pooled estimate from SR Wright 2025)[17] (n > 70 000 women) ***24 studies on PFOA (pooled estimate from SR Fu 2025)[97]*** ***27 studies on PFHxS (pooled estimate from Ru 2024)[99]*** ***27 studies on PFNA (pooled estimate from SR Wright 2023)[98]***	PFOS ,PFOA, PFNA : no downgrading PFHxS: downgrading for imprecision	Upgrading for PFOS, PFOA, PFNA, PFHxS dose-response relationships	PFOS: **moderate** PFOA: **moderate** PFNA: **moderate** PFHxS : **low**
Low birth weight (<2500g)			
7 studies (pooled estimate from SR Yang 2022)[62] n= 13 829	PFOS: no downgrading PFOA: downgrading for imprecision PFNA: downgrading for imprecision	No upgrading	PFOS: **low** PFOA and PFNA: **very low**
Small for gestational age			
10 studies (pooled estimate from SR Yang 2022)[62] n= 7155	PFOA: downgrading for imprecision PFOS: downgrading for imprecision and inconsistency PFHxS: downgrading for imprecision and inconsistency PFNA: downgrading for imprecision	No upgrading	PFOA, PFOS, PFHxS, PFNA: **Very low**
Congenital heart disease[c]			
3 studies (n= 1 312) ***No pooling***	Downgrading for risk of bias	No upgrading	**Very low**
Vaccine response			
13 studies (pooled estimate from SR Crawford 2023)[120] (n= 4 830)	PFOA, PFOS: downgrading for inconsistency PFHxS: downgrading for risk of bias	PFOS, PFOA, PFHxS: Upgrading for dose-response	PFOS and PFOA, PFHxS: **low**: PFNA and PFDA: **very low**

Evidence base of human epidemiological studies	**Downgrading**	**Upgrading**	**Certainty of evidence$**
	Risk of bias, inconsistency, indirectness, imprecision, publication bias	***Dose-response, magnitude of effect, residual confounding***	***Start point of observational studies is low***
	PFNA: downgrading for risk of bias and imprecision PFDA: downgrading for inconsistency and imprecision		
Infections during infancy and early childhood			
14 studies (pooled estimate from SR Rosen 2025)[18] (n= 13 800)	Downgrading for imprecision[d]	No upgrading	**Very low**
Acute Lymphoblastic leukemia in children			
2 studies (n=1044) ***No pooling***	Downgrading for risk of bias	No upgrading	MeFOSAA: **very low**

Note: The number of included studies and participants varies by PFAS compound. For each outcome, the largest available sample size is reported, which typically corresponds to analyses of PFOA or PFOS. $The certainty of evidence rating might differ between different PFAS compounds, also depending on which PFAS compounds have been studied. When there was a particular signal for a certain PFAS, a dedicated certainty rating was provided in the conclusion column. When there is no specific mention of a PFAS compound, the rating can be considered for all studied PFAS with the understanding that the set of compounds differs across studies (most of the time it includes PFOA, PFOS, PFHxS). When there was no pooled estimate it was not possible to reliably judge imprecision or magnitude of effect.

[a] *Starling study was identified after the SR by Quan 2026 and therefore not included in the pooled estimate*

[b] *There were 15 primary studies identified, but only 13 reported an effect measure*

[c] *The outcome was much broader: congenital abnormalities. However, only for congenital heart disease multiple studies were identified.*

[d] *Rosen pooled the data per individual PFAS and per infection outcome (risk, rate or a composite outcome) resulting in many different exposure-outcome combinations of which the vast majority were non-significant*

9.4 Implications of our findings for occupational exposure

Guidance on PFAS blood testing in individuals with occupational exposure is constrained by the limited evidence available on adverse health effects in occupational cohorts and by the absence of widely accepted or legally enforceable biological limit values for PFAS. In addition, our review of existing medical guidance specific to occupational exposure did not identify any established recommendations or deviations from standard occupational medical surveillance.

Based on the considerations outlined above, routine PFAS blood testing to inform clinical management is not recommended. In contrast, biomonitoring in occupational settings may be appropriate when needed to characterize exposure and support risk evaluation.

Occupational exposure represents a distinct context in which risk assessment and periodic health evaluations are mandatory. Biomonitoring can be part of that approach, although it is not explicitly required under current regulatory frameworks. Several scientific bodies including ECHA's RAC, the German Human Biomonitoring Commission, and the HBM4EU consortium conclude biomonitoring in occupational setting is the more appropriate approach for PFAS exposure assessment.

