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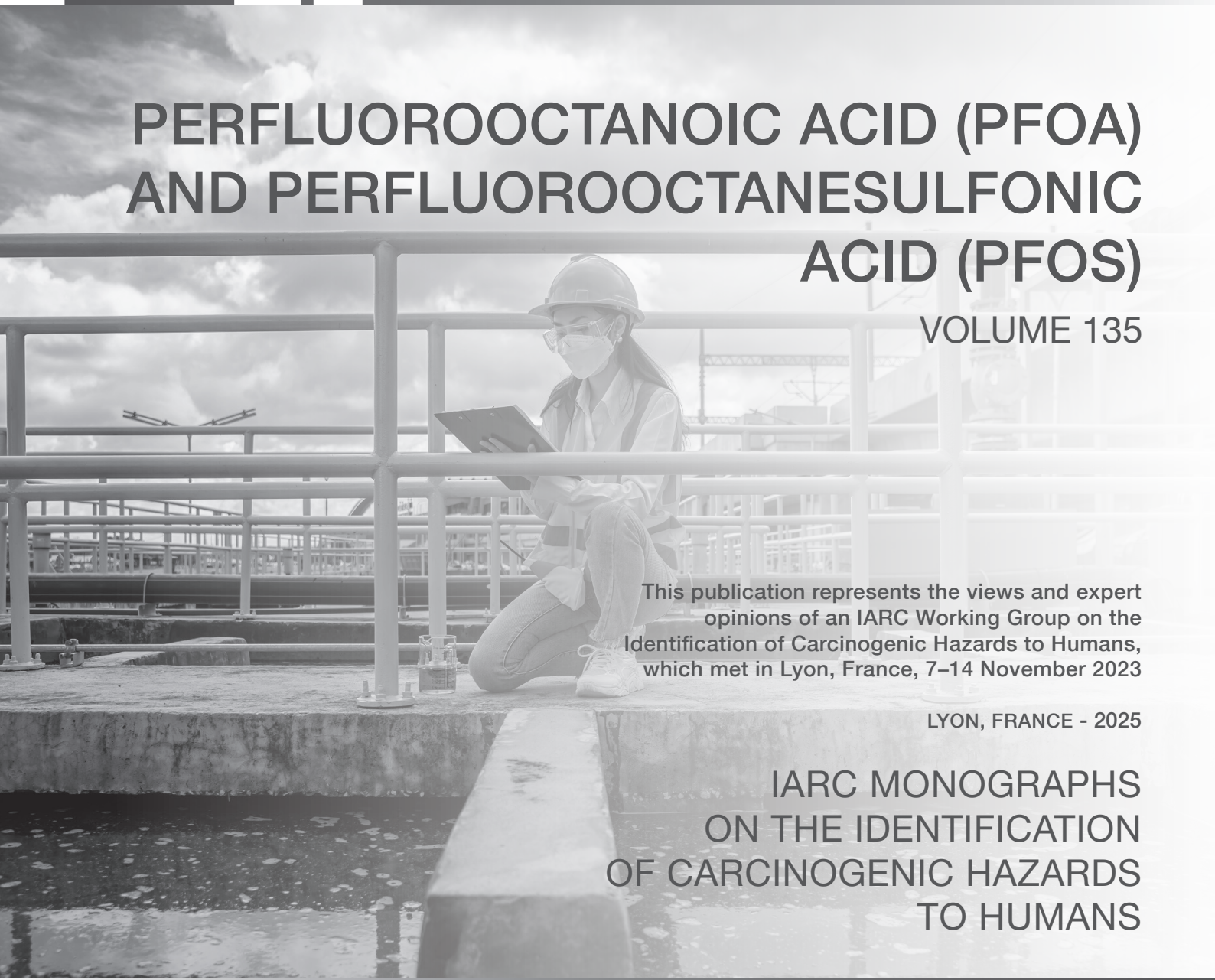

PERFLUOROOCTANOIC ACID (PFOA) AND PERFLUOROOCTANESULFONIC ACID (PFOS)

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5. SUMMARY OF DATA REPORTED

5.1 Exposure characterization

Perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) are per- and polyfluoroalkyl substances (PFAS) with a carbon chain length of eight carbons. The carbon–fluorine bond is one of the strongest bonds known in nature, making PFOA and PFOS extremely resistant to degradation in the natural environment. Both PFOA and PFOS exist as linear and branched isomers, and their salts exhibit different physicochemical properties to those of the pure acid form. PFOA and PFOS and their respective salts will be in an acid–base equilibrium in aqueous solutions such as in the human body and are present mainly as their conjugate bases perfluorooctanoate and perfluorooctane sulfonate, respectively. All isomeric forms and their salts should be considered as included within the definition of the agents reviewed in the present monograph.

