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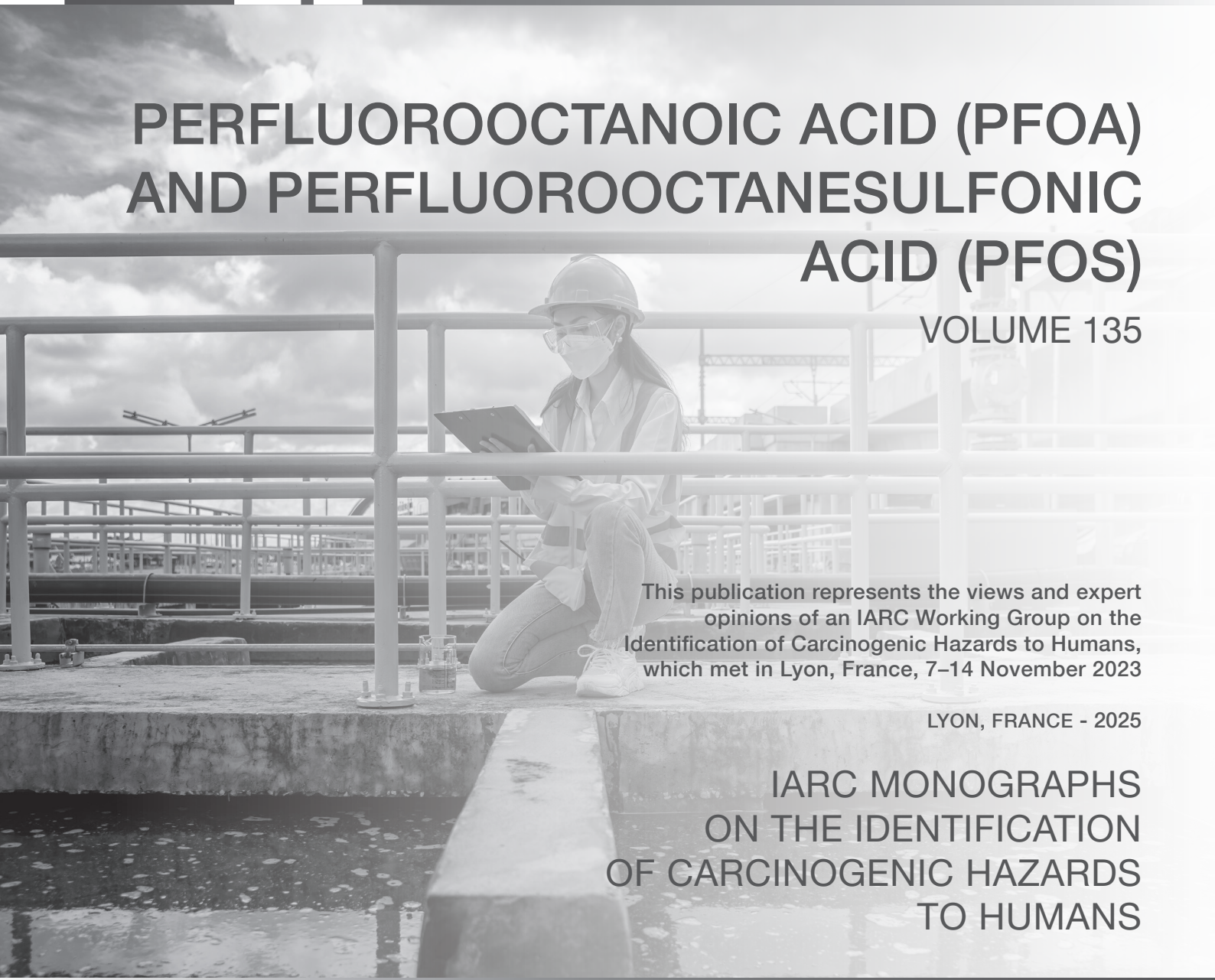

PERFLUOROOCTANOIC ACID (PFOA) AND PERFLUOROOCTANESULFONIC ACID (PFOS)

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IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

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6. EVALUATION AND RATIONALE

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of perfluorooctanoic acid (PFOA). Positive associations have been observed between PFOA and renal cell carcinoma and cancer of the testis.

