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The impact of PFOS on health in the general population: a review†

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Perfluorooctane sulphonate (PFOS) is a persistent organic pollutant that is toxic, bioaccumulative and undergoes wide transportation across all environmental media. It has been widely detected in environmental samples but there is limited information about the health effects on humans from environmental exposure. This paper presents the findings of a review of the literature on the impact of PFOS on the health of the general population. Fifteen relevant epidemiological studies were identified that looked at the association between human PFOS exposure and a range of health related outcomes. Small but statistically significant associations have been reported with PFOS and total cholesterol, glucose metabolism, body mass index (BMI), thyroid function, infertility, breast feeding, uric acid and attention deficit/hyperactivity disorder (ADHD). The true significance of these findings is uncertain due to the inconsistencies in some of the study results and the limitations of the literature. The majority of studies were cross-sectional and considered surrogate markers of health (*e.g.* cholesterol levels). The available literature is also limited in ascertaining the link between PFOS concentrations in the environment, exposure pathways and health effects. We conclude that the current evidence is inconclusive and further large-scale prospective cohort studies would be useful to assess the association between environmental exposure to PFOS, appropriate biomarkers (*e.g.* serum levels of PFOS) and health outcomes.

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Environmental impact

Perfluorooctane sulphonate (PFOS) is a persistent organic pollutant that is toxic, bioaccumulative and undergoes wide transportation across all environmental media. It has been widely detected in environmental samples but there is limited information about the health effects on humans from environmental exposure. The current evidence on reported adverse health outcomes is inconclusive and thus further large-scale prospective cohort studies would be useful to assess the association between environmental exposure to PFOS, appropriate biomarkers (*e.g.* serum levels of PFOS) and health outcomes.

Introduction

Perfluorooctanesulfonic acid (PFOS), or perfluorooctane sulfonate, is a man-made fluorosurfactant, commercially available in the form of salts, derivatives and polymers. PFOS-related substances have been used as a component of Aqueous Fire-Fighting Foam (AFFF) and for providing grease, oil and water resistance to materials such as textiles, carpets and paper. PFOS or PFOS-containing substances are released to the environment at their manufacture, during their use in industrial and consumer applications and from disposal after their use. There is limited information on the mechanism which causes the degradation of PFOS-containing substances to PFOS but it is assumed to be mediated by microbial action or by metabolism in larger organisms.[1–3] No transformation of PFOS itself has been observed in environmental media such as soil, sediment, sludge, water. Environmental monitoring undertaken at sites remote from potential sources has shown elevated levels of PFOS throughout the northern hemisphere indicating occurrence of a long range transport.[1,3,4]

Human exposure to PFOS or PFOS-containing substances may occur *via* a number of media and routes *e.g.* ingestion (including accidental/involuntary ingestion of non-food materials), dermal contact, inhalation, drinking water.[1] Factors such as place of residence, age, nature of media *etc.* may also influence the exposure. Studies show that, for the general population, ingestion of fish and drinking water are the main routes of exposure although drinking water as a source is regarded negligible where there is a high consumption of fish.[5] The

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estimated average PFOS intake of the general adult populations of four European countries such as Italy, the Netherlands, Sweden and the UK is in the range of 45–58 μg per kg body weight per day based on the mean consumption of fish and fishery products.[5] The differences in total intake by the population may be attributed to differences in dietary (consumption of fish) and lifestyle habits, and the possible presence of other potential PFOS sources. A varying but typically small quantities of PFOS in the blood samples from cohorts of people with no known occupational exposure to perfluorocarbons (PFCs) have been reported which indicate that exposure to the chemicals even in pristine environments is widespread.[6,7] The available evidence on PFOS toxicity has been reviewed by expert committees in the UK, and for humans, they have not classified it as carcinogenicity, mutagenicity and teratogenicity.[6,8] Therefore for risk assessment purpose, it has been regarded as a thresholded substance and a tolerable daily intake has been derived rather than the index dose.[6,8]