The production of PFOA and PFOS began in the 1940s and steadily increased until the late 1990s, and companies located in the USA, Europe, and Japan were responsible for most of the manufacturing. However, in the early 2000s, there was a geographical shift in the production of PFOA and PFOS to other parts of the world (primarily in emerging Asian economies) and a shift towards production of other PFAS.

PFOA and PFOS have unique properties (e.g. hydrophobicity and oleophobicity, surface-active properties, chemical stability, and thermal resistance). They may be present in products as main ingredients, or as unreacted raw materials, undesired reaction by-products, or cross-contaminants along the production and supply chains. Ammonium perfluorooctanoate (APFO) – a salt of PFOA – has been used extensively to manufacture fluoropolymers, such as polytetrafluoroethylene (PTFE). Applications for fluoropolymers, as well as direct uses for PFOA, include household products with non-stick coatings; textiles for outdoor or personal protection applications; personal care products; seals and gaskets; coatings for cables and wires; electronics, solar panels and electrolyte fuel cells; carpets; cleaning and impregnating agents; construction materials; and surface coatings for conferring stain, oil and water resistance on carpets, textiles, leather products, and paper or cardboard for food and feed packaging.

With some applications that overlap those of PFOA, such as waxes, carpets, and food and feed packaging, PFOS has additionally been used in the semiconductor industry; as a hydraulic fluid additive; as an etchant and antireflective coating in photolithography processes; in the fabrication of imaging devices; as a mist suppressant in electroplating operations; in building and construction materials, including paints and varnishes; in

insulation; in dyes and ink; and in wetting, levelling, and dispersing agents. PFOS has been used extensively in class B firefighting foams known as aqueous film-forming foams (AFFFs).

PFOA and PFOS occur in the whole ecosystem, including air, water, dust, soil, and food, but levels vary greatly in different geographical regions due to pollution sources such as industrial sites, firefighter-training areas, waste deposits, and contaminated wastewater. The transport of PFOA and PFOS in air and surface water leads to their deposition in oceans, soil, and groundwater.

Foods are contaminated with PFOA and PFOS through atmospheric deposition and uptake from water and soil, including from use of biosolids as fertilizer. Animal-based foods are contaminated through water, feed, soil, and air. The highest concentrations have been measured in fish, seafood, and eggs.

Occupationally exposed populations have some of the highest exposure to PFOA and PFOS, with the leading route of exposure consisting of inhalation, as well as potentially dermal absorption and ingestion of dust. Biomonitoring data indicate exposure in diverse occupational settings, with the highest levels in primary manufacturing (up to median values of thousands of nanograms per millilitre of serum) and lower levels in secondary manufacturing, public safety, and services. Not all occupations have been characterized for PFOA and PFOS exposure. Measures in the work environment such as air frequently indicate that concentrations of PFOA and PFOS are higher in facilities manufacturing or using PFAS-laden products than in other occupational environments.

PFOA and PFOS are detected in blood samples in all populations worldwide who have been tested. The general population in non-polluted communities is mainly exposed to PFOA and PFOS via the diet and drinking-water. Additional exposure via consumer products and building materials may occur. In communities located in the proximity of polluted sites, the general population is mainly exposed via drinking-water. Biomonitoring in general populations mainly in North America and Europe has shown serum concentrations in the low nanograms per millilitre range and that concentrations have decreased since the early 2000s. Median concentrations in serum samples collected in contaminated communities have been measured in the hundreds of nanograms per millilitre range.

The term "precursor compounds" refers to PFAS known to break down or transform into PFOA or PFOS in the environment or biota, including in humans. Although estimates vary according to exposure scenario, it has been estimated that a substantial proportion of the body burden of PFOA and PFOS may originate from exposure to precursors. Direct exposure to PFOA and PFOS may decline as a result of regulation or voluntary efforts; however, production and use of precursors may contribute to ongoing exposure.

