Comparatively International Probabilistic Cumulative Risk Assessment on Perfluorinated Compounds

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Introduction

Perfluoronated Compounds (PFCs) have been found in rivers and lakes and in many types of animals on land and in the water. Studies with animals fed PFOS or PFOA for a long period showed effects on the stomach, liver and thyroid hormones. For PFOS, the increase in serum total cholesterol in adults, and the decrease in antibody response at vaccination in children were identified as the critical effects. For PFOA, the increase in serum total cholesterol was the critical effect. (EFSA 2016; Knutsen et al. 2018). PFCs can induce the activation of the peroxisome proliferator-activated receptor-alpha (PPARα) receptor in the liver (Stahl et al. 2011); hepatotoxicity and tumor induction have been observed in mice. In epidemiological studies, PFCs have been commonly found in human serum, breast milk, and cord blood (Kärrman et al. 2010; Lindstrom et al. 2011). Previous studies have mainly focused on collecting the content of PFCs in food in various regions, and seldom did health risk assessment and comparison in different regions of the world. The purpose of this study is to make a comprehensive health risk assessment and comparison by assembling the health risk data of PFOA, PFOS, PFHxS, and PFNA in various regions.

Materials & Methods

The human health risk assessment of PFCs was conducted based on guidance from the U.S. Environmental Protection Agency (EPA, 1992), comprising the following four steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization. PFOA, PFOS, PFHxS, PFNA residues data from seafood, vegetable, fruit, meats, egg, to dairy products in 19 countries, including Bangladesh, Belgium, Canada, Cambodia, China, France, Greece, Italy, Japan, Korea, Netherlands, Norway, Philippines, Poland, Spain,Sweden, Taiwan, Vietnam, and the United States of America were assessed in the present studies.

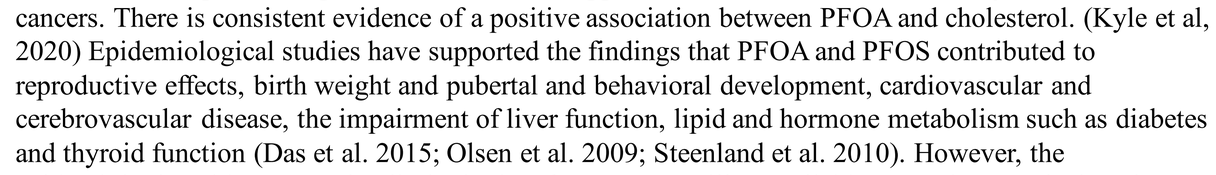

Figure 1. Four steps of human health risk assessment

Hazard identification

The World Health Organization's International Agency for Research on Cancer (IARC) has classified PFOA as “possibly carcinogenic to humans” (Group 2B), based on limited evidence in humans that it can cause testicular and kidney cancer, and limited evidence in lab animals (IARC 2016). PFOS is also considered an animal carcinogen by EPA (EPA, 2005). In animal studies, toxicologists have seen that high doses of both PFOS and PFOA cause cancer, physical development delays, endocrine disruption, and neonatal mortality. In older animals, toxicological studies have shown that the compounds cause liver and pancreatic tumors (Kellyn et al. 2007). Most of the studies showed that liver was the target organ for PFOA and PFOS (Chain et al. 2018). Mode of action (MOA) was considered to be the binding between both PFOS and PFOA with peroxisome proliferator–activated receptors (PPARs-alpha), a class of receptors associated with carcinogenesis. Nevertheless, the identified carcinogens of PFHxS and PFNA are still uncertain nowadays. There are few related Mode of action (MOA) studies on PFHxS and PFNA. However, these two compounds were basically likely to be at the same viewpoint as for PFOA and PFOS (Jensen and Warming 2015). PFNA and other biologically persistent PFCs, including PFOA and PFOS, cause immunotoxicity in animal toxicology studies (Lau et al, 2012).

For cancer, the epidemiologic evidence remains supportive but not definitive for kidney and testicular cancers. There is consistent evidence of a positive association between PFOA and cholesterol. (Kyle et al, 2020) Epidemiological studies have supported the findings that PFOA and PFOS contributed to reproductive effects, birth weight and pubertal and behavioral development, cardiovascular and cerebrovascular disease, the impairment of liver function, lipid and hormone metabolism such as diabetes and thyroid function (Das et al. 2015; Olsen et al. 2009; Steenland et al. 2010). However, the epidemiologic evidence remains limited. Therefore, we are still unavailable to reach a conclusion about a causal relationship between exposure.

Dose-response assessment

The most recent and updated derivations of tolerable daily intake levels of PFOA and PFOS have been conducted by EFSA (2018) and US EPA (2018).