PFOS was, however, classified as a persistent organic pollutant (POP) in 2009 reinforcing its earlier classification as 'persistent' (P), 'bio-accumulative' (B), and 'toxic' (T).[9] One of the main producers of PFOS phased out production by 2002.[10] Regulations are increasingly being put in place to limit PFOS use and to find alternative substances. In the UK, PFOS cannot be used in new fire fighting foams, but those already in the market before the legislation was introduced were permitted for use until June 2011. Concerns may remain about potential chronic exposures to PFOS due to environmental persistence and toxicity, even after all future use of PFOS containing substances is halted.

PFOS has been shown to cause health effects in animal studies and data available relating to occupational exposure have been reviewed.[4,6,11] There is a relative paucity of data on the exposure to and impact of PFOS on the general population. In view of the ubiquitous nature of PFOS and changes in regulatory policies, it is important to consolidate what is known about the health impact of PFOS in non-occupational settings. This review does not cover the health impacts of perfluorooctanoic acid (PFOA), another (per)fluorinated organic surfactant, which is primarily used as an emulsifier in industrial applications.

This paper summarises current knowledge about the association between PFOS and health outcomes in the general population and aims to improve the availability of information for public health responses to any environmental PFOS contamination and incidents.

Methods

The PubMed database was searched up to early July 2011, to identify all the relevant published literature. In formulating the search strategy, the PFOS review undertaken by the UK Committee on Toxicity in Food, Consumer Products and the Environment (COT) was also consulted.[6] The following terms were used: "Fluorocarbons/adverse effects" [MESH] OR "perfluorooctane sulfonic acid" OR "pfos" OR "perfluorochemical" OR "perfluorooctane sulfonate" AND "Humans" [Mesh] OR "Epidemiology" [MESH]. The resulting papers were screened on title first to identify those NOT about PFOS. The residual papers were screened using the following inclusion criteria:

- case studies, case series, observational studies (case–control, cohort, cross-sectional) or randomised trials
- study includes a measurement/description of PFOS exposure in the cases/population at risk or an indirect measure of exposure to PFOS (*e.g.* serum levels)
- a specific health outcome or marker is considered.

Results

The literature search identified 477 papers (Fig. 1). A review of titles identified 239 potentially relevant papers addressing PFC as contaminants (papers related to PFC in therapeutic settings were eliminated). A review of the abstracts identified 43 publications addressing health effects, all in English. Of the 43 publications, 15 papers were related to prenatal exposure, 6 to occupational exposure, and 4 were not original research *i.e.* did not contain any experimental data or findings, resulting in 18 papers relating to health effects in the general population. In light of a recent systematic review looking at the association between PFOS and foetal development,[12] the papers on foetal health and birth were excluded. The 18 papers were reviewed and 3 (ref. 13–15) were excluded as no specific health outcomes were investigated. The remaining 15 papers were included in this review (Fig. 1 and ESI Table 1†).

Cancer

Eriksen *et al.*[16] considered cancer incidence in a nested case–control study within a large prospective cohort of individuals aged 50–65 years ($n = 57\,053$). The exposure measurement was that of blood plasma PFOS, and the outcome was a diagnosed case of bladder, liver, pancreas or prostate cancer made during the 12 year follow-up period. During the follow-up period there were 1240 incidences of cancer and the authors report "virtually complete" case ascertainment from the Danish national registers. A random sample of 772 controls were selected with a comparable sex distribution. After adjusting for cancer specific confounding factors, the incidence rate ratios by quartile of PFOS exposure did not demonstrate a significant association between PFOS and the risk of cancer at the studied sites. This was a high quality study with a long follow-up period and

