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REVIEW

Current Status of Per- and Poly-Fluoroalkyl Substances (PFAS) Exposure on Lung Cell Biology and Pulmonary Outcomes along Human Health Risk Assessment Steps

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Abstract

Purpose of Review This review aims to summarize the effects of per- and poly-fluoroalkyl substances (PFAS) exposures on the lung, emphasizing data coverage across steps of human health risk assessments.

Recent Findings There is expansive literature characterizing PFAS contamination in water, but recent studies have identified PFAS as a component of air pollution, thus impacts on the lung have been an increasing point of inquiry. Mounting evidence from human clinical/epidemiological, animal, and in vitro investigations supports relationships between PFAS exposures and adverse pulmonary outcomes including asthma, allergies, infections, and cancer. Focusing on toxicology studies using animal and in vitro lung cell models, exposures to PFAS modulated inflammation/immune responses, oxidative stress, mucus production, surfactant properties, and epithelial barrier integrity, representing important mechanisms impacting pulmonary health.

Summary There are expanding datasets linking PFAS exposures to adverse pulmonary outcomes; however, these data originated from mostly oral/ingestion exposure and not from volatilized or aerosolized PFAS exposure designs. Furthermore, there is a general lack of data informing dose-response modeling and risk characterization, representing gaps needed to characterize pulmonary health risks.

Keywords PFAS · Lung toxicity · Pulmonary health · Chemical risk · Animal · In vitro

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Introduction

Introduction to PFAS

Per- and polyfluoroalkyl substances (PFAS), also known as "forever chemicals", encompass a large and diverse class of synthetic compounds characterized by their strong carbon-fluoride bonds [1]. PFAS have been produced since the 1940s and are commonly used in numerous consumer and industrial products, because of their heat, water, and stain resistant properties [2, 3]. Since PFAS are manufactured in large quantities and, concurrently, break down very slowly, they can bioaccumulate in the environment and have been detected in water [2–5], air [2, 3, 6], soil [2, 3, 7, 8], and animal tissue [9]. Notably, studies have found that PFAS can also bioaccumulate in human tissues including the lung, kidney, liver, breast milk, and brain [10–13]. Exposure to certain levels of PFAS has been found to lead to adverse health effects such as cancer, immunosuppression, thyroid disease, reproductive issues, kidney and liver diseases, and lung diseases [3, 13–16]. The application of long-chain "legacy" PFAS, such as perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), is being phased out due to their extreme persistence and documented adverse health effects [17]. Soon after, short-chain PFAS replacements were introduced as safer, less bioaccumulative alternatives for legacy compounds; however, there is growing evidence that replacement PFAS are equally persistent and toxic as their long-chain predecessors, making PFAS an ever-evolving and growing public health issue [17, 18].

Human Health Impacts of PFAS Exposure on the Lungs

While direct pulmonary exposure to PFAS poses the most proximate threat to lung health, indirect exposure to PFAS can also affect the lungs, as PFAS are readily absorbed into the bloodstream and distributed throughout the body [15]. Direct exposure to the lungs can occur through inhalation of PFAS present in polluted outdoor and indoor atmospheres; indirect exposure to the lungs likely occurs through ingestion from contaminated water or food products, as well as dermal absorption through contact with PFAS-containing products or contaminated surfaces [14, 19]. Notably, the lungs have been found to be a biological sink for PFAS in both adults and fetuses, suggesting that the lungs are a target for PFAS-induced toxicity [11, 20]. Numerous epidemiological studies have been conducted to better understand the relationship between PFAS exposure and adverse pulmonary impacts in humans, largely, by measuring blood serum concentrations of PFAS in individuals with or without specific lung conditions. In the past five years, several reviews and meta-analyses have already synthesized the findings from these studies [15, 21–26]. Briefly, PFAS exposure in children has been associated with changes in risk for asthma [21–23, 25] and acute respiratory infections [24, 25]. Children, generally, are more highly exposed to PFAS and have greater serum concentrations of PFAS than adults, making perinatal and childhood development a plausible period of vulnerability to PFAS-induced toxicity in the lungs [27, 28]. Compared to studies in children, there are far fewer that examine the effects of PFAS on pulmonary health in the adult population. PFAS exposure during adulthood has been linked to abnormal lung function [29] and chronic obstructive pulmonary disease (COPD) [16, 30] and may also be associated with lung cancer [26, 31]. These findings in humans emphasize the need for additional epidemiological studies and provide strong motivation to leverage animal, in vitro, and in silico models to better understand the underlying mechanisms of PFAS-induced lung toxicity.

What is Chemical Risk Assessment?

Evaluating PFAS exposures through the lens of human health risk assessments represents a critical step towards translating human population and lab-generated data into real-world chemical regulation and policy, as well as clinical guidance/interventions. Briefly, chemical risk assessment represents a process for evaluating and quantifying the chance of harmful effects to human health or ecological systems resulting from exposure(s) to an environmental stressor (or multiple stressors) [32–35]. The steps of a human health risk assessment are commonly organized into four sections: First, hazard characterization represents the process of determining whether exposure to a stressor (or group of stressors) can cause an increase in incidence of adverse health effects and includes weight of evidence approaches that incorporate mechanistic plausibility of effects occurring in humans. Second, dose-response modeling represents the process to derive how the incidence or likelihood of adverse health effects are related to the amount of exposure to the stressor. Third, exposure characterization represents the process of estimating the magnitude, frequency, and duration of human exposure to a stressor. This information can be based upon direct measures of exposure or, more commonly, indirectly by considering measured concentrations in the environment, models of chemical transport and fate in the environment, and estimates of human intake over time. Lastly, risk characterization represents an integrative synopsis of information from the first three steps of the risk assessment, resulting in a summary of the presence (or absence) of risks, information about how risk was assessed, assumptions and uncertainties that remain, and where policy choices are advised based upon an overall conclusion

about risk [32–35]. Note that steps 2 and 3 often occur concurrently and are sometimes switched in order within risk assessment documents.