International, national, and regional authorities have developed occupational exposure thresholds for PFOA, PFOS, and/or related compounds, restrictions on the use of PFOA and PFOS in consumer products, and regulatory standards or guidance values for these PFAS in environmental media. PFOA and its salts and PFOS and derivatives are listed in Annex A (elimination) and Annex B (restriction), respectively, in the Stockholm Convention on Persistent Organic Pollutants. Drinking-water is a major focus for the regulation of PFOA and PFOS. Additional restrictions, regulations, and guidance values continue to be developed and have generally become more stringent over time.

5.2 Cancer in humans

More than three dozen studies were available for the evaluation of the carcinogenicity of PFOA and PFOS in humans; this represents a substantial increase over the number available during the previous evaluation of PFOA in Volume

110 of the *IARC Monographs* (Some Chemicals used as Solvents and in Polymer Manufacture). Most of these were cohort studies (including nested case–control and case–cohort studies), but there were also some population-based or hospital-based case–control studies. The studies were conducted within three different types of populations: (i) workers exposed to high levels of PFOA and/or PFOS during employment at industrial plants manufacturing or using these chemicals; (ii) general populations of residents exposed to high environmental levels of PFOA and/or PFOS, primarily through drinking-water near sites contaminated by chemical production or use; and (iii) populations exposed to background levels of these compounds primarily through food and drinking-water. The studies were conducted mainly in the USA and Europe, although several studies were carried out in China. Exceptionally, the Working Group performed an ecological analysis of the association between average serum concentrations of PFOA and the rates of orchiectomies for a set of 21 municipalities in the Veneto region of northern Italy, where drinking-water had been heavily contaminated by pollution from a local chemical plant, described below. Orchiectomies were found to be a highly reliable surrogate for testicular cancer in this region.

Despite the overall large number of available studies, for most cancer types there were fewer than 10 studies that examined risk for the type. The most informative studies for the evaluation were large cohort and nested case–control studies from all three exposure scenarios described above. There were three occupational cohorts from the USA: at a PFOA-manufacturing plant in Minnesota, a fluoropolymer-manufacturing plant (using PFOA) in West Virginia, and a fluorochemical plant in Alabama where PFOS was extensively used. There was an additional small occupational cohort of workers in another fluorochemical plant (with mainly PFOA exposure) in Veneto, Italy. This plant was the source of the contamination in that area. The most informative occupational cohort was from the facility in West Virginia. The Mid-Ohio Valley (West Virginia and Ohio) general population (part of the C8 Science Panel Cohort and exposed to high background levels of PFOA), a prospective cohort based on the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial participants, and other prospective cohorts of populations exposed to background levels of PFOA or PFOS exposure were also considered highly informative.

An important consideration in the evaluation of the human cancer evidence was the quality of the exposure assessment methodology used in the studies. The highest-quality studies used pre-diagnostic, targeted serum analyses for individual PFAS compounds, based on samples collected at least several years before cancer diagnosis. These were features of most of the nested case–control and case–cohort studies. One potential concern was the fact that most studies in the general population relied on a single time point measurement of PFOA or PFOS in serum, and it was unclear how representative such single time point exposure measures were for long-term exposure assessment in relation to cancer. This concern was allayed by the Working Group's evaluation of the possible impact of such exposure misclassification, given the long serum half-life of the compounds in humans and the resulting high correlation between repeated time point measures of exposure available for two of the studies. The Working Group therefore concluded that only minor bias towards the null would probably result from this source of exposure uncertainty, at least over a 5–8-year time period.

The main concern across the set of studies related to the potential for co-exposure to other potentially carcinogenic PFAS compounds (e.g. PFOA and PFOS together, or with other PFAS compounds). In the most informative studies, the researchers adjusted statistically for the effects

of the other compounds, or the Working Group concluded that exposure to one of the compounds –either PFOA or PFOS – was predominant (this was generally the case for the occupational and high-environmental-exposure studies). Other types of confounding were not a major concern in the set of studies, particularly for kidney and testicular cancer, as relatively few strong risk factors are known, and correlations of these risk factors with occupational or environmental exposures to PFOA or PFOS are anticipated to be low. In addition, for some other cancer types, e.g. breast, estimates were well adjusted for important potential confounders.

