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: perfluoroctanoic 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 lipophilicity, 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 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.³ 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.⁴ These findings are supported by studies in vivo and in vitro in experimental animals and humans.

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 lipophilicity, 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.

² Occupationaly 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.

³ Since the previous classification of PFOA (as “possibly carcinogenic to humans”, Group 2B) by the IARC Monographs in 2014, 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 significant positive trend in the incidence of pancreatic acinar cell adenoma or adenocarcinoma (combined).

⁴ 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. 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. These findings are supported by studies in vivo and in vitro in experimental animals and humans.
The views expressed are those of the authors and do not necessarily represent the decisions, policy, or views of their respective institutions.

The evidence for PFOA and PFOS in populations exposed to these chemicals is compelling. Studies have shown a positive association between low-level exposure to these chemicals and an increased risk of renal cell carcinoma, thyroid cancer, and testicular cancer.

For renal cell carcinoma, the evidence is consistent across multiple studies, with positive findings in populations exposed to PFOA or PFOS. The mechanistic evidence includes the induction of toxic effects in experimental systems, which support the association observed in human populations.

For testicular cancer, the evidence is based on the association observed in populations exposed to these chemicals. The mechanistic evidence includes the induction of cellular effects, such as apoptosis and cell proliferation, which are consistent with the observed epidemiological findings.

For thyroid cancer, the evidence is based on a few studies with positive findings. The mechanistic evidence includes the induction of thyroid-mediated effects, which support the association observed in human populations.

In conclusion, the evidence for the association of PFOA and PFOS with renal cell carcinoma, testicular cancer, and thyroid cancer is compelling and consistent with the mechanistic evidence. Further research is needed to understand the underlying mechanisms and to develop strategies to reduce exposure and mitigate the potential health effects of these chemicals.