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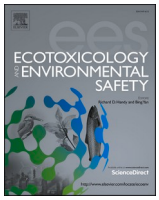

Respiratory toxicity of perfluorooctanesulfonic acid (PFOS) via Inflammasome involvement

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ABSTRACT

Per- and polyfluoroalkyl substances (PFAS), widely used as durable additives in various consumer products for their water- and oil-repellent properties, persist environmentally and bioaccumulate, raising substantial health concerns. The primary route of human exposure towards PFAS is via contaminated food and drinking water, however, mounting evidence highlights inhalation as additional, critical route of exposure. In particular, inhalation of perfluorooctane sulfonate (PFOS) adversely affects respiratory health through immune disruption, oxidative stress, and impaired barrier function, particularly evident during prenatal exposure. Recent evidence reveals that emerging, anthropogenic PFOS exposure activates innate immune pathways conserved over millions of years of evolution leading to inflammation and tissue injury. PFOS has been shown to trigger the AIM2 inflammasome via mitochondrial damage and DNA release, inducing pyroptosis and IL-1β secretion leading to prolonged inflammation and tissue injury. Beyond inflammasomes, the cGAS/STING axis, which is closely co-regulated with the inflammasome, recognizes ectopic DNA and contributes to PFOS-induced inflammatory responses. Co-exposures to airborne pollutants or infections might additionally amplify these effects, as demonstrated by increased expression of AIM2, cGAS, and STING in lung cells following bacterial or particulate challenges. This commentary highlights the critical need for mechanistic research on PFOS-triggered innate immune signalling and potential harmful co-exposure interactions particularly in the lung to better assess health risks and inform regulatory policies for these persistent environmental contaminants.

Per- and polyfluoroalkyl substances (PFAS), often termed "forever chemicals", are synthetic compounds extensively utilized in various industrial and consumer products as processing aids, added to materials for their non-sticky, water-repellent and oil-resistant qualities often enhancing the material's durability and resistance to degradation (DeLuca et al., 2022). Their environmental persistence and bio-accumulative nature have raised significant health concerns globally (Cousins et al., 2020; Arnesdotter et al., 2025). The primary route of human exposure towards PFAS is either occupational or via contaminated food and drinking water, personal care and cleaning products, however, mounting evidence highlights inhalation as important secondary route of exposure (DeLuca et al., 2022; Solan and Park, 2024a). Here, particularly house dust and airborne volatiles play an important role as sources for PFAS inhalation (DeLuca et al., 2022; Vestergren et al., 2008; Vieira et al., 2025)

Recent research has illuminated a novel mechanism by which perfluorooctane sulfonate (PFOS), a frequently used PFAS compound, activates the innate immune system, leading to inflammation and tissue damage. The seminal publication by Wang and colleagues shed new insight on its mode of action, showing that PFOS activates the cytosolic double-stranded (ds) DNA receptor AIM2 (Absent in Melanoma 2), an essential member of the inflammasome family (Wang et al., 2021). The authors reported that PFOS activates the AIM2-inflammasome in a process involving the Ca^{2+}-PKC-NF-κB/JNK-BAX/BAK axis inducing mitochondrial DNA release triggering IL-1β secretion via pyroptosis, a form of programmed cell death associated with inflammation and tissue damage in lung, liver and kidney. The role of the AIM2-inflammasome is further supported by experimental mouse studies. *Aim2* deficient mice have reduced PFOS-induced inflammation and tissue damage in the respective organs. Further, PFOS exacerbated the allergic response in an ovalbumin murine allergy model, which was attenuated in Aim2 deficient mice (Wang et al., 2021). Zhang and colleagues underscore the involvement of PFOS-induced inflammasome activation by conducting a comprehensive meta-study including 321 publications building a systematic evidence map for inflammation induced by various PFAS compounds, including PFOS (Zhang et al., 2023). The authors specifically highlight the emerging evidence for the eminent role of inflammasome activation, IL1β release and pyroptosis by PFOS exposure related tissue damage, amongst others. To visualize this context, inflammasome-relevant biomarkers (NfkB, IL1β, Caspase 3, IL-5 and IL-1 (fam)) in studies evaluating PFOS exposure are shown in Fig. 1.

Together, this suggests a critical role of activating the AIM2-inflammasome in PFOS-mediated tissue injury and inflammation furthermore identifying AIM2 as important receptor in response to environmental organic pollutants.

In view of cellular stress and even pyroptosis in response to PFOS exposure with the release of endogenous (mitochondrial) DNA, we raise the possibility that other DNA-dependent pathways may be involved in the inflammatory response to PFOS exposure, particularly the lung. We consider a role of DNA sensors such as (i) Toll-like receptors (TLRs), (ii) the NLRP inflammasome and (iii) Cyclic GMP-AMP synthase - Stimulator of interferon genes (cGAS/STING) pathways in response to PFOS exposure. (i) TLRs are a major danger recognition receptor family involved in the inflammatory response, notably cell surface TLR2 and TLR4, (Zhang et al., 2023; Chen et al., 2026) but also endosomal TLR9 which recognises intracellular CpG-rich DNA (Kawai and Akira, 2010).