Among the occupational cohort studies, in the Minnesota and Alabama cohorts, findings were mostly null, but the studies and case numbers were small and there were limitations related to potential survivor bias and/or weaknesses in exposure assessment, which would be expected to cause bias downwards or towards the null. The Veneto occupational cohort was small and showed some evidence (albeit weak) of positive findings for a few cancer sites.

5.2.1 PFOA

The cancer sites with the strongest evidence of an association with PFOA were kidney and testis. For kidney cancer, two independent studies were considered most informative: the set of three partly overlapping studies of workers and residents in West Virginia and Ohio (the Mid-Ohio Valley Study), and the general population case–control study nested within the PLCO cohort. The studies set in the Mid-Ohio Valley consistently showed increased risk of kidney cancer related to PFOA exposure. A clear increase in risk of renal cell carcinoma (which accounts for 80–90% of kidney cancers) with indication of an exposure–response relation was seen in the PLCO cohort, which had much lower exposure than the Mid-Ohio Valley study. In contrast, no increase in kidney cancer incidence or mortality was seen in the occupational studies in Minnesota or in the International TFE (tetrafluoroethylene) cohort, which were considered to be less informative because they were small, were subject to survivor effects, and/or had exposure assessment limitations. Two other prospective studies in general population cohorts provided equivocal evidence for renal cell carcinoma: in the Multiethnic Cohort (MEC), which was considered informative, positive findings were seen only in White participants, but not overall or in African-American, Japanese-American, Latino, or Native Hawaiian participants; and in the Lifelink subcohort of the Cancer Prevention Study II cohort, for which there were concerns about survivor bias, positive findings were seen only among women exposed to PFOA. Taken together, the body of epidemiological evidence indicated that a positive association between PFOA and renal cell carcinoma is credible, but positive findings have not been consistently observed among the most informative studies, and chance, bias, and confounding by other PFAS in some of the studies could not be ruled out with reasonable confidence. For other subtypes of kidney cancer, no conclusions could be drawn about an association with PFOA.

For cancer of the testis, the most informative studies for the evaluation of PFOA were the set of Mid-Ohio Valley studies, a study of Air Force servicemen with exposure levels similar to those in the general population of the USA, and the ecological analysis of orchiectomies in relation to average serum PFOA concentrations, conducted in the Veneto region, Italy, among municipalities with different levels of PFOA contamination. A positive finding was observed in the Mid-Ohio Valley study and in the Veneto ecological analysis, but not in the Air Force study overall. Mortality studies were deemed to be less informative, because of the high survivability of testicular cancer and the unknown impact of determinants of survival. In summary, there were indications in two independent populations for

an increased risk of testicular cancer associated with PFOA serum concentrations in residents exposed at high levels. In the third informative study, a null association was seen, but exposure levels were at background in this population, which meant that a low exposure contrast existed in the population, making a positive effect, if present, difficult to detect, and did not preclude effects at higher levels of exposure. Overall, the Working Group concluded that a positive association between PFOA and testicular cancer is credible; however, chance and/or bias could not be ruled out as explanations for these findings, given the small number of cases in the few available studies, concerns about co-exposure to other PFAS compounds, and the fact that one of the positive studies was of ecological design.

For breast cancer, most epidemiological studies gave generally null results for all types of breast cancer combined. However, the epidemiological studies with prospective serum samples for PFOA showed a slightly elevated but uncertain association with PFOA. The two most informative studies were null overall but were the only prospective studies that examined postmenopausal breast cancer cases by estrogen receptor/progesterone receptor (ER/PR) status. Both found nonlinear positive associations with ER-negative and PR-negative postmenopausal breast cancer. The statistical power was low in studies examining associations with specific tumour subtypes or stratified by levels of endogenous hormone levels (pre- or postmenopausal cancer), limiting the ability to identify causal associations. Moreover, there were few data on risk of breast cancer above background levels of PFOA exposure. Overall, the available epidemiological evidence was not considered consistent enough to permit a conclusion about the presence of a causal association between exposure to PFOA and breast cancer.

For other cancer types, there was little consistent evidence of an association with PFOA, and the results were considered inconclusive regarding the presence or absence of a causal association.

