Per- and Polyfluorinated Substances (PFAS); a Literature Review

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This literature review aims to assess contemporary research on human exposure to Per- and Polyfluorinated Substances (PFAS) using the PubMed database. A series of research papers were acquired and examined, revealing novel exposure routes (firefighting, blood transfusions), associations with renal cell carcinoma, impact on DNA methylation, and links to pregnancy and early infant health. PFAS is also associated with adiposity, heart disease, and impaired immune response post-vaccination. The literature suggests potential interventions through blood and plasma donations. Limitations in the scope and scale of research, along with gaps in the understanding of the carcinogenic potential of PFAS and the efficacy of interventions in reducing PFAS exposure, were identified. Further public health research should address these gaps and limitations to enhance our understanding and address the negative health outcomes associated with PFAS exposure.

Keywords

Per- and Polyfluorinated Substances (PFAS) • Human exposure • Epidemiological studies • Intervention strategies • Public health implications • Toxicity • Health outcomes

Introduction

Per- and Polyfluorinated Substances (PFAS) are a group of hydrophobic lipophobic chemicals with the capability of repelling water and oils. PFAS are commonly referred to as the forever chemicals, owing to their long half-life ranging from several years to multiple decades, and persistence in the human body and environment (Domingo & Nadal, 2019). This long life span is due to the atomic geometry and structure of the chemical. PFAS chemicals have been used in an industrial setting

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for several years, commonly found in non-stick cookware, food packaging, and water-repellent clothing (Domingo & Nadal, 2019). While novel pathways for exposure exist in air and food, water contamination is the most common vector for exposure (CDC, 2021).

PFAS is a studied and listed toxicant with an acute LD50 (the amount of the substance that causes death in 50% of studied organisms) in rats ranging between 430–680 mg/kg (CDC, 2021). Additionally, in vivo testing with rats has determined statistically significant Hepatic, Immune, Reproductive, and Developmental impairment with exposure to PFAS (CDC, 2021). Additionally, in vitro testing (tests conducted outside of a living organism, but rather in a controlled laboratory) associated PFAS exposure with the potential of being carcinogenic (CDC, 2021).

Methods

Despite increasing concern centered around PFAS and exposure, contemporary literature regarding exposure in humans is deficient. This paper aims to analyze health literature available in the PubMed database, an open-source biomedical and scientific database maintained by the National Library of Medicine at the National Institutes of Health, focusing on human exposure to Per- and Polyfluorinated Substances (PFAS). The criteria for the existing literature to be included within the review dictated that the article must be a peer-reviewed clinical trial with a defined cohort published between 2015 and 2023 (while the paper must have been published by 2015, several studies retrospectively analyzed data gathered before 2015, but published results as early as 2015). The PubMed database was fed five search terms to acquire the contemporary sources for the literature review, which were then read and reviewed to examine the current health literature available on PFAS. The terminology used in the PubMed database to collect sources for the literature review included “PFAS” “Exposure” “Human” “Cohort” and “Clinical Trial”. A total of fourteen sources were found in the database which included these search criteria.

A Scope of Existing Literature

Novel Routes of Exposure

Research from two sources determined exposure routes and levels of bioaccumulation in humans. One paper by Hansen, (2016), and another study by Averina (2020). The research into this realm has focused on areas, activities, or behaviors that have confirmed high levels of PFAS and how through human contact bioaccumulation of the chemical increases. For instance, research was conducted on populations of firefighters who frequently encounter PFAS in fire-resistant foam. Such research is extremely beneficial in tailoring policy interventions on the behavioral and structural level to curb exposure to PFAS. Two of the fourteen studies rendered by the search explored and investigated novel routes of PFAS exposure.

Findings from ongoing research by Solrunn Hansen, a professor at UiT University of Norway, shed light on the bioaccumulation of PFAS. Through comparison of differing rates of consumption of fish from lakes affected by aqueous film foaming foams (a precursor chemical which emulsifies into PFAS) to PFAS serum (amount of a substance present in the liquid component of blood, known as serum) concentrations in a cohort (Hansen et al., 2016). The research discovered a biological gradient increase of PFAS accumulation in the bloodstream as more fish from the affected

water were consumed to a statistically significant degree (Hansen et al., 2016). This knowledge is important for both public health authorities and individual consumers. PFAS is a known toxicant, and as such avoiding exposure by limiting consumption of contaminated fish is an important tool for decreasing the potential of exposure to PFAS.