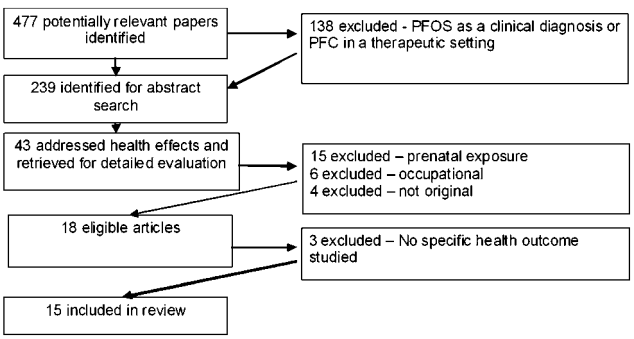

Fig. 1 Flowchart showing summary of literature search.

prospective exposure measurement. However the number of cases of some types of cancer was small (713 for prostate and 67 for liver). The half life of PFOS in humans is estimated to be between 139 days and 8.7 years;[6,11] therefore the participants' exposure status may have changed during the follow-up period.

Fertility and breastfeeding

Fei *et al.*[17] in a cohort study investigated the association between PFOS and female fertility in a sample from the Danish National Birth Cohort (DNBC), using a random sample (3%, $n = 1400$) drawn from the 43 045 women who gave birth to a singleton (not a twin or other multiple birth) with no congenital deformity. The exposure criterion was maternal serum PFOS measured at 4–14 weeks gestation and the outcome was infertility (use of infertility treatment or a time to pregnancy of >12 months), which was measured using self-reported time to pregnancy or use of fertility treatment collected at 12 weeks gestation. The study also calculated fecundity odds ratios (FOR), which are the odds of falling pregnant in a given month by PFOS exposure. PFOS exposure (by quartile) was shown to be significantly associated with an increased risk of infertility (1st quartile OR 1, 2nd quartile OR 1.7 (95% CI: 1.01–2.86), 3rd quartile OR 2.34 (95% CI: 1.40–3.89), 4th quartile OR 1.77 (95% CI: 1.06–2.95) test for trend, $p = 0.025$) and with a decreasing risk of fecundity (1st quartile 1, 2nd quartile FOR 0.7 (95% CI: 0.56–0.87); 3rd quartile FOR 0.67 (0.53–0.84); 4th quartile FOR 0.74 (0.58–0.93) test for trend, $p = 0.002$).

Fei *et al.*[18] in another cohort study randomly selected 1400 pregnant women from the DNBC to investigate whether PFOS maternal blood concentrations correlate with duration of breastfeeding. Maternal blood samples were taken at the first antenatal visit (weeks 4–14 of pregnancy) for PFOS measurement. Data on breastfeeding were collected by telephone interviews at 6 and 18 months after the birth. The study indicated that higher maternal concentrations of PFOS may be associated with a shorter duration of breastfeeding. However this association was restricted to multiparous women per 10 ng mL^{-1} increase in PFOS concentrations. There was no consistent association observed among primiparous women.

Joensen *et al.*[19] conducted a cross-sectional study of Danish military recruits to look at the association between serum PFOS and testicular function. A sample of recruits was chosen based on their testosterone levels (53 with highest testosterone concentrations and 52 with lowest testosterone concentrations); however the study did not find any significant difference in the PFOS levels of these two groups; when the groups were combined in a subsequent analysis (adjusted for the time of blood and semen samples), there were no significant associations between PFOS and markers of testicular function. However, there were non-significant negative associations with PFOS and some markers of testicular function (*e.g.* sperm concentration/count, motility and morphology, testosterone).