5.2.2 PFOS

For PFOS, there were fewer available studies than for PFOA. The evidence was suggestive but sparse or inconsistent for three cancer sites: the testis, thyroid gland, and breast. For breast cancer, there was little evidence of an association between PFOS exposure and all types of breast cancer combined. However, the two most informative studies, one from France and one from the USA, which were the only prospective studies to examine the association by hormone receptor breast tumour subtype, found an imprecise but increased risk of hormone receptor-positive breast cancers associated with higher levels of PFOS. However, there were null findings among postmenopausal women in two cohorts from China and the USA, for which there was no stratification by receptor status (most postmenopausal breast cancers are hormone receptor-positive). Given the inconsistencies across studies, the Working Group considered that the available evidence on risk of breast cancer conferred by PFOS exposure was inconclusive.

For testicular cancer, the only informative studies were conducted among the Air Force servicemen in the USA and in the population exposed to contaminated drinking-water near a military airfield in Ronneby, Sweden. In the Air Force study, overall a positive but imprecise association was observed for PFOS exposure, after controlling for exposure to PFOA and other PFAS compounds. For the Ronneby study (in which PFOS levels were much higher than PFOA levels), a positive association was observed for testicular cancer, but co-exposure to perfluorohexanesulfonic acid (PFHxS) was a concern. For thyroid cancer, some positive evidence related to PFOS

exposure came from the less-informative occupational studies; among women in the Ronneby Register cohort study in Sweden; and in a hospital-based case–control study in New York, USA, in which exposure was at background levels. But in a well-conducted population-based study conducted among women in Finland who were exposed at background levels, findings for PFOS were null after adjusting for other PFAS compounds. There was evidence of an inverse association in two case–control studies in China that were considered less informative. For kidney cancer, there were several informative studies, but the findings were largely null. Overall, the evidence for all cancer types was considered to be inconclusive for PFOS exposure.

5.3 Cancer in experimental animals

5.3.1 PFOA

Treatment with PFOA caused an increase in the incidence of an appropriate combination of benign and malignant neoplasms, in both sexes of a single species, in a well-conducted study that complied with Good Laboratory Practice (GLP).

PFOA was administered by oral administration (in feed) in one well-conducted study that complied with GLP, in male and female Sprague-Dawley rats. In males, there was a significant increase in the incidence of hepatocellular adenoma (includes multiple), with a significant positive trend. There was a significant positive trend in the incidence of hepatocellular carcinoma. There was a significant positive trend in the incidence of hepatocellular adenoma or carcinoma (combined), with the incidence being significantly increased. There was a significant positive trend in the incidence of acinar cell adenoma of the pancreas (includes multiple), with the incidence being significantly increased. There was a significant positive trend in the incidence of acinar cell adenomas or adenocarcinoma (combined) of the pancreas, with the incidence being significantly increased. In females, there was a significant increase in the incidence of adenocarcinoma of the uterus. There was significant positive trend in incidence of pancreatic acinar cell adenoma or adenocarcinoma (combined).

In another well-conducted study that complied with GLP, PFOA was administered in the feed of male and female Sprague-Dawley rats. PFOA increased the incidence of testicular Leydig cell adenoma in males.

In a non-GLP study on oral administration (in feed) in male Sprague-Dawley rats only, PFOA increased the incidence of hepatocellular adenoma, Leydig cell tumours, and pancreatic acinar cell adenoma. In a study in female CD-1 mice treated by gavage, there was a positive trend in the incidence of liver haemangiosarcoma in females. PFOA was shown to promote hepatocarcinogenesis in two feeding studies in male Wistar rats and two feeding studies in rainbow trout.

5.3.2 PFOS

Treatment with PFOS caused an increase in the incidence of an appropriate combination of benign and malignant neoplasms in one sex (female) of a single species (rat) in a well-conducted study that complied with GLP.

PFOS was administered by oral administration (in feed) in one study that complied with GLP, in male and female Sprague-Dawley rats. In males, there was a significant positive trend in the incidence of hepatocellular adenoma, with the incidence being significantly increased. In females, there was a significant positive trend and significant increase in the incidence of hepatocellular adenoma, and hepatocellular adenoma or carcinoma (combined).

PFOS was also shown to promote hepatocarcinogenesis in one feeding study in male and female rainbow trout.