An in-depth investigation by Maria Averina, a PhD researcher at the University Hospital of North Norway, sought to determine the potential of exposure to PFAS as well as other inorganic heavy metals through blood transfusion. The study sought to examine three separate cohorts of donors across Norway (Averina et al., 2020). The results of the study indicated that PFAS serum concentrations were found to be over the concentration limit of 0.91 ng/ml in 100% of the donors tested (Averina et al., 2020). Additionally, that concentration increased in concert with the age of the donors. Research suggests that blood and plasma transfusion is a novel route of transmission of PFAS (Averina et al., 2020). This preliminary research is important for health officials in avoiding worsening health outcomes by contaminating patients and increasing their PFAS concentrations through transfusions. Further, it raises the concerns for and requirement of donor screening of PFAS to maintain the safety and quality of donated blood and avoid the negative health outcomes associated with PFAS exposure.

Renal Cell Carcinoma

The most common kidney cancer, renal cell carcinoma, is a serious health condition requiring treatment and observation. Linking renal cell carcinoma to PFAS exposure will fill a gap in the carcinogenic understanding of PFAS as well as the disease itself. Only one of the fourteen studies acquired by the review parameters explored the relationship between PFAS and Renal Cell Carcinoma.

The study in question was conducted by Joseph J Shearer, a Ph.D. researcher at the NIH National Cancer Institute. The study examined the odds ratio of development in a cohort of pre-diagnostic cohort when compared to serum concentrations of PFAS in the cohort to a 95% confidence interval (Shearer et al., 2021). The odds ratio test yields three results, an odds ratio (OR) which indicates the odds of the event occurring, a confidence interval OR which indicates significance, as well as a p-value which determines the strength of the test when less than 0.05. The results found a positive association with renal cell carcinoma risk when exposed to PFAS (doubling in serum concentration, OR continuous = 1.71, 95% CI = 1.23 to 2.37, P = .002) and a greater than twofold increased risk among those in the highest quartile vs the lowest (OR = 2.63, 95% CI = 1.33 to 5.20, p = .007) (Shearer et al., 2021). Thus, the study found that PFAS concentration was a risk factor for renal cell carcinoma to a significant degree (Shearer et al., 2021). This research is extremely beneficial for public health officials in the strategy to mitigate renal cell carcinoma. By mitigating exposure to PFAS officials can prevent a potential vector of disease. The topic requires further testing to determine the strength of the association.

DNA methylation

DNA methylation is the chemical reaction in which methyl groups are added to DNA, and the addition affects the transcription and translation interactions within the body. Transcription and translation are biological processes responsible for the creation of proteins. Complications with these processes arise due to methylation and result in epigenetic defects and health issues. PFAS

has been linked to methylation, but associations are weak, and the area has not been actively studied (CDC, 2021). Of the fourteen studies, only one focused on DNA methylation.

A study conducted by Yiyi Xu (2020), a researcher at the University of Gothenburg, sought to compare serum PFAS concentrations with DNA methylation in blood samples of a cohort exposed to PFAS in drinking water (Xu et al., 2020). The results determined that DNA methylation was found to be associated with PFAS exposure through drinking water in the high vs low exposure group (Xu et al., 2020). However, there was no statistical association between PFAS concentrations and epigenetic age acceleration (Xu et al., 2020). The link between PFAS and methylation is helpful in risk assessment efforts. Public health officials can use this information to assess the potential risks associated with PFAS exposure, and thus develop targeted strategies for risk reduction and reduction.

Pregnancy and Early Infant Health

In vitro testing has found PFAS to be potentially harmful in development and early life. As such, understanding the endpoints of pregnant women exposed to PFAS is extremely critical for public health officials understanding of infant and early life health. Of the fourteen studies rendered in the search 2 covered pregnancy and early child life (Preston et al., 2020). (Timmermann et al., 2022).

A clinical study conducted by Clara Timmerman, a Ph.D. researcher at the University of Copenhagen, examined the relationship between PFAS serum concentration, prolactin (a breastfeeding-inducing hormone), concentrations, and breastfeeding (Timmermann et al., 2022). COX regression was used to determine the relationship between the three factors (concentrations of PFAS and prolactin, vs. breastfeeding termination (Timmermann et al., 2022). COX regression is a statistical model used for analyzing the time for an event of interest to occur. The study sought to understand the endpoint between exposure and termination of breastfeeding, a behavior that is important in early life development. The results of the study concluded that the observed and tested PFAS increased serum concentrations were associated with a statistical increase in terminating breastfeeding at any given time after childbirth. However, Serum PFAS was not statistically associated with reductions in prolactin concentrations, suggesting alternative bio-mechanical pathways interference by PFAS (Timmermann et al., 2022). Breastfeeding is a critical component of development in infants, the understanding of PFAS's role in terminating breastfeeding enhances the medical field's understanding of the pollutant's role in infant development. Further, the study's findings indicate the need for increased research to determine the importance and impact of PFAS on infant development.