Cholesterol

Three studies were identified that investigated serum lipids as an outcome and all had a cross-sectional design. Steenland *et al.*[20] investigated a subgroup (people over 18 years of age, not on cholesterol lowering medication) from the "C8 Health Project", a cohort of 69 030 (estimated 80% participation rate) residents or former residents of Ohio and West Virginia who had potentially consumed water contaminated by PFOA, and although there were no obvious sources of PFOS at these sites it was detected in the studied population. Multivariate linear regression analysis demonstrated a "highly significant" increase in all lipid outcomes, except HDL, for each increasing decile of PFOS (p values not presented). The increase in cholesterol from the lowest to highest decile of serum PFOS was 11–12 mg dL^{-1}. The study also reported a significant positive association between quartile of serum PFOS and hypercholesterolaemia (defined as total cholesterol $\geq$240 mg dL^{-1}). The adjusted odds ratios of hypercholesterolaemia, by increasing quartile of serum PFOS, were 1.0, 1.14 (95% CI: 1.05–1.23), 1.28 (95% CI: 1.19–1.39) and 1.51 (95% CI: 1.40–1.64). This study had a high participation rate, but the outcome measurement was limited by the lack of fasting blood samples. The authors attempted to adjust for this in the analysis, but found that generally the patterns did not change when fasters and non-fasters were considered separately. It is not clear whether serum PFOA was controlled for in the analysis of PFOS.

The second study, by Nelson *et al.*,[21] was a cross-sectional study of a subgroup from the National Health and Nutrition Examination Survey (NHANES) in 2003–2004. This study looked at the association between serum PFOS and cholesterol in 20–80 year olds who were randomly selected to have their PFC levels measured ($n = 860$) and showed that the increase in total cholesterol from the lowest to the highest quartile was 13.4 mg dL^{-1} (95% CI: 3.8–23.0). The association between PFOS and HDL varied by sex and age group.

In a third study, Frisbee *et al.*[22] investigated potential associations between perfluoroalkyl acids (PFOA and PFOS) and lipids in children and adolescents. As in Steenland *et al.*,[20] the study looked at a subgroup ($n = 12\,476$: aged 1.0 to 17.9 years) from the "C8 Health Project". In order to assess possible age and developmental confounding, age was considered as a continuous variable and as 2 strata (aged 1.0–11.9 years and 12.0–17.9 years). In linear regression after adjustment for covariables (age, sex, BMI, z score, exercise, and fasting status), there was a significant association of PFOS with increased total cholesterol (Total-C), high density lipoprotein-C (HDL-C), and low-density lipoprotein (LDL-C). Using general linear model analysis of covariance, there was an 8.5 mg dL^{-1} and a 5.8 mg dL^{-1} increase in the adjusted mean levels of Total-C and LDL-C, between the first and fifth quintiles of PFOS. Neither PFOA nor PFOS was found to be associated with an increased risk of abnormal triglycerides. Overall the findings of Frisbee *et al.*[22] are consistent with those of the Steenland *et al.*[20] study with adults (>18 years age) *i.e.* increase in blood serum PFOS leads to corresponding increase in Total-C and LDL-C.

Insulin resistance/glucose homeostasis/metabolic syndrome

Nelson *et al.*[21] investigated the association between PFOS and insulin resistance (calculated using the homeostatic model

assessment, HOMA) in individuals aged 12–80 years (sample size not stated). No significant associations between PFOS and insulin resistance were detected. Lin *et al.*[23] conducted a very similar cross-sectional study using samples from the 1999–2000 and 2003–2004 NHANES ($n = 1443$) to investigate associations between blood serum PFOS and markers of glucose homeostasis (including blood glucose, insulin, insulin resistance and β cell function (both calculated using HOMA2) and metabolic syndrome. Multiple regression analysis did not demonstrate any significant associations between PFOS and markers of glucose metabolism in adolescents (12–19 years). However, in adults (>20 years), in the fully adjusted model, increasing PFOS was associated with a significant ($p = 0.001$) increase in insulin (β coefficient per unit log PFOS of 0.14 ± 0.05), insulin resistance (0.14 ± 0.05) and β cell function (0.15 ± 0.05). The study did not detect any significant association between metabolic syndrome and blood serum PFOS in adults or adolescents. Although this study did not present any data on the association between PFOS and cholesterol, the authors conclude that PFOS was "unfavourably" associated with HDL.