Results of chemical risk assessments have direct translational consequences, as they dictate the concentrations/durations at which exposures are deemed safe versus adverse across different human populations [32–37]. Risk values can further be used to quantify the risk of health outcomes resulting from exposure conditions in population-level studies. Risk mediation strategies can then be formulated, based off risk assessment findings, to best protect human and environmental health. Mediation strategies can include government policy and regulation, community engagement and/or citizens-based science, and clinical practices to intervene with patients at high risk of deleterious exposures that may impact their health [32–37].

Purpose of Review

We are at a pivotal moment in PFAS research, in which studies are now being published at increased rates with goals of understanding the health consequences and underlying biological mechanisms of disease affected by this pervasive category of chemical exposures. What remains unclear is how these growing datasets might fit into a human health risk assessment paradigm. Here, we converge the fields of PFAS toxicology, human health risk assessment, and pulmonary health as a point of focus to better understand current strengths and limitations in extant data for informing human health risks. The overall structure of the review is depicted in Figure 1.

Literature Search

Methodology

The lung was prioritized as a target organ for this literature review due to a growing interest in PFAS-associated pulmonary health outcomes. To provide further focus, toxicology-relevant study designs using animal models and in vitro lung culture models were summarized. We recognize that human epidemiology studies can heavily influence human health risk assessments as well, and future efforts should review this data category.

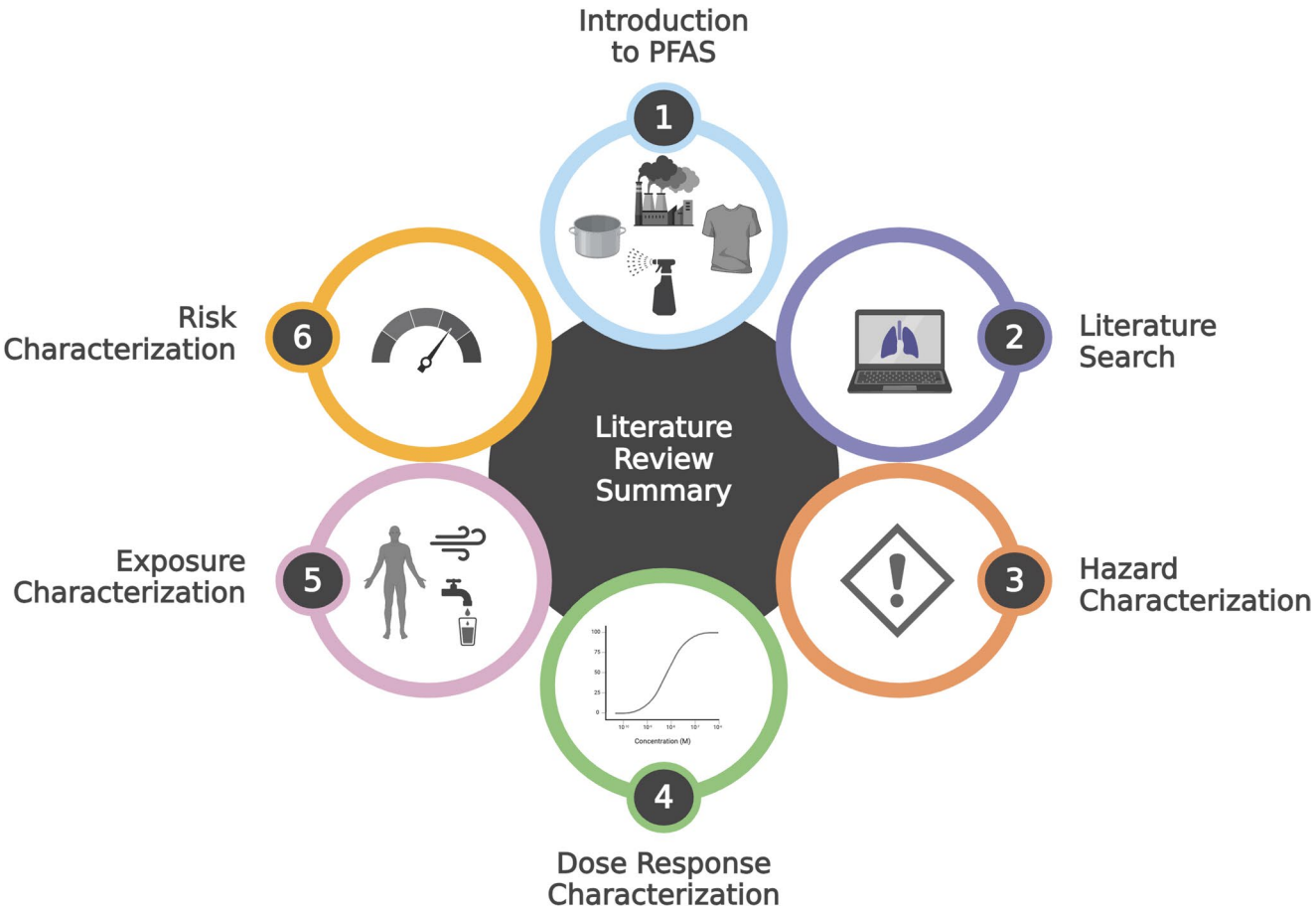

Fig. 1 Organizational structure of literature review

When identifying articles to review, literature published in the last five years (2020–2025) was prioritized to align with the journal's scope; however, earlier studies were also included to share important findings and historical perspectives. To identify relevant animal and in vitro studies, literature queries were performed in PubMed using search strings. The words PFC, PFAS, or individual PFAS names were searched in combination with key words and phrases including lungs, lung health, lung function, pulmonary toxicity, respiratory toxicity, lung epithelial, airway epithelial, in vivo, in vitro, rodent, mouse, and rat. Examples of queries were as follows: "PFAS" AND "lungs" AND "in vivo", "PFOS" AND "lung health" AND "rodents", "GenX" AND "pulmonary toxicity" AND "mouse", "PFAS" AND "respiratory toxicity" AND "in vitro", "PFC" AND "lung epithelial" AND "in vitro".