5.4 Mechanistic evidence

5.4.1 PFOA

Regarding the absorption, distribution, metabolism, and excretion of PFOA, data were available from studies in humans and from experimental systems. Studies in experimental animals demonstrated high bioavailability after oral exposure, which was presumed to be similar in humans. Absorption via dermal and inhalation routes has been demonstrated in rodents; in humans, there is some evidence that these exposure routes may also be relevant. On the basis of its structure and physicochemical properties, PFOA is unlikely to readily diffuse across cellular membranes; membrane transporters mediate tissue distribution and cell uptake. PFOA can bind to specific proteins, including albumin in serum and liver-type fatty acid-binding protein (L-FABP). Partitioning of PFOA to the liver and kidney can differ across species. There is no evidence in humans or experimental animals that PFOA is biotransformed; PFOA is eliminated by excretion. PFOA undergoes enterohepatic recirculation. Biliary and urinary excretion are the major elimination pathways in humans, with women of reproductive age also eliminating PFOA via blood loss during menstruation, placental transfer to the fetus, and lactational transfer to infants. Urinary excretion is predominant in rodents. In humans, half-lives are in the order of years; half-lives in experimental animals range from hours to months. The basis of species differences in distribution and elimination is not well understood.

There was consistent and coherent evidence that PFOA exhibits key characteristics of carcinogens.

PFOA induces epigenetic alterations. Consistent and coherent evidence came from numerous studies in exposed humans showing that exposure to PFOA alters DNA methylation. Several studies using umbilical cord and peripheral blood leukocytes, or dried blood spots from exposed humans, showed associations between blood PFOA and gene-specific methylation. A robust human epigenome-wide association study showed persistence of PFOA-associated 5′-C-phosphate-G-3′ dinucleotide (CpG) methylation between birth and adolescence. This study was of great importance as it investigated developmental reprogramming that may influence human cancer susceptibility. In additional studies in exposed humans, alterations were found in the expression of cancer-related microRNAs (miRNAs) in relation to PFOA exposure. There were no data in primary human cells. Consistent and coherent evidence from experimental systems, both in vivo and in vitro, suggested that PFOA induced changes in DNA methylation, histone modifications, or miRNA expression in multiple tissues, including the liver or kidney.

PFOA is immunosuppressive. Consistent and coherent evidence from multiple well-conducted studies in different populations of exposed humans, including children and adults, demonstrated that exposure to PFOA is associated with increased risk of infectious disease and decreased vaccine response to diverse antigens. These findings were corroborated by consistent and coherent evidence from studies in primary human cells showing that PFOA decreases the production of cytokines and reduces lymphoproliferation. Additionally, consistent and coherent evidence from multiple studies in rodents has demonstrated that PFOA administration alters antibody responses to T-cell dependent antigens. In some studies in rodents, alterations in leukocyte populations were reported.

PFOA induces oxidative stress. The few available studies in exposed humans were not informative. There was consistent and coherent evidence in human primary cells that PFOA exposure increases reactive oxygen species (ROS) production, alters antioxidant function, or increases markers of lipid peroxidation. Consistent and

coherent evidence from experimental systems showed induction of oxidative stress by PFOA, including increased levels of oxidatively damaged DNA in cell lines or 8-oxo-2′-deoxyguanosine (8-oxodG) in the urine and liver in rodents. Several studies in experimental systems showed that biomarkers of oxidative stress induced by PFOA were reduced by co-treatment with antioxidants.

PFOA modulates receptor-mediated effects. Data were available for peroxisome proliferator–activated receptors alpha and gamma (PPARα, PPARγ), constitutive androstane receptor/pregnane X receptor (CAR/PXR), hepatocyte nuclear factor 4 alpha (HNF4α), aryl hydrocarbon receptor (AHR), estrogen, androgen, thyroid, progesterone, and glucocorticoid pathways. In exposed humans, the data were suggestive of an association between PFOA exposure and modulation of thyroid, androgen, and progesterone pathways. Data for the remaining receptor pathways in exposed humans were sparse or absent. Consistent and coherent evidence in human primary cells showed that PFOA modulates the action of PPARα and CAR/PXR. Data for human primary cells suggested that PFOA modulates the action of both estrogen and PPARγ. Data for the remaining receptor pathways in exposed human primary cells were sparse. There was consistent and coherent evidence from numerous studies performed in experimental systems, including human cell lines, that exposure to PFOA modulates the activity of PPARα and CAR/PXR, as well as PPARγ. There was suggestive evidence that PFOA alters serum estradiol and testosterone concentrations in rodents. There was a paucity of information for PFOA in other receptor pathways in experimental systems.