BMI/waist circumference

Nelson *et al.*[21] further considered the association between PFOS and BMI and waist circumference and found that the relationships varied by sex and age group. Males under 60 years had a negative association between PFOS and BMI (those aged 12–19 years in the highest PFOS exposure quartile had a BMI 2.76 kg m^{-2} (95% CI: −4.08 to −1.43) lower than the lowest PFOS exposure quartile and those aged 20–59 years in the highest PFOS exposure quartile had a BMI 1.8 kg m^{-2} (95% CI: −4.02 to 0.43) lower than the lowest exposure quartile). Whilst males between 60 and 80 years had the opposite association (highest PFOS exposure quartile had a BMI 1.55 kg m^{-2} higher than the lowest exposure quartile), there was no evidence of an association in women. Although no results were presented in the paper, Nelson *et al.* report that the association between PFOS and waist circumference was similar to that for BMI. Although this study used appropriate sampling weights in the analysis, the exclusion criteria led to 61% of the potential sample being excluded.

Thyroid hormones

Meltzer *et al.*[24] used the NHANES sample from 3 consecutive studies (1999/2000, 2003/04, 2005/06) to investigate the association between blood serum PFOS and thyroid disease in adults aged over 20 years ($n = 3974$). The outcome was self-reported thyroid disease or use of thyroid medication. Multivariate logistic regression did not demonstrate any significant differences in the odds of ever having thyroid disease or of currently having thyroid disease treated with medication, with increasing quartile of PFOS exposure in either sex. The analysis was adjusted to take into account the selection of the cohort but the authors included a sample size calculation in their paper which showed that the detected measures of association in the study were lower than those used in the sample size calculation. Therefore the study was underpowered. To increase power, the authors combined the lowest two quartiles of PFOS exposure and repeated the analysis. This showed that men in the highest quartile of PFOS exposure had a significantly higher risk of current thyroid disease controlled with medication compared to the baseline (OR: 2.68 (95% CI: 1.03–6.98), $p = 0.043$). The authors reported that the possible analysis from this sample was limited as the sample from NHANES participants who were selected to have their PFC levels measured did not overlap with the sample from people who had thyroid hormones measured.

Dallaire *et al.*[25] considered the association between PFOS and thyroid hormones in a cross-sectional study of a stratified random sample of adult Inuit residents in Canada, who have a putative exposure to PFOS through their traditional seafood based diet. No information about the PFOS levels in the diet was included in the paper. Exposure was measured using blood plasma PFOS (detected in 70% of samples) and this is the only study where PFOS was not detected in all the samples. This may be a consequence of the limit of detection of the test which was reported to be 100 ng L^{-1}, compared to, for example 2 ng L^{-1} in Meltzer *et al.*[24] The study demonstrated a significant negative association between PFOS and thyroid stimulating hormone (TSH) (adjusted β coefficient: −0.102, $p \leq 0.05$), total triiodothyronine (tT3) (adjusted β coefficient: −0.017, $p \leq 0.05$) and thyroid binding globulin (TBG) (adjusted β coefficient: −0.034, $p \leq 0.01$) and a significant positive association between PFOS and free thyroxine (fT4) (adjusted β coefficient: 0.014, $p \leq 0.05$). All these associations remained significant when adjusted for fish consumption and the sampling weights used in the analysis. However, the significance of these findings is difficult to determine as the authors report that the majority of the study population had normal thyroid hormone levels (95% TSH, 96.5% fT4, 99.2% fT3, 86.3% TBG).

Pirali *et al.*[26] undertook a comparison of PFOS in the blood serum of 21 patients with thyroid disease and 10 post-mortem controls as well as PFOS levels in thyroid tissue (28 cases and 7 controls). No information was provided on sample recruitment or how cases and controls from the blood serum and thyroid analysis were related (*e.g.* any overlap of participants). PFOS was found in all the surgical thyroid samples at levels much lower than those seen in the blood serum (thyroid tissue PFOS median: 5.3 ng g^{-1} (range: 2.1–44.7) and blood serum PFOS median: 11.4 ng mL^{-1} (range: 0.5–92.9)).