Inclusion criteria for articles encompassed the following: Articles were required to have evaluated PFAS exposures, spanning legacy and/or replacement PFAS, co-exposures including PFAS, and lung disease models with PFAS exposure. All routes and methods of exposure were included. Articles were also required to have evaluated outcomes and/or molecular alterations apparent in the lower respiratory tract (i.e., lung or lung cells). Exclusion criteria for articles included in vitro studies that investigated any cell type besides lower respiratory tract epithelial cells. Articles identified by this review process were organized into summary-level tables and were used as the basis for sections summarizing available data pertinent to hazard characterization and dose-response modeling. A short narrative review was provided for sections summarizing available exposure and risk characterization steps. Review articles were additionally leveraged to identify gaps in the research and to provide foundational knowledge; primary references from relevant reviews were cited when appropriate.

Literature Search Findings

Using the literature search methodology described above, we identified 37 total articles for inclusion, spanning 28 articles using animal designs (15 adult and 13 developmental bioassays) and nine using in vitro designs focusing on lungs as a target tissue. The citations, experimental designs, and key findings of these studies are detailed in Supplemental Table S1, and full chemical names and identifiers across the discussed PFAS in the Hazard Characterization and Dose-Response Characterization sections are summarized in Supplemental Table S2. Highlighting recent studies, 15 articles using animal models and four using in vitro models have been published within the past five years and are summarized in the Key References section. Below are summaries of key data published relevant to steps of the human health risk assessment process.

Hazard Characterization

Animal Studies Evaluating Hazards of PFAS on the Lung

Over the past two decades, 28 rodent exposure studies have investigated the effects of PFAS on lung health. Many of these studies examined the impacts of legacy PFAS compounds, most notably PFOS and PFOA, due to their prevalence and pervasiveness in the environment. In these studies, PFAS were introduced orally (including via drinking water consumption and oral gavage) or via inhalation (including whole-body or nose-only inhalation, intranasal instillation, and oropharyngeal aspiration [OPA]) (Supplemental Table S1). Regardless of exposure route, PFAS compounds induced biological responses in the lung and caused a variety of adverse pulmonary outcomes. In adult rodents, the most common effects include structural injury and dysfunction [38–41], inflammation [40–46], and immune system dysregulation [40–47]. Recently, studies from the past five years have shown that PFAS exposure can modulate susceptibility to various lung conditions and pulmonary insults [43, 46, 48–51]. For instance, PFOA and a PFAS mixture of PFOS, PFOA, PFNA, PFHxS, and GenX altered the expression of genes involved in respiratory virus responses including *Ace2* and *Tmprss2*, which play an important role in the initiation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [46, 50]. PFOA also increased tumor nodules and metastasis in a mouse model of lung cancer [51], while PFOA and PFOS both modulated the pulmonary response to allergen-induced airway hyperresponsiveness (AHR) and asthma [48, 49]. One study evaluating GenX exposure in mice via OPA identified activated inflammatory responses in the lungs and dampened innate immune responses to inhaled carbon black nanoparticles [43].

Rodents have been used to understand the developmental impacts of PFAS exposure on lung maturation and function, particularly in prenatal and perinatal periods of development during which PFAS can pass through the placental barrier and can be transferred through breast milk [52–54]. These studies involved exposing dams to PFAS via drinking water, oral gavage, or contaminated food and examining fetal, neonatal, juvenile, and adult offspring – with or without continued PFAS exposure (Supplemental Table S1). Notably, developmental studies have not currently leveraged inhalation exposure methods, highlighting an important gap in knowledge. Prenatal and perinatal exposures induced effects in the lungs including minor to severe morphological abnormalities [55–60], inflammation and oxidative stress [55–60], metabolic dysfunction [56, 61–63], and vulnerability to allergen-induced AHR and

asthma [64, 65]. In the last five years, studies have found that PFAS can induce sex-specific changes in offspring. One study showed juvenile males, but not females, had thicker alveolar septa and decreased pro-inflammatory markers in the lungs after perinatal PFOS exposure [59]. Another study found that perinatal PFOS exposure exacerbated house dust mite (HDM)-induced allergic asthma in adult offspring; however, male offspring had increased macrophage and eosinophil counts in bronchoalveolar lavage fluid (BALF) and inhibition of HDM-induced signaling pathways in the lungs, while female offspring had increased mucus production, decreased macrophage percentages in BALF, increased eosinophil percentages in BALF, increased M2 macrophage polarization, and aggravation of HDM-induced signaling pathways in the lungs [65]. These adult and developmental exposure studies highlight a need for additional research into the effects of PFAS on pulmonary health with a special emphasis on replacement PFAS compounds and sex-specific outcomes.