PFOA alters cell proliferation, cell death, or nutrient supply. The evidence in PFOA-exposed humans was suggestive on the basis of high-throughput metabolomic analyses showing alterations in pathways related to nutrient and energy supply. Evidence from primary human cells suggested that PFOA increases cell proliferation. Transcriptomic analyses from primary human cells suggested that PFOA modulates gene signalling pathways involved in cell proliferation and oncogenesis. Metabolomic analyses from primary human cells suggested that PFOA increases activity in glycolytic pathways. Consistent and coherent evidence in multiple experimental systems showed that PFOA induces cell proliferation, migration, or invasion in human cell lines and cell proliferation or hyperplasia in multiple tissues in rodents, including in PPARα-null mice.

There was suggestive evidence that PFOA is genotoxic. A single study in exposed humans reported increased levels of DNA strand breaks; results from other studies using less-relevant end-points were mixed. The results of studies in human primary cells were negative. Evidence in experimental systems suggested that PFOA causes DNA damage. Available studies in rodents in vivo showed largely negative results for DNA damage and micronucleus assays.

There was suggestive evidence that PFOA induces chronic inflammation. Data in exposed humans were not informative. In most studies in human primary cells, decreased production of pro-inflammatory markers occurred after PFOA exposure. The results of several studies in rodents suggested that PFOA induces small increases in severity or incidence of chronic inflammation in the stomach, liver, or pancreas. The results of studies of inflammatory markers in experimental systems were mixed, with results differing depending on the model, tissue, and assay.

There was a paucity of data for the following key characteristics: is electrophilic or metabolized to an electrophile, alters DNA repair or genomic instability, or causes immortalization.

PFOA and its ammonium salt were tested in the Toxicology Testing in the 21st Century (Tox21) and Toxicity Forecaster (ToxCast) research programmes. However, the analytical

purity quality control rating for these data was labelled "unknown/inconclusive".

5.4.2 PFOS

Regarding the absorption, distribution, metabolism, and excretion of PFOS, data were available from studies in humans and from experimental systems. Studies in experimental animals demonstrated high bioavailability after oral exposure, which was presumed to be similar in humans. Absorption via dermal and inhalation routes has been demonstrated in rodents; in humans, these exposure routes may also be relevant. On the basis of its structure and physicochemical properties, PFOS is unlikely to readily diffuse across cellular membranes; membrane transporters mediate tissue distribution and cell uptake. PFOS can bind to specific proteins, including albumin in serum and L-FABP. Partitioning of PFOS to the liver can differ across species. There is no evidence in humans or experimental animals that PFOS is biotransformed; PFOS is eliminated by excretion. PFOS undergoes enterohepatic recirculation. Biliary and urinary excretion are the major elimination pathways in humans, with women of reproductive age also eliminating PFOS via blood loss during menstruation, placental transfer to the fetus, and lactational transfer to infants. Urinary excretion is predominant in rodents. In humans, half-lives are on the order of years; half-lives in experimental animals range from weeks to months. The basis of species differences in distribution and elimination is not well understood.

There was consistent and coherent evidence that PFOS exhibits key characteristics of carcinogens.

PFOS induces epigenetic alterations. Consistent and coherent evidence from numerous studies in exposed humans showed that exposure to PFOS alters DNA methylation. Several studies using umbilical cord and peripheral blood leukocytes, or dried blood spots from exposed humans, showed associations between blood PFOS and gene-specific methylation. A robust human epigenome-wide association study showed persistence of PFOS-associated CpG methylation between birth and adolescence. This study was of great importance as it investigated developmental reprogramming that may influence human cancer susceptibility. In additional studies in exposed humans, alterations were found in the expression of cancer-related miRNAs in relation to PFOS exposure. There were no data in primary human cells. Consistent and coherent evidence from studies in experimental systems, both in vivo and in vitro, suggested that PFOS induced changes in DNA methylation, histone modifications, or miRNA expression in multiple tissues, including the liver or kidney.

