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Carcinogenic risk of emerging persistent organic pollutant perfluorooctane sulfonate (PFOS): A proposal of classification

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ABSTRACT

Perfluoroalkyls are stable synthetic chemicals, able to repel oils, fats and water. These compounds have been used in the manufacturing of products such as Teflon®, lubricants, paints, fire-fighting foams, coatings for pans, carpets, clothes, and paperboard for packaging, among others. It is believed that populations are exposed constantly to them. Its regulation in the world is under development and several controversies are in the course of litigation. One occupational study shows bladder cancer risk. This paper intends to review scientific information on the most critical perfluoroalkyl compound and proposes a procedure to get a cancer-risk categorization which PFOS can cause to populations. Methods: As a guiding axis, we used the IARC process for developing monographs of carcinogenic risks. We used the SIGN guides for evaluating the quality of studies in human populations; and finally, we used the Squire method for evaluating studies in laboratory animals. Inadequate evidence of carcinogenicity was found in human studies mainly due to chance, threshold effect and confounders. In experimental animal studies, inadequate evidence of carcinogenicity was found in view of the number of affected species, different types of neoplasms, dose-response relationship and genotoxicity found in *in-vivo* and *in-vitro* studies. In this proposal, we concluded that cancer risk for PFOS, according to the IARC method, is not classifiable as carcinogenic to humans (group 3).

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1. Introduction

Perfluorinated compounds (PFCs) are synthetic chemicals that possess unique properties, such as high stability and extremely low surface tension. Many PFCs are insoluble in water and organic solvents, and can repel dust, water and oils (Jensen and Leffers, 2008). According to a study by the Organization for Economic Co-operation and Development (OECD), around 850 PFCs are known, including, perfluorooctane sulfonic acid or perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) (Fig. 1), which are considered the most important due to their high health-risk potential (Schulte, 2006), and especially due to their widespread use as Teflon®.

The PFCs molecules consist of a hydrophobic/lipophilic carbonated chain and a hydrophilic functional group. The hydrogen atoms of the carbonated chain are completely replaced by fluorine atoms. The 2-p orbital of fluorine is larger than the 1s orbital of hydrogen (Fig. 1), resulting in a decrease of surface tension properties, so these PFCs can repel dust, water, oils and fats, and also have a high chemical, thermal, biological and UV rays stability (Hansen et al., 2001; Arsenault et al., 2004). Because of these unique properties, the PFCs are used in different industrial processes and products such as refrigerating agents, fire-fighting foams, hydraulic fluids for the aviation industry, leather products, metal plating, for food packaging, floor polishes, coatings and additives for carpets and fabrics, and in the photographic and photolithography industry (Paul et al., 2009).

In general, it is considered that average global levels are around 20–30 ng PFOS/mL in blood samples (Fig. 2), and the levels of PFOA and other perfluoroalkyl carboxylic acids are below this range (Jensen and Leffers, 2008; Kannan et al., 2002 and Martin et al.,

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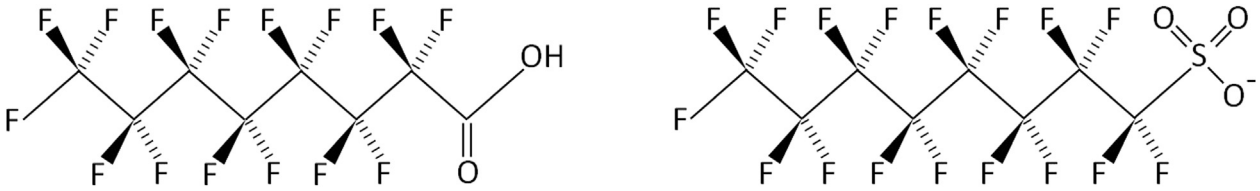

Fig. 1. Formulae of PFOA (left) and PFOS (right).

2010). Also, the environmental stability, persistence, bioaccumulative tendency and lack of biodegradation of PFOS and its related products are considered to have led to increased concerns over their body burden in humans and wildlife (Renner, 2001; Deon and Mabury, 2007; Lau et al., 2007).

Some studies suggest multiple toxicities correlated with PFOS, such as immunotoxicity, hepatotoxicity, carcinogenicity, and developmental and reproductive effects (Lau et al., 2007; Wang et al., 2010, 2012). Epidemiologic studies have shown an association between exposure to PFOS and the incidence of bladder cancer (Alexander and Olsen, 2007). In May 2009, PFOS and related compounds were listed in Annex B of the Stockholm Convention as Persistent Organic Compounds (POPs) candidates (Martin et al., 2010; Stockholm Convention, 2011; 2012).

The risk of exposure to PFOS was estimated by examining the probability of exceeding points of departure, or toxicity reference values. This is a function of PFOS concentration in human blood samples (Yeung et al., 2006). Protective values, the benchmark internal concentrations (BMICs), for risk characterization are as follows: immunotoxicity of 1.3 ng/mL (Grandjean and Budtz-Jørgensen, 2013), 33 μg/mL weight gain during lactation (3M Company, 2003), 44 μg/mL for liver toxicity (3M Company, 2003) and 62 μg/mL for liver tumor formation (Seacat et al., 2003). Concentrations of PFOS in 95% of the U.S. population were less than 100 ng/mL in blood serum (Olsen et al., 2003). In 85% of the Chinese population, concentrations were less than 100 ng/mL but in the 95th percentile, PFOS concentration could increase to 146 ng/mL (Yeung et al., 2006). These margins of exposure suggest that PFOS posed little or no intermediate risk to the population except for immunotoxicity risk (1.3 ng/mL) that even for the average global levels (around 20–30 ng PFOS/mL) this burden seems to be easily achieved.

Regarding studies performed in animals, there only exists one chronic test, which was carried out with Sprague-Dawley rats (Butenhoff et al., 2012), but according to Chang et al. (2014), the association seen between thyroid follicular cell adenoma and PFOS exposition should be considered a spurious finding in light of the absence of any response in the corresponding highly exposed group. So, in this case it is proposed to review some other animal studies exposed to PFOS, which even though subchronic, use an appropriate method of evaluation.

Respecting occupational and environmental studies performed in humans, Chang et al. (2014) again performed a critical review of four studies of PFOS in occupationally exposed workers and six studies in environmentally exposed communities. In these, the authors observed weak, inconsistent offset by negative associations, not in keeping with a positive exposure-response gradient and not coherent with the toxicological findings (Chang et al., 2014). But in this document, there is no mention of neither the flaws or defects present in those studies nor if there was a possibility to find a different conclusion if the study could have overcome those problems. This document proposes using a proper method to perform critical appraisal of cohort and case-control studies.

The present research paper aims to use different methods to assess and properly classify the cancer risk of PFOS, using as a

Fig. 2. PFOS in human blood reported by several countries (ng/mL). Source: Jensen and Leffers, 2008; Kannan et al., 2002 and Martin et al., 2010.