A pilot study was conducted by Bloom *et al.*[27] to explore hypotheses about the association between blood serum PFOS and thyroid hormones. This study looked at 31 out of 38 people from the New York State Angler Cohort Study (0.2%, $n = 18\,082$) who completed a dioxin exposure sub-study. This population was chosen as sport-fish consumption is a potential source of PFC exposure. After control for confounders (*e.g.* age, gender, ethnicity, BMI, cigarette smoking), the authors did not find any evidence of an association between blood serum PFOS and TSH or fT4.

Chan *et al.*[28] investigated whether exposure to PFOS was associated with maternal hypothyroxinemia. The study looked at pregnant women from Edmonton, Canada (in 2005–2006), who underwent a triple screen blood test at 15–20 weeks' gestation as part of ante-natal care. Thyroid hormones, fT4 and

TSH, were measured in blood serum from 974 women, and from these they measured PFCs in the sera of 96 hypothyroxinemic cases (normal TSH, the lowest 10th percentile of fT4) and 175 controls (normal TSH, fT4 between the 50th and 90th percentiles). Analyses conducted by conditional logistic regression indicated that the concentrations of PFOS in this population were not associated with hypothyroxinemia among pregnant women. The outcome did not change when adjusted for maternal age, weight, race, and gestational age at blood collection and the findings do not support a causal link between PFC exposure and maternal hypothyroxinemia in the studied population.

Uric acid

Steenland *et al.*[29] published a further study using the "C8 Health Project" cohort to investigate the association between blood serum PFOS and uric acid in adults aged 20 years or older (n = 54 591). Adjusted linear regression analysis demonstrated a highly significant positive linear trend in uric acid by blood serum PFOS ($p < 0.0001$) with a predicted increase in uric acid from the lowest to the highest decile of PFOS exposure of 0.22 mg dL^{-1} ($p < 0.0001$). Quintile of blood serum PFOS also had a significant positive association with hyperuricaemia (defined as >6 mg dL^{-1} uric acid in women and >6.8 mg dL^{-1} in males). The adjusted odds ratios as quintile of PFOS increase were 1, 1.02, 1.11, 1.19 and 1.26.

Attention deficit/hyperactivity disorder (ADHD)

Hoffman *et al.*[30] conducted a cross-sectional study using samples from the 1999–2000 and 2003–2004 NHANES (n = 571; 12–15 years of age) to investigate the associations between blood serum PFOS (as one of the PFCs) and ADHD. A parental report of previous ADHD diagnosis (by a doctor or health care professional) was considered as the primary dependent variable in the sample selection. The demographic variables age, sex, and race/ethnicity were included as covariates. Socioeconomic status and environmental contaminants (lead, environmental tobacco smoke (ETS)) were considered as potential confounders. The study showed a positive (p-value <0.5) dose–response relationship between parent-reported ADHD and blood serum PFOS concentrations modelled as continuous predictors. The adjusted odds ratio (OR) for reported ADHD in association with a 1 μg L^{-1} increase in blood serum PFOS was 1.03.

Discussion

A systematic search of the literature identified 15 papers that looked at the association between PFOS and a range of health outcomes in the general population. In all but one of the studies, PFOS was detected in the blood serum or plasma of all the participants which demonstrates the ubiquitous nature of this man-made substance. There were only three cohort studies. The first, a large prospective cohort study did not demonstrate an association between PFOS and cancer incidence (bladder, liver, pancreas or prostate).[16] The second cohort study demonstrated a significant association between PFOS and self-reported female infertility[17] and the third study, by the same authors,[18] showed an association between PFOS and duration of breastfeeding. The remaining epidemiological studies were cross-sectional in design and reported some small but significant associations between PFOS and the health outcome measured (ESI Table 1†). The studies of Pirali *et al.*[26] and Bloom *et al.*[27] were limited in statistical power and therefore no conclusion can be drawn from their findings. Similarly, the case–control study by Chan *et al.*[28] did not show any association between exposure to PFOS and hypothyroxinemia in pregnant women.