In Vitro Studies Evaluating Hazards of PFAS on the Lung

In contrast to the animal studies, only nine in vitro studies have been conducted to evaluate the impacts of PFAS exposure on lung cells. These studies utilized human (including A549, Calu-3, HBEC3-KT, 16HBE14o-, and BEAS2B) and rodent (including MLE-2, L2, and RLE-6TN) epithelial cell lines by exposing cultured cells to PFAS for durations ranging from 24 h to seven days at concentrations ranging from 10^{-5} µM to 1000 µM (Supplemental Table S1). Four of the studies, all of which were conducted over eight years ago, focused on perfluorocarbons [66–69]. Perfluorocarbons are a distinct subset of PFAS that have a completely fluorinated carbon backbone (no C-H bonds) and can include functional analogs, making them largely chemically and biologically inert [70, 71]. Notably, in vitro exposures to perfluorocarbons have a mostly protective effect toward lung epithelial cells by creating a biophysical barrier that reduces lung cell injury and inflammation [66–69]. While somewhat surprising, their highly stable and unreactive composition hinders them from being easily absorbed by tissues or broken down into toxic metabolites, making them useful in numerous clinical applications [71].

In the four recent studies from the past five years, more environmentally-prevalent short-chain and long-chain PFAS were investigated using lung epithelial cell lines. All four studies examined PFOS, two of the four evaluated PFOA and PFBS, at least one of the studies examined PFBA, 8:2 FTOH, and GenX, and one also evaluated a PFAS mixture (Supplemental Table S1). As a whole, in vitro exposures to PFAS in these studies induced pro-inflammatory responses such as upregulating the caspase-3/GSDME signaling pathway [44, 58], impaired barrier integrity including disrupted tight junctions [72, 73], and induced endoplasmic reticulum stress [44, 58, 72, 73]. One of the studies generated a mixture of PFOA, PFOS, PFBA, PFBS, and GenX and observed the activation of the NLRP3 inflammasome and release of pro-inflammatory cytokines [44]. Overall, the in vitro studies indicate that airway epithelial tissues are responsive to PFAS exposure; however, there is a clear need for additional in vitro research investigating pulmonary responses since current research is limited. Notably, only one of the in vitro studies leveraged air–liquid interface (ALI) epithelial cell culture prior to exposure with PFAS [66]. ALI more closely mimics the airway surface lining of a human respiratory tract, as the culture system allows for cellular differentiation and pseudostratification (when applicable). It also enables inhalation-relevant (liquid or gaseous) exposures on the apical surface, yielding a better understanding of how inhaled contaminants may impact the lung epithelium [74].

Dose-Response Characterization

Dose-response characterization of data generated from studies such as those summarized in Supplemental Table S1 represents an important risk assessment step, ultimately informing how much of an exposure is needed to elicit enough change in biological response to potentially induce an adverse health outcome. To clarify terminology, the term "dose" is commonly used for this step, though depending on the administration/study design, this term can be exchanged with the term "concentration" when describing and analyzing the exposure conditions. Dose-response characterization can result in defined No-Observed-Adverse-Effect Levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) in cases when data are not sufficient for dose-response modeling (i.e., only 1, 2, or 3 doses included) [33]. In modern-day risk assessments, however, it is preferred to evaluate responses covering as much of the totality of possible doses as possible. This is achieved by plotting responses across multiple doses and implementing mathematical modeling of dose-response curve fits to extrapolate response estimates for values not specifically tested in the experiment. There is current discussion surrounding the optimal number of exposure doses that should be included in such assessments, though it is clear that more than three doses (or concentrations) are required in addition to the vehicle controls, at a minimum, to test model fits across standard dose-response modeling algorithms [75, 76]. Further evaluation of resulting curve fits results in the derivation of a benchmark doses (BMD) or benchmark concentrations (BMC), representing the lowest modeled

estimate of a dose (or concentration) eliciting a detectable concerted change in an endpoint in response to a chemical exposure [75, 76]. Resulting BMDs or BMCs are then used as points of departure (PODs) that are translated further in a risk assessment. For example, PODs can be divided by uncertainty factors (UFs) yielding Reference Doses (RfDs), defined as an estimate of daily oral exposures to the human population (including sensitive groups based on underlying disease, such as asthmatics, or life stages, such as children or the elderly) that is likely to be without an appreciable risk of deleterious effects during a lifetime, often in units of mg/kg/day [33]. Similarly, Reference Concentrations (RfCs) are used to assess inhalation risks, where concentration refers to levels in the air, often in units of mg/m^3 or $\mu g/m^3$ [33].

Among the 28 adult and developmental studies identified to characterize PFAS-induced pulmonary toxicity in rodents, only one developmental study was suitable to evaluate a dose-response effect on the lungs by including more than three exposure doses. Briefly, pregnant CD-1 mice were exposed to 0, 1, 3, 5, or 10 mg/kg PFOA via daily oral gavage from gestational day (GD) 1 to GD 17; fetal offspring were collected on GD 18 to examine the lungs for PFOA-induced histological and transcriptomic alterations [61]. Despite observing no morphological changes in any of the exposure groups, they found that the expression of 44, 45, 193, and 336 genes were significantly ($p \leq 0.0025$) altered in fetal lung when prenatally-exposed to 1, 3, 5, and 10 mg/kg PFOA, respectively [61]. The differentially expressed genes, primarily in the two highest exposure groups, were associated with lipid homeostasis regulation including mitochondrial and peroxisomal fatty acid catabolism [61]. Notably, two other studies, one adult and one developmental, exposed rodents to three different concentrations of PFAS; however, these do not satisfy the minimum requirement of four distinct exposure concentrations required for dose-response modeling [40, 60]. The overall lack of animal studies characterizing pulmonary dose-response outcomes is concerning and identifies a need for more studies of this nature to better understand PFAS-derived PODs and the associated health risks.