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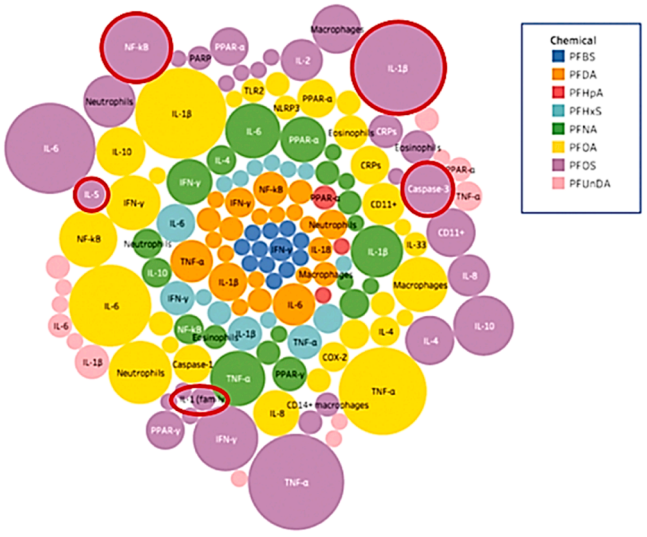

Fig. 1. Inflammation biomarkers assessed in the meta study by (Zhang et al., 2023) for PFAS exposure arranged by chemical. PFOS-induced, inflammasome-relevant markers of the IL1 pathway are circled in red. Figure reproduced and adapted with permission. The size of each bubble represents the number of studies evaluating inflammation (Zhang et al., 2023).

(ii) NLRP-Inflammasomes represent another family consisting of NLRP, Apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and caspase, which assemble and activate caspases with the release of mature IL-1β causing inflammation (Zhang et al., 2023; Mills et al., 2017; Coll et al., 2015; Haneklaus and O'Neill, 2015; Shin et al., 2026). Unlike canonical NLRP3 activation, which involves a priming step for sensor oligomerization and a subsequent activation signal, sufficiently expressed AIM2 can be activated through direct recognition of cytosolic dsDNA, triggering inflammasome assembly (Dubey et al., 2025). cGAS recognises cytosolic dsDNA, producing cGAMP that activates STING with downstream type I and II interferons (IFN) production leading to inflammation (Hopfner and Hornung, 2020). Increased STING expression activates NF-κB leading to induce transcription of pro-inflammatory cytokines (e.g. TNF, IL6), including inflammasome dependent cytokines for priming (e.g., pro-IL-1β, pro-IL-18) and inflammasome NLRP3. It has been shown that the cGAS/STING pathway directly regulates inflammasome activation and vice versa making these two intertwined and activated pathways particularly relevant for the response towards PFOS exposure (Liu et al., 2024; Zhang and Zhang, 2025; Zhang et al., 2022).

Solan and Park have furthermore highlighted the negative impact of PFOS inhalation on respiratory health via immune disruption, oxidative damage, and disruption of epithelial barriers (Solan and Park, 2024b). In addition, respiratory PFOS exposure reduced resistance to respiratory infections and vaccines in children impeding on proper immune functions. However, our current evidence is fragmented, and laboratory findings do not always align with human data (Solan and Park, 2024b). This contradicting base of scientific evidence is underlined by the body of epidemiological data on respiratory PFOS exposure and incidence of asthma as summarized by Arnesdotter et al (Arnesdotter et al., 2025). but highlights and strengthens the need to better understand and distinguish found evidence and correlations.

Together with the important respiratory exposure route, there is an urgent need of inhalation-centric research, advanced assay techniques, and broader PFOS screening to improve risk understanding, inform the public and advise the regulatory authorities. Furthermore, co-exposure with ambient air pollutants or respiratory infections may modulate the susceptibility of our lungs to PFOS. To gain a mechanistic understanding of the potential implications of co-exposure towards airborne PFOS and air pollution, we mined a single-cell RNA sequencing dataset of lungs from mice instilled with air pollution, soot-like surrogate carbon particles (CNP) or LPS exemplary for bacterial infection (Voss et al., 2025). In response to airway exposure to CNP or LPS for 12 h, there was an increased gene expression of the DNA-receptors *Aim2*, as well as cGAS *(Mb21d1)* and STING (*Tmem173*) predominantly in monocytes, dendritic cells and alveolar macrophages, highlighting their potentially important role in the PFOS related respiratory health outcomes. Interestingly, soot particle exposure induced expression of the genes coding for STING in AT2 cells and for cGAS in AT1 cells, making the alveolar epithelium particularly sensitive to PFOS in a second-hit scenarios (dataset accessible under https://breath.mh-hannover.de/toxatlas.html (Voss et al., 2025)). These findings indicate a mechanistic hypothesis for increased human respiratory vulnerability to PFOS following air pollution exposure based on conserved cellular roles, rather than a direct prediction of disease outcomes. This respiratory stem cell niche is responsible for regeneration after injury (Strunz et al., 2020), and obviously associated with respiratory barrier disruption (Solan and Park, 2024b). Therefore, understanding the mechanistic role of TLRs, inflammasomes and cGAS/STING pathways and activation in response to PFOS exposure particularly in the lungs is a major challenge of research.

In summary, recent findings implicate PFOS through a mode of action involving the inflammasome and likely cGAS/STING pathways, as potent activator of the innate immune responses of the lung, making inhalative PFOS exposure particular worrisome. These innate mechanisms can contribute to chronic inflammation, tissue damage, and immune dysregulation. With chronic respiratory diseases and infections amongst the top leading causes of death worldwide, and air pollution the second leading cause of noncommunicable disease-related deaths, a deeper mechanistic understanding is urgently needed to implement health risk assessments and regulatory strategies for these manmade compounds.

CRediT authorship contribution statement

Tobias Stoeger: Writing – review & editing, Writing – original draft. **Bernhard Ryffel:** Writing – review & editing, Writing – original draft. **Carola Voss:** Writing – review & editing, Writing – original draft.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the authors used ChatGPT in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. Carola Voss reports financial support was provided by German Research Foundation. Bernhard Ryffel reports financial support was provided by European Union. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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