Limitations

The main limitation of the reviewed studies was the study design. Two of the 15 papers[26,27] were descriptive and the remaining epidemiological studies were of varying quality and design (ESI Table 1†). To determine whether there is a causal relationship between an exposure and an outcome a cohort design should be used, but only three of the identified papers had this design and these studies also had limitations. The first, Eriksen *et al.*,[16] had a long follow-up period (12 years), and a robust method of case ascertainment; however the exposure measurement was only conducted once despite the follow-up period being longer than the half life of PFOS. The lack of a significant association between PFOS and cancer is reassuring, and expected due to the lack of mutagenic properties; however this may also have been due to the sample size, and further studies may be needed to explore whether there are any associations.

The second cohort study, Fei *et al.*,[17] demonstrating a significant association between blood serum PFOS and self-reported female infertility was limited by selection bias. They chose a population of women with a successful pregnancy to study the risk of infertility. Therefore it is possible that the detected association is underestimated and may actually be higher. This study was further limited by the self-reported outcome measurement which has the potential to introduce recall bias. In another cohort study Fei *et al.*[18] indicated that higher maternal concentrations of PFOS may be associated with a shorter duration of breastfeeding. However this association was restricted to multiparous women and no consistent association was observed among primiparous women. The association observed may be non-causal as studies indicate that the women who previously breastfed are more likely to do so again and a reduction in PFOS may occur through excretion (as shown in Karrman *et al.*;[31] Tao *et al.*[32]).

Ten of the epidemiological studies had a cross-sectional design where the exposure and outcome were measured simultaneously and therefore they were not able to demonstrate any causal association between PFOS and health outcome. However their findings can be used to develop further research hypotheses.

Most of the studies in this review were based on samples from large population based cohorts, including the well validated NHANES[24] and the DNBC.[16] The sampling methods used

in these studies improve the generalisability of the findings and reduce the potential for selection bias. However the sample size available for study from the NHANES study was reduced to a third due to the small proportion of participants randomly selected to have PFC measurements.

There is a possibility that participants may have been exposed to unmeasured PFCs. Adequate control of other relevant exposures is likely to be a major limitation. All of the studies described how the PFOS exposure was measured: thirteen used blood serum PFOS and two used blood plasma PFOS. One study adjusted their analysis for the presence of albumin and found that it did not generally alter the results.[21] None of the studies provides any information about environmental sources of PFOS (*e.g.* drinking water, diet) to characterise the association between environmental levels, exposure pathways, human levels and health outcomes.

Eight studies[16–18,20,24,28–30] in this review looked at health endpoints (cancer, infertility, thyroid disease, hypercholesterolaemia, breastfeeding, ADHD); the remaining studies looked at surrogate outcomes (*e.g.* cholesterol levels). Therefore more work is needed to determine the significance of surrogate outcomes and how they relate to health status. Furthermore, in one study approximately 95% of the participants had thyroid hormone levels within the normal range which makes it difficult to determine the significance of the reported association between PFOS and thyroid hormones.[25]

The use of self-reported outcome variables in two of the studies is unlikely to introduce recall bias as participants are unlikely to be aware of their blood serum PFOS levels. However, Meltzer *et al.*[24] combined all thyroid diseases into a single category which limits the scientific interpretation of the findings.

We identified a paucity of literature on the association between PFOS in the wider environment and health in the general population and found only a small number of eligible studies that covered a wide range of health outcomes. We were not able to find enough information to complete a meta-analysis. A further limitation of our review was the exclusion of a single study that was not in the English language.

Coherence with evidence

The COT review[6] reported that there is "equivocal evidence for carcinogenicity" of PFOS from animal studies which is in keeping with the findings of this review. Eriksen *et al.*[16] did not detect a significant association between PFOS and cancer incidence, but they only looked at four types of cancer, with a small sample size. There was a potential threshold relationship between PFOS exposure and prostate cancer that was interpreted as a chance finding.