There is *inadequate evidence* in humans regarding the carcinogenicity of perfluorooctanesulfonic acid (PFOS).

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of PFOA.

There is *limited evidence* in experimental animals for the carcinogenicity of PFOS.

6.3 Mechanistic evidence

There is *strong evidence* that PFOA exhibits multiple key characteristics of carcinogens in exposed humans, in human primary cells, and in experimental systems.

There is *strong evidence* that PFOS exhibits multiple key characteristics of carcinogens in exposed humans, in human primary cells, and in experimental systems.

6.4 Overall evaluation

PFOA is *carcinogenic to humans* (Group 1).

PFOS is *possibly carcinogenic to humans* (Group 2B).

6.5 Rationale

6.5.1 PFOA

The Group 1 evaluation for PFOA is based on the combination of *sufficient evidence* for cancer in experimental animals and *strong* mechanistic evidence of key characteristics of carcinogens in exposed humans. The evidence for cancer in experimental animals was *sufficient* because exposure to PFOA caused an increase in the incidence of an appropriate combination of benign and malignant neoplasms in both sexes of a single species (rat) in one study that complied with GLP. The mechanistic evidence was *strong* in exposed humans because PFOA induces epigenetic alterations and is immunosuppressive. In exposed humans, PFOA induces epigenetic alterations in the form of gene-specific methylation and cancer-related miRNAs. These effects are supported by evidence of epigenetic alterations in multiple experimental systems. In exposed humans, PFOA is immunosuppressive, increasing risk of infectious disease and decreasing vaccine response to diverse antigens. These effects are supported by evidence

of immunosuppression in human primary cells and experimental systems. In addition, in human primary cells and experimental systems, PFOA induces oxidative stress and modulates receptor-mediated effects. Additionally, in experimental systems, PFOA alters cell proliferation, cell death, or nutrient supply.

Also, for PFOA, the evidence for cancer in humans was found to be *limited* for renal cell carcinoma and cancer of the testis. Despite the increase in the number of available human cancer studies since the previous evaluation by the *IARC Monographs*, the results were somewhat inconsistent across the studies. For renal cell carcinoma, positive findings were observed in three studies conducted in partly overlapping occupationally and environmentally exposed populations and in a fourth population with background exposure. However, positive findings were not observed overall in two other background-exposed populations. For testicular cancer, there were two studies with positive findings: one cohort study and a second ecological study that had limitations. For other cancer types, there were only sporadic positive findings in the informative studies (e.g. breast), and for all these other cancer types, the evidence was *inadequate*.

6.5.2 PFOS

The Group 2B evaluation for PFOS is based on *strong* mechanistic evidence. There is *strong* evidence that PFOS exhibits multiple key characteristics of carcinogens in exposed humans, human primary cells, and experimental systems. There is strong evidence that PFOS in exposed humans induces epigenetic alterations in the form of gene-specific methylation and cancer-related miRNAs. These effects are supported by evidence of epigenetic alterations in multiple experimental systems. In exposed humans, PFOS is immunosuppressive, increasing risk of infectious disease and decreasing vaccine response to diverse antigens. These effects are supported by evidence of immunosuppression in human primary cells and experimental systems. In human primary cells and experimental systems, PFOS modulates receptor-mediated effects and induces oxidative stress. Additionally, in experimental systems, PFOS alters cell proliferation, cell death, or nutrient supply.

In addition, the evidence for cancer in experimental animals was *limited*. Exposure to 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 study that complied with GLP. The evidence regarding cancer in humans was found to be *inadequate*, because among the relatively few available studies, positive findings were seen only sporadically and inconsistently for a few cancer sites (i.e. breast, testis, and thyroid).