A second study conducted by Emma Preston, from the Chan School of Public Health, sought to determine the relationship between PFAS concentrations and glucose tolerance during pregnancy (Preston et al., 2020). This was conducted by determining serum FPAS concentrations and the effects of exposure to multiple PFAS on continuous glucose 1-hour post–50-g GCT, using Bayesian kernel machine regression (BKMR) (Preston et al., 2020). Due to the nature of glucose testing, multivariate analysis was used to limit the effect of confounding variables such as age and BMI. Ultimately the testing determined that PFAS was not statistically associated with glucose tolerance categories (Preston et al., 2020). Suggestive evidence however did find that associations of PFAS concentration and glucose tolerance differed greatly across vulnerable population subgroups (Preston et al., 2020). While the study did not determine a causal relationship between

PFAS exposure and glucose tolerance, the research did uncover a potential association in vulnerable groups. This enhances the need for further research to understand this link and potentially raise public health awareness within these groups.

Adiposity and Heart Disease

Contemporary literature has (non-significantly) linked PFAS serum concentrations to increased risk of obesity and heart disease (CDC, 2021). Understanding the endpoint of heart disease and obesity regarding PFAS exposure is extremely critical in curbing the burden and DALYs (disability-adjusted life year) impacted by the issue. Heart disease is the number one cause of death in the U.S., and obesity is a growing issue specifically in that region (Ahmad and Anderson 2021). Public health should pay special attention to the issue and its potential causes regarding PFAS. Of the fourteen studies acquired by the search five included clinical trials into adiposity or heart disease.

A randomized clinical trial conducted by Andres Cardenas, from Harvard Medical School, sought to determine the relationship between PFAS concentration and adiposity, between two cohort groups of intervention and placebo, measuring over a 15-year follow-up. PFAS measured at baseline and 2 years after randomization (Cardenas et al., 2018). The results found the PFAS had differing effects by treatment group. Each doubling in PFAS was associated with a 1.03-cm increase in hip girth in the Diabetes Prevention Program trial for the placebo group (95% CI, 0.18–1.88 cm; P = .02) but not the lifestyle intervention group (-0.09 cm; 95% CI, -0.82 to 0.63 cm; P = .80). No associations were observed for changes in mean waist circumference (Cardenas et al., 2018).

Similarly, a randomized control trial was conducted by Pi-I D. Lin, from Harvard Medical School, sought to compare the risk of hypertension and blood pressure level to PFAS serum concentrations, using the same 2-treatment cohort as the study by Andres Cardenas (Lin et al., 2020). The results of the study determined a statistically significant association between doubling PFAS concentrations and systolic blood pressure at baseline (β per doubling: 1.49 mmHg, 95% CI: 0.29, 2.70), with a non-significant association of PFAS and hypertension within the placebo and treatment arm (Lin et al., 2020).

A similar randomized control study conducted by Gang Liu, a nutritionist at Harvard School of Public Health, compared PFAS measured at baseline while body weight was measured at 6, 12, 18, and 24 months. The cohort included obese men and women assigned to 1 of 4 diet groups (Liu et al., 2020) PFAS concentrations were not significantly associated with concurrent body weight or weight loss during the first 6 months. However, in women higher PFAS concentrations at baseline were associated with statistically significant higher levels of weight regain (Liu et al., 2020).

Lastly, within the category, a randomized control study conducted by Andres Cardenas, This study quantified and measured baseline concentrations of 9 PFAS types randomized to a lifestyle intervention or a placebo. The study found that doubling PFAS concentrations was associated with higher insulin resistance to a significant degree. However, there was no statistically significant association between PFAS and the development of Diabetes (Cardenas et al., 2017).

The findings of these studies are extremely beneficial in the creation and approach of public health policy regarding obesity and heart diseases. The links between PFAS exposure and insulin resistance, weight regain, as well as blood pressure highlight the importance of addressing pollutant exposure as a potential solution to reducing the burden of obesity and heart disease. The findings of

these studies suggest that public health practitioners should investigate PFAS reduction as a means of reducing the burden of heart disease and obesity.

Vaccination and Immune Response

PFAS has been linked to an impaired response to antigens in CDC literature (CDC, 2021). Ensuring vaccination is safe and efficacious is a tenet and cornerstone of public health. As such, Public Health agencies should pay special attention to critical endpoints regarding PFAS exposure and immune response.

A clinical study conducted by Katrine Kielsen, a researcher from the University of Denmark, sought to understand the relationship between PFAS and anti-body response post-vaccination (Kielsen et al., 2016). The results found that doubling PFAS concentrations reduced diphtheria antibody concentrations by as much as twelve percent (Kielsen et al., 2016). The diphtheria antibody is crucial for providing immunity against diphtheria, a decreased concentration increases the susceptibility to diphtheria and the resulting negative health outcomes (Kielsen et al., 2016).