Steenland *et al.*[20] and Nelson *et al.*[21] both demonstrated a similar small but significant positive association between PFOS and cholesterol but neither study demonstrated a convincing association between PFOS and HDL cholesterol. Frisbee *et al.*[22] also indicated a significant association between PFOS and increased Total-C, HDL-C, and LDL-C. These studies used a cross-sectional design; therefore it is not possible to conclude a cause–effect relationship between PFOS and cholesterol and the association might have been confounded by selection bias from underlying demographic risk factors because sorting cohort by dose may disproportionately increase more younger female and low-BMI individuals in the lowest dose quartile used as the referent population.[33] Although the observations appear inconclusive, overall the findings are consistent with animal studies that have demonstrated elevated cholesterol as an effect of PFOS exposure.

Animal studies show that chronic PFOS exposure causes disruption of thyroid hormones, specifically an increase in TSH and a decrease in total T3.[6,11] Two studies were identified that investigated this association of which Dallaire *et al.*[25] demonstrated an effect on thyroid hormones that was different from that seen in animals. Specifically, it showed that PFOS was related to a decrease in TSH, T3 and TBG and an increase in T4. However, the majority of study participants had normal thyroid hormone levels; so the clinical significance of this association is difficult to determine. Another study[28] did not observe any association between exposure to PFOS and hypothyroxinemia.

The COT reviews reported that PFOS exposure in rats, but not mice, was associated with reductions in the mean number of viable foetuses[6,11] and the only study (*i.e.* Fei *et al.*[17]) in this review to look at female fertility demonstrated that PFOS exposure was associated with self-reported infertility in women. But the limitation of this study is the selection bias that results from using a cohort of women with a successful pregnancy to determine the risk of infertility.

The COT review did not report evidence of any effect of PFOS on glucose metabolism, male fertility, or body size. There were two studies in this review that looked at glucose metabolism but only one[23] demonstrated some significant associations, observed only in adults. Male fertility (testicular function) was only investigated in one small study[19] ($n = 546$) that did not demonstrate an association.

The animal studies reviewed by the COT do not explicitly consider body weight, although there was a suggestion that body weight in rats may be reduced with exposure, as relative liver weight increased while absolute weight remained unchanged. Nelson *et al.*[21] demonstrated an association between body size and PFOS in males only and the direction of the association was different in men under and over 60. This reduces the confidence in this being a "true" toxicological effect and it may be due to unmeasured or unknown confounders.

In comparing animal studies with human data, caution is necessary as the adverse health effects observed in animal studies were associated with exposure concentrations/doses likely to be significantly higher than those expected in the general population. There are also differences in toxicokinetics between animals and humans.[6,11]

PFOS has the potential to cause toxicity in humans but it is not known at what blood serum or blood plasma concentrations these adverse effects will begin to develop. The COT[6,11] considers PFOS as a threshold substance, as there is no evidence that it is mutagenic, and have defined a tolerable daily intake (TDI). It remains unclear how levels of environmental contamination relate to exposure at levels above this TDI. If the

associations reported in this review are true causal effects of PFOS, then its impact on health, from the levels the general population are exposed to, appears to be small. However PFOS was only recently identified as a persistent pollutant and the evidence base is still in its infancy.

Conclusions

Based on the available studies, there is presently insufficient evidence to describe the potential impact of PFOS in the environment on the health of the general population.

Assessing the public health consequences of environmental exposures to PFOS requires further investigation. Human epidemiological studies focus on how blood serum or plasma levels of PFOS relate to health effects. However, there is a need to link PFOS levels in the environment to the level of exposure in humans, the resulting blood serum levels and any health effects. This currently remains a gap in the evidence base.

Integrated research is needed that characterizes exposure to PFOS at the individual level and relates this to measured blood serum levels and any health effects.

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