EFSA (2008)	EFSA (2018)	US EPA (2016)	US EPA (2018)
PFOS; TDI= 150 ng/kg bw per day	PFOS; TDI= 150 ng/kg bw per day	PFOS; TDI = 20 ng/kg bw/day	PFOS; TDI = 13 ng/kg bw/week
PFOA; TDI= 1500 ng/kg bw per	PFOA; TDI= 0.16 µg/kg bw per	PFOA; TDI = 20 ng/kg bw/day	PFOA; TDI = 6 ng/kg bw/week
day	day		

Table 1. Recent derivations of tolerable daily intake levels of PFOA and PFOS

Although PFHxS and PFNA still have been inadequately studied or clarified, they were assumed with thresholds due to the mode of action, instead of genotoxicity (Authority 2008), were involved in peroxisome proliferator-activated receptor-alpha (PPARα) receptor in liver as same as PFOA and PFOS were. Therefore, the current study mainly focused on noncarcinogenic effects with dose thresholds.

Exposure assessment

Databases from Pubmed, EPA, EFSA, and National Food Consumption Database (Taiwan). This study collected food concentration data on PFOS, PFOA, PFNA, PFHxS (including seafood, dairy products, vegetables, fruits, meat, eggs, etc.) over the past ten years.

In addition to United State (Schecter et al. 2010) and Canada (Tittlemier et al. 2007), foodstuff from Sweden (Berger et al. 2009; Vestergren et al. 2012), Spain (Domingo et al. 2012; Ingrid Ericson et al. 2008; Fernández-Sanjuan et al. 2010; Gómez et al. 2011; Jogsten et al. 2009), Italy (Guerranti et al. 2013; Nania et al. 2009; Squadrone et al. 2014), France (Munschy et al. 2013), Belgium (Cornelis et al. 2012), Norway (Haug et al. 2010), Netherlands (Noorlander et al. 2011), Greece (Vassiliadou et al. 2015), Germany (T. Stah et al. 2011), Poland (Sznajder-Katarzyńska et al. 2018) in Europe region and Bangladesh (Habibullah-Al-Mamun et al. 2017), China (Zhenni et al. 2016; Wu et al. 2012; Yang et al. 2012; Zhang et al. 2010; Zhao et al. 2011), Japan (Fujii et al. 2015; Fujii et al. 2019; Fujii et al. 2020), Korea (Heo et al. 2014), Taiwan (Chen et al. 2018) in Asian countries were assessed in the present study.

Using Crystal-Ball software to simulate Monte-Carlo simulation, the average daily dose (ADD) from diet in each region was calculated, the ADD was calculated as:

$$\underline{\mathbf{ADDi = (Ci \times IRi) / BW}}$$

Risk characterization

For contaminants with threshold, the hazard quotient (HQ), adopted by regulatory authorities such as US EPA to describe the risk category of a chemical substance, represents a toxicity endpoint and are calculated as follows:

$$\underline{\mathbf{HQ=ADDi / TDI}}$$

Hazard index (HI) for a specific PFC was the summation of all the calculated HQ for each country. If hazard Index (HI) is greater than 1, the risk assessment should either be refined and risk management measures should be taken.