Blood and Plasma Donations

Lastly, a randomized control trial sought to test the efficacy of blood and plasma transfusions as a potential intervention for PFAS exposure. Conducted by Robin Gasiorowski, from Macquarie University, the study sought to understand whether frequent blood and plasma donations would lower PFAS serum concentration in a cohort of firefighters exposed to PFAS (Gasiorowski et al., 2022). The results found that the mean level of PFAS was reduced significantly by plasma donation (–2.9 ng/mL; 95% CI, –3.6 to –2.3 ng/mL; $P < .001$), and blood donation (–1.1 ng/mL; 95% CI, –1.5 to –0.7 ng/mL; $P < .001$) but remained unchanged in control. For PFAS, significant reductions were found in the plasma donation but not significant in the blood or control group (Gasiorowski et al., 2022). This study offers a practical approach to reducing the concentration of PFAS and is a beneficial tool for public health officials. Specifically, for populations such as firefighters who are subjected to high rates of exposure. Public health officials should review the implications of plasma donation for addressing PFAS exposure in populations.

Limitations Across Contemporary Literature

Across most of the literature, a persistent limitation within clinical research was the cohort size and representation. Many of the studies struggled to fit a large response pool or have large cohorts for testing. Of particular interest were the studies of "Cord blood gene expression supports that prenatal exposure to perfluoroalkyl substances causes depressed immune functionality in early childhood" as well as "Associations between serum concentrations of perfluoroalkyl substances and DNA methylation in women exposed through drinking water". These studies lacked participants, such that confounding factors and biases within the data had a drastic effect on the statistical power and validity of the study. Similar to this issue a recurring gap within the existing literature was the homogeneity of the cohort population. Of particular interest in this was the study "Effect of Plasma and Blood Donations on Levels of Perfluoroalkyl and Polyfluoroalkyl Substances in Firefighters in Australia: A Randomized Clinical Trial". This study focused on populations with firefighters, due

to the nature of the work, by in large firefighters are in better physical shape than an average person, which in turn may make them more resilient to negative health outcomes. Finally, a common factor that was a limitation was the age of the cohort and the date of recording. Of particular interest were the studies "Association of Perfluoroalkyl and Polyfluoroalkyl Substances with Adiposity" and "Per- and poly-fluoroalkyl substances and blood pressure in pre-diabetic adults-cross-sectional and longitudinal analyses of the diabetes prevention program outcomes study". These studies retrospectively analyzed cohorts from 1996. However, generally within average serum concentrations of PFAS have dropped drastically since then, as the cohort failed to create a representative trial of average participants comparable to the population today. Additionally, a potential limitation of this review is the chosen search terms. The inclusion of "clinical trial" may have created a skew in results towards studies fitting such a criterion. In turn, this would potentially overlook relevant epidemiological cohort studies, ignoring potentially relevant data.

Gaps within the Literature

Throughout the literature, several gaps occurred in the research. One of the more prevalent was a lack of studies regarding the carcinogenic potential of PFAS. As stated, PFAS has been associated with cancer development during in vitro testing with rats (CDC, 2021). Of the linked studies, only one had covered renal cell carcinoma; however, the lack of data regarding cancer incidence and burden was seemingly surprising and disquieting. Future public health should seek to fill this gap and investigate the carcinogenic potential of PFAS exposure.

Additionally, in vitro testing in mice has associated PFAS concentrations with negative endpoints in early childhood development (CDC, 2021). Specifically, locomotion, infantile weight, growth, and survival. None of the research covered any aspect of the topic of early life developments in response to PFAS exposure (CDC, 2021). While one study examined breastfeeding termination in response to PFAS serum concentrations, the lack of research into infantile health in response to PFAS presents a glaring gap within public health research. Public health research should focus on closing this gap and understanding the critical endpoints of exposure to PFAS in developing children, as they are an at-risk population with a specific statistical likelihood of developmental defects.

Lastly, a glaring gap within the research data was the validity of potential interventions for PFAS exposures within humans. The terminology and search criteria for this literature scope included a defined human population cohort, with a clinical trial, exposed to PFAS, however only a single intervention for the reduction of serum level PFAS occurred in the entirety of the results. Due to both the acute and long-standing toxicity associated with exposure to PFAS, public health should exhaust more resources into the research on potential therapies and reductions of serum levels of PFAS in humans, especially due to their extremely long half-life and ability to persist in both the environment and human body.

Conclusion

Per- and Polyfluorinated Substances (PFAS) are a group of chemicals that have both acute long long-term health complications. This research scope sought to evaluate the existing literature on clinical trials regarding the exposure of humans to PFAS. Using these parameters, fourteen sources were found. After evaluation, limitations in the research included understanding both the

carcinogenic, developmental, and interventions for PFAS exposure. Ultimately, public health bodies must invest more time, effort, and resources into the study of PFAS exposure to ensure a greater understanding and ability to combat the growing health burden caused by the forever chemical.

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