PFOS is immunosuppressive. Consistent and coherent evidence from multiple well-conducted studies in different populations of exposed humans, including children and adults, demonstrated that exposure to PFOS is associated with increased risk of infectious disease and decreased vaccine response to diverse antigens. These findings were corroborated by consistent and coherent evidence from studies in primary human cells showing that PFOS decreases production of cytokines and reduces lymphoproliferation. Additionally, consistent and coherent evidence from multiple studies in rodents has demonstrated that PFOS administration alters antibody responses to T-cell dependent antigens. In some studies in rodents, alterations in leukocyte populations were reported. One study in mice showed that PFOS increased morbidity and mortality after influenza A infection.

PFOS induces oxidative stress. There was suggestive evidence in exposed humans that PFOS induces oxidative stress, with several studies showing associations between PFOS and various oxidative stress markers in serum or urine. Two of three studies that measured urinary 8-oxodG with high specificity gave positive results. There

was consistent and coherent evidence in human primary cells that PFOS exposure increases ROS production, alters antioxidant function, or increases markers of lipid peroxidation. One study in human primary cells showed that biomarkers of oxidative stress induced by PFOS were reduced by co-treatment with antioxidants. There was consistent and coherent evidence from experimental systems that PFOS induces oxidative stress. In cell lines, PFOS increased levels of ROS production. PFOS increased markers of lipid peroxidation and altered antioxidant function in rodent tissues. Several studies in experimental systems showed that biomarkers of oxidative stress induced by PFOS were reduced by co-treatment with antioxidants.

PFOS modulates receptor-mediated effects. Data were available for PPARα, PPARγ, CAR/PXR, HNF4α, AHR, estrogen, androgen, thyroid, progesterone, and glucocorticoid pathways. In exposed humans, the data were suggestive of an association between PFOS exposure and modulation of thyroid, estrogen, androgen, progesterone, and glucocorticoid pathways. Data for the remaining receptor pathways in exposed humans were sparse or absent. Consistent and coherent evidence in human primary cells showed that PFOS modulates the action of PPARα and CAR/PXR. Data from human primary cells suggested that PFOS modulates the PPARγ pathway. Data for the remaining receptor pathways in human primary cells were sparse. Consistent and coherent evidence came from numerous studies in experimental systems, including human cell lines, and showed that exposure to PFOS modulates the activity of PPARα and CAR/PXR. Consistent and coherent evidence from experimental systems showed that PFOS modulates the androgen and thyroid pathways. Evidence from human cell lines and receptor assays suggested that PFOS modulates the PPARγ pathway. Several studies in experimental systems suggested that PFOS modulates the estrogen pathway. There was a paucity of information for PFOS in other receptor pathways in experimental systems.

PFOS alters cell proliferation, cell death, or nutrient supply. The evidence in PFOS-exposed humans was suggestive on the basis of high-throughput metabolomic analyses showing alterations in pathways related to nutrient and energy supply. Evidence from primary human cells suggested that PFOS increases cell proliferation, migration, or invasion. Transcriptomic analyses from primary human cells suggested that PFOS modulates gene signalling pathways involved in cell proliferation and oncogenesis. Metabolomic analyses from primary human cells suggested that PFOS increases activity in glycolytic pathways. Consistent and coherent evidence in multiple experimental systems showed that PFOS induces cell proliferation, migration, or invasion in human cell lines and cell proliferation or hyperplasia in multiple tissues in rodents.

There was suggestive evidence that PFOS is genotoxic. Results from the few studies in exposed humans were mixed. The results of studies in human primary cells were negative. Evidence in experimental systems suggested that PFOS causes DNA damage. Studies in rodents showed mixed results for DNA damage and micronucleus assays.

There was suggestive evidence that PFOS induces chronic inflammation. Data in exposed humans were not informative. In most studies in human primary cells, decreased production of pro-inflammatory markers occurred after PFOS exposure. The results of studies in rodents suggested that PFOS increases inflammation. The results of studies of inflammatory markers in other experimental systems were mixed, with results differing depending on the model, tissue, and assay.

There was a paucity of data for the following key characteristics: is electrophilic or metabolized to an electrophile, alters DNA repair or genomic instability, or causes immortalization.

PFOS and its potassium salt were tested in the assay battery of the Tox21 and ToxCast research programmes. However, the analytical purity quality control rating for these data was labelled "unknown/inconclusive".