Carcinogenicity of perfluorooctanoic acid and perfluorooctanesulfonic acid

In November, 2023, a Working Group of 30 scientists from 11 countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to finalise their evaluation of the carcinogenicity of two agents: perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), including their corresponding isomers and salts.

PFOA was classified as "carcinogenic to humans" (Group 1) based on "sufficient" evidence for cancer in experimental animals and "strong" mechanistic evidence in exposed humans. The evidence for cancer in experimental animals was "sufficient" because an increased incidence of an appropriate combination of benign and malignant neoplasms was observed in both sexes of a single species in a Good Laboratory Practice (GLP) study. The mechanistic evidence was "strong" in exposed humans because PFOA was found to induce epigenetic alterations and to be immunosuppressive. Additionally, there was "limited" evidence for cancer in humans for renal cell carcinoma and testicular cancer. PFOS was classified as "possibly carcinogenic to humans" (Group 2B) based on "strong" mechanistic evidence. The evidence for cancer in experimental animals was "limited" for PFOS, and the evidence regarding cancer in humans was "inadequate". These assessments will be published in Volume 135 of the *IARC Monographs*.[1]

PFOA and PFOS are perfluoroalkyl and polyfluoroalkyl substances (PFAS) that have had widespread use in industrial applications and consumer products due to their hydrophobicity and lipophobicity, surface-active properties, and chemical stability. PFOA has been used extensively in the manufacture of fluoropolymers. Applications for fluoropolymers and PFOA include surface coatings for stain, oil, and water resistance on household products, carpets, textiles, and food packaging; personal care products; seals; coatings for cables and wires; and construction materials. PFOS has some overlapping applications with PFOA—such as in waxes, carpets, and food packaging—and has also been used to make imaging devices, semiconductors, dyes, and ink, and in photolithography and electroplating processes. PFOS has been used extensively in class B firefighting foams known as aqueous film-forming foams. PFOA and PFOS are extremely resistant to degradation and are found globally, but environmental levels vary greatly in various regions due to different pollution sources.

Occupationally exposed populations have some of the highest exposures to PFOA and PFOS, with inhalation as the main exposure route, as well as potentially dermal absorption and dust ingestion. The highest exposure occurs in fluorochemical manufacturing. The general population is mainly exposed to PFOA and PFOS via diet and drinking water, and potentially via consumer products. In communities near polluted sites, the general population is mainly exposed via drinking water. PFOA and PFOS are detected in blood samples in studied populations worldwide, and median levels are up to a hundred times higher in communities near polluted sites. Some of the body burden might also originate from precursors, which are PFAS that transform into PFOA or PFOS in the body. There is no evidence that PFOA or PFOS are biotransformed. They accumulate in various tissues, including blood, liver, and lung. They are found in the placenta, cord blood, and embryonic tissues, and can be transferred to infants via breast milk. Both agents undergo enterohepatic recirculation and kidney reabsorption. They are excreted in urine and faeces with half-lives on the order of several years in humans, or in the range of hours to months in experimental animals.

Since the previous classification of PFOA (as "possibly carcinogenic to humans", Group 2B) by the *IARC Monographs* in 2014,[2] many new studies have investigated the association between exposure to PFOA and cancer in experimental animals and humans, as well as mechanistic endpoints relevant to the key characteristics of carcinogens. In male Sprague-Dawley rats, PFOA in the feed caused hepatocellular adenoma, hepatocellular adenoma or carcinoma (combined), pancreatic acinar cell adenoma, and pancreatic acinar cell adenoma or adenocarcinoma (combined), and a statistically significant positive trend in the incidence of hepatocellular carcinoma. In female Sprague-Dawley rats, PFOA caused uterine adenocarcinoma and a statistically significant positive trend in the incidence of pancreatic acinar cell adenoma or adenocarcinoma (combined).[3]

Regarding mechanistic evidence, PFOA induces epigenetic alterations. In exposed humans, numerous studies showed associations between serum PFOA in mothers and gene-specific DNA methylation in their children. A robust human epigenome-wide association study showed persistence of PFOA-associated CpG methylation between birth and adolescence.[4] The findings are highly relevant to carcinogenicity as they pertain to developmental reprogramming that might influence human cancer susceptibility. Additional studies in exposed humans found alterations in the expression of cancer-related miRNAs associated with PFOA exposure.[5] These findings are supported by studies in vivo and in

Lancet Oncol 2023

Published **Online**
November 30, 2023
https://doi.org/10.1016/S1470-2045(23)00622-8

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Declaration of interests
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TF reports providing expert opinion for plaintiffs in cases of exposure to PFOA.

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Declaration of interests
DW reports receiving support for travel from the International Association of Firefighters. All other observers declare no competing interests.

Upcoming meetings
March 19–22, 2024: Advisory Group to Recommend Priorities for the *IARC Monographs* during 2025–2029
June 11–18, 2024: Volume 136: Talc and acrylonitrile
November 5–12, 2024: Volume 137: Hydrochlorothiazide, voriconazole, and tacrolimus

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vitro. PFOA is immunosuppressive. Multiple well conducted studies in different populations of exposed humans, including children and adults, have shown that exposure to PFOA is associated with increased risk of infectious diseases and decreased vaccine response to diverse antigens.[6,7] These findings are corroborated by evidence of decreased production of cytokines and reduced lymphoproliferation in human primary cells and by altered antibody responses to T-cell-dependent antigens and leukocytes in rodents. In addition, PFOA induces oxidative stress, modulates receptor-mediated effects (via PPARα, CAR/PXR, and PPARγ), and alters cell proliferation, cell death, and nutrient and energy supply in human primary cells and experimental systems. The mechanistic evidence is also supported by metabolomic and transcriptomic data.

For PFOA, there was "limited" evidence for renal cell carcinoma and testicular cancer in humans. Compared with the available evidence in the previous evaluation (which was also found to be "limited" for cancers of the kidney and testis),[2] additional positive findings for renal cell carcinoma were found in one population with low-level exposure,[8] but not in the main analyses of two other studies in populations with low-level exposure. For testicular cancer, additional evidence was a positive association in an ecological analysis conducted by the Working Group of available data on orchiectomies from the Veneto region of Italy, and a US study finding no associations.[9] For all other cancers, the evidence was "inadequate", as there were only sporadic positive findings.

Similarly to PFOA, PFOS induces epigenetic alterations[4,5,10] and is immunosuppressive in exposed humans.[6,7] The evidence for PFOS is corroborated by consistent and coherent findings both in human primary cells and experimental systems. PFOS equally induces oxidative stress in human primary cells and experimental systems. Notably, PFOS also modulates thyroid-mediated and androgen-mediated effects in experimental systems, and PPARα and CAR/PXR in both human primary cells and experimental systems. Metabolomic and transcriptomic data support the mechanistic evidence.

The evidence for cancer in experimental animals was "limited" for PFOS because an increased incidence of an appropriate combination of benign and malignant neoplasms was observed in one sex of a single species in a study that complied with GLP. PFOS in the feed caused hepatocellular adenoma, and hepatocellular adenoma or carcinoma (combined), with positive significant trends in female Sprague-Dawley rats.[11] The evidence regarding cancer in humans was found to be "inadequate" for PFOS because, among the few available studies, positive findings were seen only sporadically and inconsistently for a few cancer sites (ie, testis,[9] breast, and thyroid).

TF reports providing expert opinion for plaintiffs in cases of exposure to PFOA. RW's next of kin works for Rowenta, a brand owned by Group SEB. All other authors declare no competing interests.

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