Regarding the interpretation of biomonitoring results, one can rely on available health-based guidance values and, where applicable, on PFAS concentrations in reference populations. However, none of these guidance values are designed to predict possible adverse health effects in individuals. The available guidance on post-test clinical follow-up is limited. With the exception of the NASEM,[1] most existing guidance documents do not recommend deviations from standard occupational medical surveillance. It is noteworthy that NASEM formulates recommendations for additional follow-up for levels above 20 ng/ml for the sum of 7 PFAS (i.e. offer additional medical screening lipid panels, liver function tests, serum creatinine, urinalysis, thyroid test, screen regularly for testicular cancer, breast cancer, ulcerative colitis). However, the scientific evidence supporting such clinical follow-up is not yet well established. This is consistent with concerns raised by U.S. medical toxicologists;[232] the United States Preventive Services Task Force regarding the ongoing controversy around screening for dyslipidemia in children; the lack of evidence-based screening tools for kidney cancer, testicular cancer, and ulcerative colitis in general practice; and the 2025 guidance from New South Wales, Australia, stating that NASEM blood levels are not appropriate for guiding clinical management.[183]

Few initiatives make PFAS blood testing available to workers (e.g. blood testing offered to army firefighters in the US), but these programmes are generally intended to support exposure assessment rather than to guide subsequent medical decision-making. As also shown in our analysis on ongoing initiatives there still exists a need for specific advice on medical management but the link between threshold PFAS blood concentrations and health outcomes are still largely lacking.

A call for research has been voiced in the 2022 FEDRIS report,[197] but no dedicated study in occupational exposure is ongoing in Belgium at the moment. In the EU-PARC initiative a study is ongoing on occupational exposure in the waste management sector.[220] Research in occupational exposure can be very informative as conducting studies in communities with elevated PFAS levels (near contaminated sites, workers in PFAS related industries, or cohorts with archived samples) might exhibit larger exposure variability and identify dose-response relationships.

More specifically on the guidance part, in France the Haute Autorité de Santé (HAS) and Société Française de Santé au Travail are developing occupational medicine guidelines for the surveillance of workers of reproductive age and pregnant women exposed to reprotoxic molecules, with an expected release by the end of 2026.[222]

From a stakeholder perspective, there is also a clear demand for access to free, voluntary, and confidential blood and/or hair testing for exposed workers to quantify PFAS body burdens, as well as for the development of dedicated health-surveillance protocols tailored to occupationally exposed populations.[198]

9.5 Evolving evidence base

The evidence base for PFAS is rapidly evolving, with numerous ongoing national and international (research) initiatives that continue to expand and refine current knowledge. An important forthcoming initiative is the WHO's effort to develop authoritative health-based guideline values including both individual compounds and PFAS mixtures. It will include a systematic evidence review including epidemiological studies as well as animal and in vitro studies for several health outcomes (see section 6.2). Another example is the US ATSDR conducting a follow-up of 5826 adults and 710 children at 8 different sites exposed to contaminated drinking water. It will collect information on health outcomes via self-reporting supplemented by clinical tests and biomarkers (thyroid, liver, kidney function, lipid profiles, sex hormones and immune biomarkers), though it will not be exempt from bias (confounding due to unmeasured risk factors associated with PFAS serum levels).[233]

Several studies are being conducted in the European PARC initiative. A longitudinal human biomonitoring (HBM) survey to investigate exposure to per- and polyfluoroalkyl substances in the most vulnerable population: pregnant women and their newborns (Luxembourg, Greece, Czechia, the Netherlands, Austria, Slovenia, Spain, Cyprus, Iceland).[164] And a study on occupational exposure in waste management.[220]

9.5.1 Types of epidemiological studies needed

The current evidence base relies partly on case-control and cross-sectional studies. These studies are particularly prone to bias. Moreover, they report more often a significant association than cohort studies (for example in gestational diabetes). Therefore, well conducted cohort studies are needed, where exposure is measured before the outcome. These can be retrospective using archived blood specimen, to avoid waiting several years for new results. Ideally, PFAS measurement should be available at different points in time, first to confirm the contamination over time, and second to explore the confounding effect of physiological changes. For example during pregnancy there is an increase in the blood volume as well as the glomerular filtration rate of kidneys, which might dilute PFAS concentration in the blood.

Moreover, the measurement of the health outcomes should be objective and confirmed by health professionals and/or diagnosis tests rather than self-reported by the patients.