Out of the nine in vitro studies investigating the effects of PFAS in lung cells, only three studies were designed to include four or more exposure concentrations. Two studies found that after 24 h of PFOS exposure at higher concentrations (e.g., 225 µM-500 µM), there was a significant decrease in cell viability [44, 58]. In one of these studies, 1 µM, 5 µM, 50 µM, and 500 µM of PFOA and PFOS were individually examined, and there were increased steady state levels of NLRP3 mRNA, demonstrated by measuring caspase-1 and HGMGB1 secretion in the media, with the increase occurring at the highest concentration of 500 µM [44]. Additionally, PFBA and GenX were found to have no effect on cell viability at any concentration between 1 µM – 1000 µM, yet PFOA decreased cell viability at higher concentrations, ≥ 100 µM [44]. This study also evaluated lung cells exposed to a mixture of five PFAS – PFOS, PFOA, PFBS, PFBA, and GenX – at doses of 10 µM, 100 µM, 200 µM, and 300 µM [44]. The mixture caused an increase in steady state mRNA levels of NLRP3, demonstrated by caspase-1 and HMGB1 release in media [44]. The third study found that after 48 h of exposure, there was a reduction in cell viability with PFOS concentrations of 30 µM and 60 µM, and there was no decrease in cell viability among the other PFAS evaluated, even at the highest tested concentration of 60 µM [73]. Pro-inflammatory responses were also tested and revealed that PFOS concentrations greater than or equal to 30 µM caused increased inflammatory responses, demonstrated by increased IL-1α and IL-1β cytokine protein release in the media [73]. Overall, there is indication that certain PFAS can induce cytotoxicity and inflammatory activation at higher concentrations within these dose response studies, yet there is still limited data to understand and define clear PFAS dose-response effects in lung cells.

Exposure Characterization

Studies Evaluating PFAS in Air and Potential Human Exposures

Recent studies examined the presence of PFAS species in air and the potential for humans to be exposed to these species through direct inhalation or through ingestion of dust. To date, many diverse species have been measured in air, and the relative abundance of each species is a function of environmental sources such as chemical manufacturing sites, industrial sites, waste sites, and products in consumer use [77–79]. Understanding the presence and potential transformation of these species, as well as potential for human exposure, is a key step in assessing risk. A summary of example studies detecting PFAS in air, and their corresponding concentration ranges, is provided in Table 1.

The potential for each PFAS to be present in air is largely dependent upon its physicochemical and structural properties. Polyfluorinated neutral PFAS (those that cannot be deprotonated) tend to dominate the profile of contaminants in both indoor and outdoor air [78, 83, 85]. These types of PFAS include the fluorotelomer alcohols (FTOHs), such as 4:2, 6:2, 8:2 FTOH, and 10:2 FTOH, which are particularly volatile, as well as fluoroalkyl sulfonamides (FASAs) and fluoroalkyl sulfonamidoethanols (FASEs) [83]. Specifically, literature suggests that FTOHs are the predominant PFAS species in indoor and outdoor air [78, 81, 83]. These compounds have been detected in homes, classrooms, and

Table 1 PFAS concentrations reported in indoor and outdoor air. PFAS concentrations were summarized across published, peer-reviewed studies measuring concentrations of airborne PFAS in different environments (published as of January 2025). Chemicals are listed alphabetically, according to chemical name. Each chemical's abbreviation and CASRN is included, as well as reported indoor and outdoor air concentration ranges

Chemical Name	Chemical Abbreviation	CASRN	Reported indoor air range (ng/m^3)	Reported outdoor air range (ng/m^3)	References
11-Chloroperfluoro-3-oxaundecanesulfonic acid	8:2 Cl-PFESA	763051-92-9	NE	0.0859–0.722	Liu et al., 2017 [80]
6:2 Fluorotelomer phosphate diester	6:2 diPAP	57677-95-9	0.00–0.47	NE	Chang et al., 2024 [81], Minucci et al., 2025 [82]
8:2 Fluorotelomer phosphate diester	8:2 diPAP	678-41-1	0.00–0.012	NE	Chang et al., 2024 [81], Minucci et al., 2025 [82]
8:2 Fluorotelomer acrylate	8:2 FTAC	27905-45−9	0.00–0.92	NE	Eichler et al., 2023 [83]
10:2 Fluorotelomer acrylate	10:2 FTAC	17741-6−5	0.00–0.40	NE	Eichler et al., 2023 [83]
Fluorotelomer alcohol 4:2	4:2 FTOH	2043-47−2	0.00070–0.210	NE	Minucci et al., 2025 [82], Haug et al., 2011 [84]
Fluorotelomer alcohol 6:2	6:2 FTOH	647-42-7	0.063–48.8	0.016–0.300	Eichler et al., 2023 [83], Minucci et al., 2025 [82], Morales-McDevitt et al., 2021 [85], Haug et al., 2011 [84], Winkens et al., 2017 [86], Chen et al., 2018 [87]
Fluorotelomer alcohol 8:2	8:2 FTOH	678-39-7	0.921–160	0.088–7.00	Eichler et al., 2023 [83], Minucci et al., 2025 [82], Morales-McDevitt et al., 2021 [85], Haug et al., 2011[84], Winkens et al., 2017 [86], Chen et al., 2018 [87]
Fluorotelomer alcohol 10:2	10:2 FTOH	865-86-1	0.00–28.898	0.012–0.620	Eichler et al., 2023 [83], Minucci et al., 2025 [82], Morales-McDevitt et al., 2021 [85], Haug et al., 2011 [84], Winkens et al., 2017 [86], Chen et al., 2018 [87]
6:2 Fluorotelomer phosphate monoester	6:2 monoPAP	57678-01-0	0.00–0.0234	NE	Chang et al., 2024 [81]
8:2 Fluorotelomer phosphate monoester	8:2 monoPAP	57678-03−2	0.00	NE	Chang et al., 2024 [81]
N-Ethylperfluorooctane sulfonamide	EtFOSA	4151-50-2	0.00–0.480	NE	Eichler et al., 2023 [83], Minucci et al., 2025 [82], Morales-McDevitt et al., 2021 [85], Haug et al., 2011 [84], Winkens et al., 2017 [86]
2-(N-ethylperfluorooctanesulfonamido)ethyl alcohol	EtFOSE	1691-99-2	0.00–14.7	NE	Eichler et al., 2023 [83], Minucci et al., 2025 [82], Morales-McDevitt et al., 2021 [85], Haug et al., 2011 [84], Winkens et al., 2017 [86]
Hexafluoropropylene oxide dimer acid	HFPO-DA	13252-13-6	0.00–0.0145	0.000017–0.0032	Chang et al., 2024 [81], Zhou et al., 2022 [88]
N-Methylperfluorooctanesulfonamide	MeFOSA	31506-32-8	0.00–0.600	NE	Eichler et al., 2023 [83], Minucci et al., 2025 [82], Morales-McDevitt et al., 2021 [85], Haug et al., 2011 [84], Winkens et al., 2017 [86]
N-Methylperfluorooctanesulfonamidoethanol	MeFOSE	24448-09-7	0.063–1.433	NE	Eichler et al., 2023 [83], Minucci et al., 2025 [82], Morales-McDevitt et al., 2021 [85], Haug et al., 2011 [84], Winkens et al., 2017 [86]
Perfluorobutanoic acid	PFBA	375-22-4	0.00–0.600	0.000084–5.20	Chang et al., 2024 [81], Minucci et al., 2025 [82], Zhou et al., 2022 [88], Chen et al., 2018 [87], Liu et al., 2018 [89]

