4th submission - Comments on the proposed restriction of universal PFAS

September 22, 2023

Conference of Fluoro-Chemical Product Japan (FCJ)

On behalf of chemical manufacturers, we, Conference of Fluoro-Chemical Product Japan (FCJ), have been working tirelessly to comply with national chemical regulations. We have supported EU's ambitious attempts to reduce risks from hazardous substances and have sincerely responded to actual measures to meet the requirements of EU chemical regulations such as REACH.

However, we believe that the proposed restriction of PFAS (Per- and Polyfluoroalkyl substances) proposed by 5 European countries is an excessive measure because it restricts more than 10,000 of organofluorine compounds (PFAS) on the grouping basis that they are persistent as substances of concern equivalent to the already regulated PFOS and PFOA. Therefore, we intend to present the following views at the public consultation of ECHA, to which is one of the actions FCJ recommends.

(1) Concerns about inconsistencies in the proposed restriction

Article 68 (1) REACH refers to the scope of the restrictions, which regulates unacceptable risks to human health or the environment that need to be addressed by society as a whole.

The proposed restriction lists persistent chemicals (which may remain in the environment longer than any other man-made chemical), bioconcentration, mobility, the possibility of long-distance transport, accumulation in plants, the possibility of global warming, and toxicological effects as concerns and reasons for the restriction. Of these, persistent is applicable to all targeted organofluorine compounds (PFAS), but other concerns are related to some compounds.

Persistency common to all organofluorine compounds (PFAS) can be rephrased as "high durability" by focusing on its advantages, however, we believe that it is not appropriate to regulate this property alone as an unacceptable risk to human health or the environment. In addition, it is not appropriate to apply the concerns about some fluorinated compounds, such as bioconcentration potential and toxicological effects, by grouping all organofluorine compounds (PFAS) together, and if the need for new regulations is to be considered in the future, the risk of each substance should be quantitatively assessed and discussed.

Therefore, as evidence that it is not appropriate to consider all PFASs together, the following section presents the theory on the physical properties of PFASs and their scientific basis. This theory and its underlying rationale require further scrutiny and scholarly

investigation. Nevertheless, in light of the available evidence, it would not be appropriate to impose blanket restriction encompassing all proposed measures. Instead, the proposed restriction should be subject to reassessment, taking into account individual substances and their associated risks.

(2) Exploring the scientific foundations of PFAS physicochemical properties: The SDA Theory”

Organic fluorine compounds (PFAS) have been used in the industry for a long time without understanding the scientific mechanism of their distinctive characteristics including, water and oil repellency. Under these circumstances, Professor Takeshi Hasegawa of Kyoto University's Institute of Chemistry addressed this knowledge gap through the development of the SDA (Stratified-Dipole Arrays) theory. This theory offers a comprehensive framework for explaining the various properties of PFASs. We recognize the essentiality of adopting an indispensable scientific approach to assess the safety of PFASs.

This SDA theory refers to "Molecules exhibit intermolecular forces of attraction that lead to self-aggregation, but hydrocarbons and PFASs exhibit distinct forms of attraction. PFAS also possess a twisted molecular structure absent in hydrocarbons, significantly influencing self-assembly. Consequently, unlike the behavior of a single molecule, PFASs, when self-aggregated, exhibit distinctive properties characterized by repulsion towards both water and oil. Such dramatic alterations in physical properties arising from molecular assembly are a rarity in hydrocarbons." (*1)

“It is known that PFAS require a minimum of seven carbon atoms (C7 and above, denoting the number of CF2 units) to initiate self-aggregation. In other words, in cases where the number of CF2 units is six or fewer, the properties of a single molecule are generally preserved. While PFAS substances are known to accumulate in the body, self-assembled molecules do not readily interact each other due to their water repellent nature. Consequently, it is assumed that PFAS compounds with longer carbon chain lengths (12 CF2 units (C12) or greater may exhibit reduced toxicity. However, the influence of proteins and water on in vivo self-aggregation remains elusive and warrants further investigation. Nevertheless, we maintain that PFAS risk assessment based on this theory should proceed. (*2)