Specifically for breastfeeding, it is important to have studies that address the relative exposure from breastfeeding versus prenatal exposure. This can be done by comparing in a group of pregnant women with similar exposure, exclusively breastfed versus exclusively formula fed infants.

9.5.2 Health outcomes to be assessed

For some concerning health outcomes the evidence basis is large (53 studies for birth weight, 21 studies on gestational diabetes), while for others the number of studies is very low (2 on acute lymphoblastic leukemia, 3 on congenital heart disease). While the focus of this study was on a selected set of concerning health outcomes, we acknowledge that the range of potential outcomes is broader than the scope of our analysis. This includes more subtle early biological responses—such as hormonal disruption—, or health effects later in life or even in the next generation (intergenerational effect), which were not specifically examined here but remain important areas for future research.

9.5.3 PFAS to be measured

Legacy PFAS such as PFOS and PFOA have been more extensively studied than other PFAS. Still, the epidemiological evidence is most often low to very low quality across health outcomes, and it will probably be difficult to improve it in the future. Indeed, future human studies may face increasing difficulty detecting associations between such PFAS exposure and adverse health outcomes because population exposure levels are steadily declining as a result of regulatory restrictions, phase-outs, and improved environmental controls. It is no longer sufficient to measure only legacy PFAS. Emerging

evidence shows that several newer or replacement PFAS, including compounds such as MeFOSAA and TFA are also linked to adverse health outcomes (e.g. MeFOSAA and ALL, the ECHA risk assessment of TFA). This underscores the need for broader analytical panels that capture both legacy and alternative PFAS. More recently studies use non-targeted analysis as a new technique to detect and identify novel PFAS. However this method is not opportune to be used for routine monitoring or quantification.

Because individuals are exposed to multiple PFAS and those most probably interact to possibly affect human health, studies need to analyse mixtures of PFAS. Most systematic reviews continue to concentrate on single-compound assessments.[16, 21] Consequently, they may fail to account for the complex synergistic or antagonistic interactions that characterize real-world co-exposures. This limitation persists largely because rigorous, cross-study meta-analytic methodologies capable of addressing mixture effects have not yet been fully established.[16]

9.6 Limitations of the study

Our study has some limitations. First, toxicological studies based on animal models were not included, limiting the integration of mechanistic evidence and the assessment of biological plausibility. However, our aim was to investigate the effects of PFAS exposure on human health and elucidate the clinical utility of PFAS testing. Moreover, the review focused on direct clinical outcomes in pregnant women and their offspring after PFAS exposure during pregnancy and/or breastfeeding. Other outcomes, such as thyroid or other endocrine outcomes may contribute to the overall health burden associated with PFAS exposure, and were not addressed because they were considered mechanistic or intermediate endocrine outcomes rather than primary neonatal/infant health outcomes. This choice does not imply that thyroid effects for example are irrelevant. EFSA and recent reviews recognise thyroid hormone disruption as a potential PFAS-related concern, but EFSA's 2020 risk assessment selected reduced antibody response to vaccination in children as the critical effect for deriving the tolerable weekly intake, reflecting the stronger basis for risk assessment at that time. Thyroid outcomes could therefore be addressed in a dedicated review focused on endocrine biomarkers, maternal thyroid function, neonatal thyroid screening results and clinical neurodevelopmental implications. This said, the outcomes analysed in this report are among the most studied ones, and the evidence base seems to be even more uncertain for others, such as the ones mentioned above.[12, 13]

Second, studies reported on associations between PFAS and health outcomes observed within the range of contamination levels in the specific study populations. It is unclear if such results can be extrapolated to populations or individuals with different levels of PFAS blood concentration. This extrapolation might be even more difficult when one considers that the associations might be non-linear, with different risk increase for different level of PFAS concentration. Moreover, the most studied molecules are legacy PFAS.

Finally, we applied an expedited approach, and limited our search to a single bibliographic database. However, this is consistent with KCE recommendations for this kind of topic. We also did not conduct new meta-analyses, although we examined primary studies for several health outcomes. In this context, refraining from pooling studies with clear methodological or clinical differences is considered good practice. In addition, we also searched the websites of regulatory agencies and national and international guidelines, for breastfeeding guidance for example.

Finally given the rapid increase in the number of publications and initiatives on this subject, the findings and conclusions of this study should be interpreted within the context of the current state of research and the data collected to date (April 2026).

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