Table 1 (continued)

Chemical Name	Chemical Abbreviation	CASRN	Reported indoor air range (ng/m^3)	Reported outdoor air range (ng/m^3)	References
Perfluorobutanesulfonic acid	PFBS	375-73-5	0.00–0.072	0.00018–2.400	Chang et al., 2024 [81], Minucci et al., 2025 [82], Winkens et al., 2017 [86], Chen et al., 2018 [87], Liu et al., 2018 [89]
Perfluorodecanoic acid	PFDA	335-76-2	0.00–0.0296	0.00004–0.650	Chang et al., 2024 [81], Minucci et al., 2025 [82], Winkens et al., 2017 [86], Chen et al., 2018 [87], Liu et al., 2018 [89]
Perfluorododecanoic acid	PFDoA	307-55-1	0.00–0.024	0.00–0.00078	Chang et al., 2024 [81], Minucci et al., 2025 [82], Zhou et al., 2022 [88], Liu et al., 2018 [89], Zhou et al., 2021 [90]
Perfluorododecanesulfonic acid	PFDoS	79780-39-5	0.00	0.000050–0.0036	Chang et al., 2024 [81], Minucci et al., 2025 [82], Zhou et al., 2022 [88]
Perfluoroheptanoic acid	PFHpA	375-85-9	0.00–0.032	0.0000064–0.320	Chang et al., 2024 [81], Minucci et al., 2025 [82], Zhou et al., 2022 [88], Winkens et al., 2017 [86], Chen et al., 2018 [87], Liu et al., 2018 [89], Zhou et al., 2021 [90]
Perfluoroheptanesulfonic acid	PFHpS	375-92-8	0.00–0.041	0.00–0.00020	Chang et al., 2024 [81], Minucci et al., 2025 [82], Zhou et al., 2021 [90]
Perfluorohexanoic acid	PFHxA	307-24-4	0.00–0.470	0.0000047–0.580	Chang et al., 2024 [81], Minucci et al., 2025 [82], Zhou et al., 2022 [88], Winkens et al., 2017 [86], Chen et al., 2018 [87], Liu et al., 2018 [89]
Perfluorohexadecanoic acid	PFHxDA	67905-19-5	0.00–0.0039	0.000021–0.0053	Chang et al., 2024 [81], Zhou et al., 2022 [88]
Perfluorohexanesulfonic acid	PFHxS	355-46-4	0.00–0.00161	0.000024–0.00191	Chang et al., 2024 [81], Minucci et al., 2025 [82], Winkens et al., 2017 [86], Zhou et al., 2022 [88], Chen et al., 2018 [87], Liu et al., 2018 [89]
Perfluorononanoic acid	PFNA	375-95-1	0.00–0.0165	0.0000046–0.370	Chang et al., 2024 [81], Minucci et al., 2025 [82], Zhou et al., 2022 [88], Winkens et al., 2017 [86], Chen et al., 2018 [87], Liu et al., 2018 [89]
Perfluorononanesulfonic acid	PFNS	68259-12-1	0.00–0.0006	NE	Chang et al., 2024 [81], Minucci et al., 2025 [82]
Perfluorooctanoic acid	PFOA	335-67-1	0.00–0.0998	0.00125–6.400	Chang et al., 2024 [81], Minucci et al., 2025 [82], Winkens et al., 2017 [86], Chen et al., 2018 [87], Liu et al., 2018 [89], Zhou et al., 2021 [90]
Perfluorooctadecanoic acid	PFODA	16517-11-6	0.00–0.0016	0.000018–0.0028	Chang et al., 2024 [81], Zhou et al., 2022 [88]
Perfluorooctanesulfonic acid	PFOS	1763-23-1	0.00–0.0050	0.00–0.240	Chang et al., 2024 [81], Minucci et al., 2025 [82], Zhou et al., 2022 [88], Winkens et al., 2017 [86], Chen et al., 2018 [87], Liu et al., 2018 [89], Zhou et al., 2021 [90]