Results & Discussions

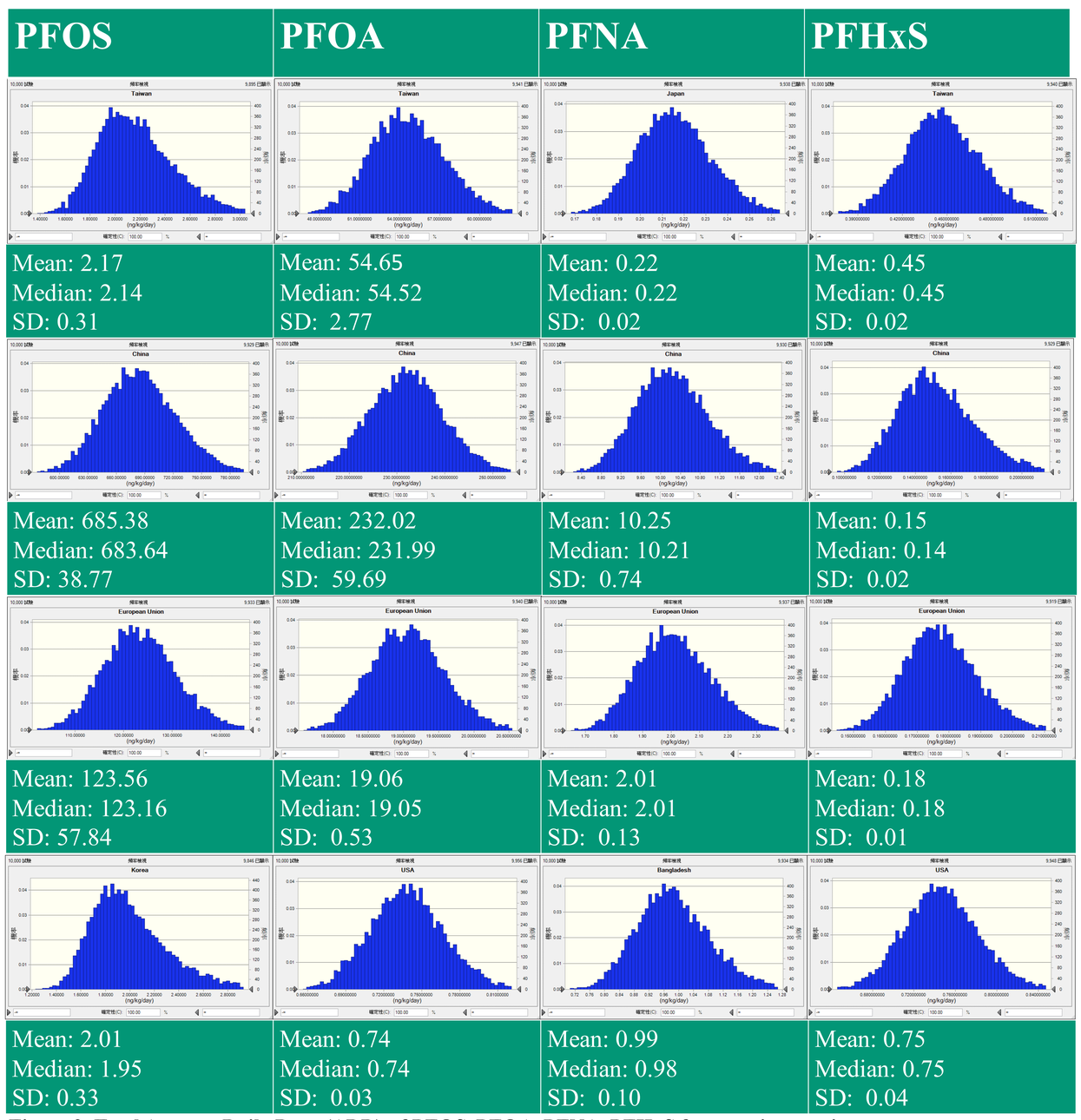

Figure 2. Total Average Daily Dose (ADD) of PFOS, PFOA, PFNA, PFHxS from various regions

Here, several calculation results with relatively significant values and relatively complete data are extracted from a large amount of data. We can find that the total average daily dose (ADD) of the four PFCs in China are dozens to hundreds of times higher than those in other regions. Reviewing the data, we speculate for several reasons: 1. Most of the food samples in China come from animal internal organs, seafood and milk. These foods have been confirmed by numerous studies to contain high residues of PFCs. 2. The environmental pollution in this area is higher than other sample areas. 3. China‘s food safety regulations are less strict.

Through the calculation results, we can find that the total average daily dose (ADD) of the four PFCs in Taiwan is not much higher than that in other regions, but the PFOA is slightly higher, which can be discussed in the follow-up research. In recent years, regulations on PFCs around the world have become increasingly stringent, and the use of PFCs by manufacturers has also decreased. However, while serum levels of PFOS, and possibly PFOA, have begun to decline in the general population due to cessation of production by US manufacturers, levels of PFNA and PFHxS appear to be increasing (Kato et al, 2011; Olsen et al, 2011) . The reasons also need to be further analyzed. This year, the US EPA also conducted further discussions and regulations on PFOS and PFOA in drinking water, which shows that people pay more attention to the health hazards of PFCs.

There are still some deficiencies in the study, for example, due to insufficient data on PFNA and PFHxS, the overall detection value may be underestimated. In addition, due to the different food cultures in different regions, the food samples collected in the literature may also be slightly different, which may also affect the prediction of risk.

The estimated daily intakes of PFOA and PFOS in Taiwan were lower than the health-based guidance values of EFSA (2018), HI values were mostly lower than one. The results of quantitative risk assessment indicated that consumption of PFOA, PFOS, PFHxS and PFNA in food would not significantly increase the incidence of noncarcinogenic risk. Therefore, although the issue of PFCs has gradually attracted attention in recent years, we also need to pay attention to the use of PFCs in daily life, but do not need to be too nervous. Various risk assessments about PFCs have a significant impact on future policy formulation and deserve our attention.

References

Authority EFS. 2008. Perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts Scientific Opinion of the Panel on Contaminants in the Food chain. Efsa Journal 6:653.

Chain EPoCitF, Knutsen HK, Alexander J, Barregård L, Bignami M, Brüschweiler B, et al. 2018. Risk to human health related to the presence of perfluorooctane sulfonic acid and perfluorooctanoic acid in food. EFSA journal 16:e05194.

EPA U. 2012. Benchmark dose technical guidance. US Environmental Protection Agency.

EPA U. 2016. Drinking Water Health Advisory for Perfluorooctanoate acid (PFOA).EPA.

Fujii Y, Sakurada T, Harada KH, Koizumi A, Kimura O, Endo T, et al. 2015. Long-chain perfluoroalkyl carboxylic acids in Pacific cods from coastal areas in northern Japan: A major source of human dietary exposure. Environmental Pollution 199:35-41.