Table 1 (continued)

Chemical Name	Chemical Abbreviation	CASRN	Reported indoor air range (ng/m^3)	Reported outdoor air range (ng/m^3)	References
Perfluoropentanoic acid	PFPeA	2706-90-3	0.00–0.15	0.00097–0.200	Chang et al., 2024 [81], Minucci et al., 2025 [82], Chen et al., 2018 [87], Liu et al., 2018 [89]
Perfluoropentanesulfonic acid	PFPeS	2706-91-4	0.00–0.093	NE	Chang 2024 et al [81]., Minucci et al., 2025 [82]
Perfluorotetradecanoic acid	PFTA	376-06-7	0.00–0.018	NE	Chang et al., 2024 [81], Minucci et al., 2025 [82]
Perfluorotridecanoic acid	PFTrA	72629-94-8	0.00–0.021	NE	Chang et al., 2024 [81], Minucci et al., 2025 [82]
Perfluoroundecanoic acid	PFUnA	2058-94-8	0.00–0.0002	0.0051–0.220	Chang et al., 2024 [81], Minucci et al., 2025 [82], Chen et al., 2018 [87]
Trifluoroacetic acid	TFA	76-05-1	NE	0.00–170	Chen et al., 2018 [87], Tian et al., 2018 [91], Mattila et al., 2024 [92], Young et al., 2024 [93]

workplaces [82–86]. They are introduced into indoor air through partitioning from furniture, textiles, carpeting, and clothing [85]. Several other PFAS species, including fluorooctane sulfonamidoethanols (FOSEs) and fluorooctane sulfonamide (FOSAs), have been detected in indoor and outdoor air in lower concentrations or frequencies [82–84]. Smaller, shorter chain PFAS, such as trifluoroacetic acid (TFA), have also been measured in outdoor air [91, 94]. These shorter chain PFAS are often degradation products of other PFAS, or even other chemical classes, further contributing to their presence in the environment [94].

The presence of PFAS species in dust is another important consideration given the potential for inhalation or direct ingestion of dust and because dust can be a reservoir for PFAS in indoor air. In particular, this presents concerns for children's health due to hand to mouth behaviors contributing to increased exposure [81]. Chang et al. (2024) estimated that, for 2 year-old children, mouthing of clothing and hand to mouth behavior contributed to about 12% of ∑PFAS intake [81]. For adults, ingestion of dust did not contribute as significantly as inhalation to ∑PFAS intake, but was an important route of exposure to ionic PFAS [81]. TFA was observed in median concentrations of greater than 100 ng/g in dust samples in recent literature [95, 96]. FTOHs, FOSEs, and FOSAs have also been measured in dust in homes [97]. Further, many PFAS compounds are present in the smallest dust size fractions, suggesting frequent partitioning from indoor air and the potential for resuspension [98].

Inhalation of PFAS remains an understudied route of exposure to PFAS, especially in comparison to ingestion of food or drinking water. While much of the exposure burden to PFAS in the general population occurs via dietary ingestion of contaminated food or drinking water, non-dietary exposures may be dominated by inhalation of polyfluorinated neutral PFAS [19, 78, 81, 99]. Further research connecting PFAS concentrations in air to toxicological effects is urgently needed. It is also necessary to connect PFAS inhalation exposure routes to absorption, distribution, metabolism, and excretion (ADME) through the lung and whole-body systems. Toxicokinetic (TK) studies have illustrated biotransformation of PFAS in rodent models and human hepatocytes, though inhalation TK studies are particularly lacking [100]. One inhalation toxicokinetics study evaluated TK of inhaled 6:2 FTOH in rats [101]. Still, this study focused on plasma concentrations of this PFAS and its associated metabolites [101]. More studies on inhalation exposure to PFAS and associated TK in the lung and whole body are now needed. Once these TK parameters are better understood, studies can then use PFAS measures from circulating blood or excreted samples to inform estimates of human inhalation and oral exposure dosing. Furthermore, expanded PFAS inhalation dosimetry and TK data can impart valuable information regarding the applicable doses, target tissues, and temporality of elimination mechanisms needed to quantify health risks to PFAS inhalation exposures.

Studies Evaluating PFAS in Water and Potential Human Exposures

PFAS exposures via oral exposure routes, including drinking water, are important to consider in the evaluation of lung health based upon previously summarized studies indicating relationships between oral ingestion

exposures and adverse lung health outcomes. It is well known that PFAS species can be present in water systems and are significantly mobile in the environment due to their unique chemical properties [3]. PFAS have been measured globally and in the United States in various bodies of water, including oceans, lakes, and rivers, as well as drinking water systems [102, 103], tap water samples [103, 104], and well water [103, 104]. The presence of PFAS species in these environmental media suggests the potential for significant human exposure and is a major challenge for remediation due to the costs and logistics associated with removing these species from water [105]. The profile of PFAS contamination in water has thus far been dominated by legacy sources such as PFOA or PFOS [102], but the emergence of legislation and efforts to phase out these sources suggests that new PFAS will become increasingly relevant soon. Other PFAS are also now being measured in water, including drinking water, spanning newer PFAS like HFPO-DA (GenX), PFBA, PFBS, PFHxA, and PFPeA, and legacy species such as PFHxS and PFNA [102].

Risk Characterization

Risk characterizations have yet to be carried out for PFAS resulting from inhalation exposure routes; however, select oral exposure routes to PFAS have been evaluated. For example, risk characterizations surrounding PFOA and PFOS in drinking water have been organized by the US EPA, leading to regulations in drinking water. In 2024, the agency finalized maximum contaminant levels (MCLs) of 4 parts-per-trillion (ppt) for PFOA and PFOS, representing legally enforceable limits of these species in drinking water [106]. Public water systems were given until 2029 to implement measures to reduce these species in their water [106]. Four other species were included in the initial regulatory language. MCLs of 10 ppt were set for PFHxS, PFNA, and HFPO-DA, while mixtures of two or more of the species PFHxS, PFNA, HFPO-DA, and PFBS were regulated using a hazard index [106]. In 2025, the agency announced its intention to rescind regulations governing PFHxS, PFNA, HFPO-DA, and PFBS, and extend the compliance deadline for the PFOA and PFOS MCLs to 2031 [106]. Nonetheless, the surviving PFOA and PFOS MCLs extend a framework for translating risk characterization of PFAS to regulatory action.

These types of risk characterizations and resulting regulatory policies have yet to be emplaced for airborne PFAS. Though indoor air pollution regulation is currently limited in practice, outdoor air pollutants can be regulated, such as the current regulation of criteria air pollutants and hazardous air pollutants [107]. It's important to note that 6.4% of the U.S. population aged ≥ 2 years has both asthma and allergy symptoms, with a greater percentage of 45.8% having only allergy symptoms [108], which based upon literature reviewed above could be exacerbated in the context of PFAS exposures, particularly via inhalation exposure routes. However, based on a growing body of literature indicating substantial impacts of PFAS on lung health, there is a current need for human health risk characterizations to be coordinated and studied by both oral and inhaled routes of exposure, which will provide the foundation needed to quantify disease risk impacted by inhalation exposures to this emerging class of contaminants.

Future Directions

The ever-evolving abundance and diversity of PFAS has made determining negative health effects complex, time-consuming, and resource-intensive. We pinpointed several potential solutions to better research PFAS-induced lung toxicity in future studies: [i] broaden the types of PFAS being studied to include more replacement PFAS compounds, [ii] incorporate more inhalation exposure models, [iii] enhance inter-disciplinary collaboration, [iv] incorporate dose-response study designs, [v] consider PFAS mixtures and co-exposures, and [vi] leverage next generation technologies to more efficiently test across the wide variety of PFAS and PFAS-related exposures. These disparities and our recommendations are highlighted in greater detail below.

Among the 37 animal and in vitro articles identified by this review, a majority evaluated legacy (long-chain) PFAS, predominantly PFOS and PFOA; however, as manufacturers shift away from using legacy compounds, there is an urgent need to better characterize the toxic effects of replacement PFAS chemistries, such as short chain and chlorinated and brominated PFAS [109], in both the environment and in humans [106]. Notably, many of the new and emerging PFAS are more volatile than their longer-chain predecessors, introducing an even greater risk for inhalation exposure than observed previously. Since airborne PFAS have been detected in common outdoor and, more recently, indoor air environments, direct exposure to the lungs is a growing concern. Only six (all in rodents) of the 37 identified articles leveraged inhalation-relevant exposure techniques. Inhalation exposures can often be more technically demanding and difficult to manage than oral, dermal, or liquid application exposures in both animal and in vitro models, creating a barrier for adopting these techniques and approaches into practice. Notably, PFAS are especially difficult to generate as an aerosol or vapor

and require advanced equipment and expertise to ensure exposures are conducted properly. Collaborative efforts across different disciplines – air chemists, engineers, toxicologists, molecular biologists, medical professionals, and bioinformaticians – can help overcome these hurdles, making inhalation PFAS studies more feasible and informative.

Given the importance of understanding dose-dependent relationships in human health risk assessments, it was surprising that this review identified only four articles (one animal and three in vitro of the 37 total studies) that incorporated a dose-response approach into their designs. Future studies should be designed that allow for the mathematical derivation of BMDs/BMCs, yielding PODs that can be integrated into human health risk assessments. Furthermore, most studies captured in this review evaluated PFAS toxicity one-chemical-at-a-time. Because environmental monitoring studies of airborne PFAS commonly detect PFAS present as mixtures [83, 110–112], it is important to design more studies evaluating the health impacts of PFAS combinations representing real-world exposure scenarios. Next-generation technologies that more efficiently incorporate more in vitro/in vivo endpoints, such as -omics based screening, and the use of high-throughput in vitro screening to screen legacy PFAS, emerging PFAS, and PFAS alternatives, are now crucial towards addressing the growing number and diversity of PFAS and PFAS mixtures [36, 113].

Conclusions

This review set out to determine the impact of PFAS exposure on lung health using the framework of a human health risk assessment. Overall, the amount of literature evaluating effects of PFAS exposures on lung tissue/cells is growing. Studies informing hazard identification support the biological plausibility of PFAS impacting lung health, with mechanisms reported to involve altered inflammation/immune response, oxidative stress, mucus production, surfactant properties, and epithelial barrier integrity. These studies have yet to be conducted using volatilized PFAS through direct inhalation exposure routes, representing a current gap. Additional gaps exist surrounding concentration-response relationships that can be modelled for derivation of risk values. Exposure data continue to increase in terms of environmental monitoring studies on indoor and outdoor atmospheres, though studies are still lacking that inform how inhaled PFAS deposit throughout the body, are metabolized, and excreted over time. These data gaps must be addressed to allow for the characterization of overall disease risk attributable to inhaled PFAS across populations.

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Declarations

Competing interests The authors declare no competing interests.

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