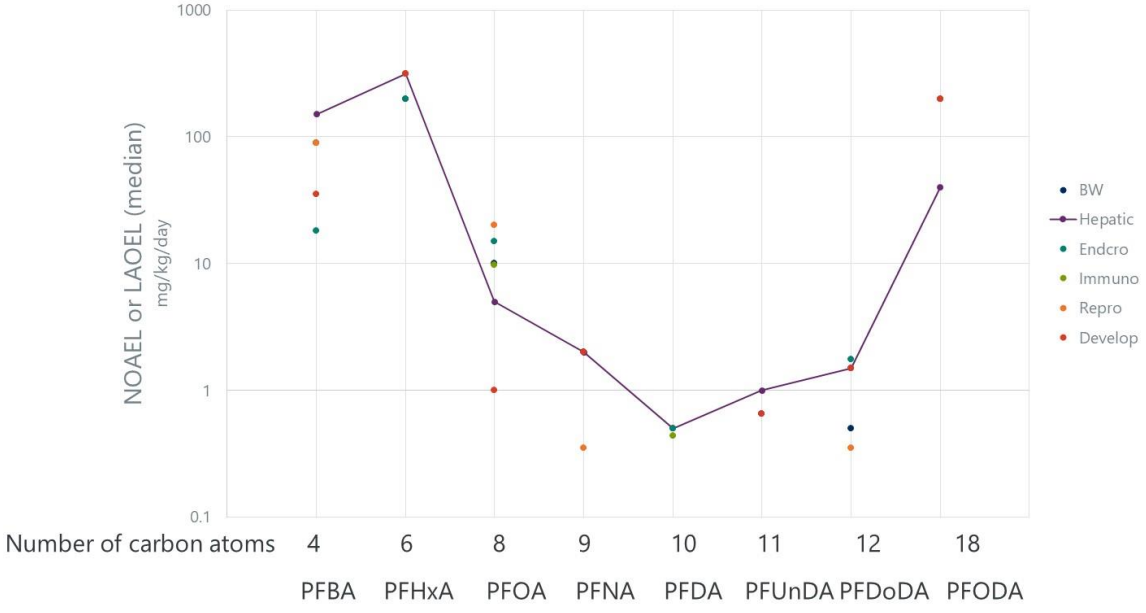
(3) Assessment of carbon chain lengths and toxicity in PFAS compounds.

Our study searched into the correlation the carbon chain length, denoted as the “C number,” and the associated toxicity of PFAS compounds, drawing upon publicly available data. Our investigation explains the reason behind the comparatively elevated toxicity observed in PFAS compounds with carbon chain length of C8 and C9. Moreover, it shows that the relationship between extended carbon chain length and toxicity does not consistently adhere to a linear pattern.

(3)-1 Evaluation of toxicity through animal experimentation (C4-C18 carboxylic acids)

Our investigation begins by examining animal data related to carboxylic acids spanning carbon chain lengths from C4 to C12, extracted from the 2021 Toxicological Profile for perfluoroalkyls published by the Agency for Toxic Substances and Disease Registry (ATSDR). Figure 1 illustrates a comparative analysis of the median NOAEL (No Observable Adverse Effect Level) and LOAEL (Lowest observed Adverse Effect Level) values for each chain length sourced from ATSDR, along with pertinent data on PFODA (C18) from the research of Hirata-Koizumi et al. When assessing the toxicity for liver of rats or mice as an indicator, it is evident that PFBA (C4) and PFHxA (C6) exhibit relatively low toxicity. With increasing carbon chain length, toxicity escalates until reaching PFDA (C10), after which longer carboxylic acids demonstrate a tendency to exhibit reduced toxicity. Notably, PFODA (C18) emerges as considerably less toxic.

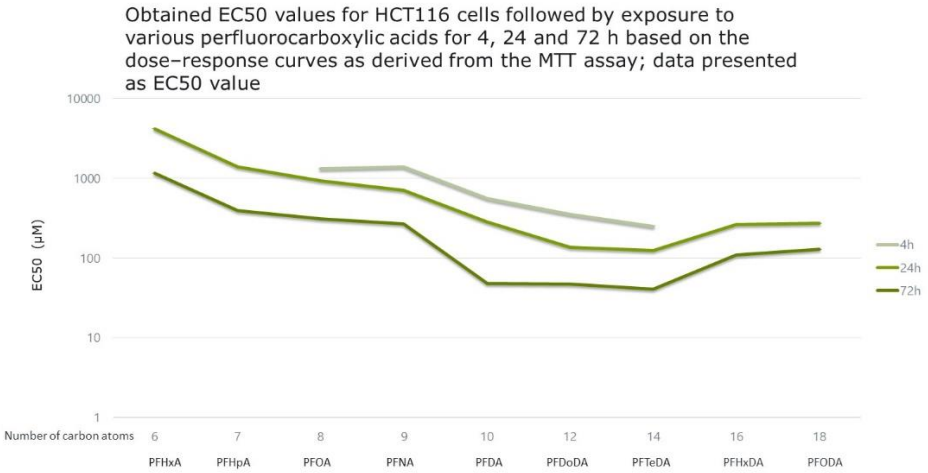
Figure -1: Relationship between carbon number and NOAEL/LAOEL



(3)-2 Correlation between carbon number and in vitro testing results.

A study conducted by Kleszczynski, K., et al. in 2007 investigates the cellular activity of carboxylic acids with varying carbon chain lengths. The outcomes of this study reveal a trend wherein toxicity tends to diminish as the carbon number increases, progressing from PFTeDA (C14) to PFHxDA (C16) and finally to PFODA (C18).

Figure -2: Relationship between carbon number and cell activity

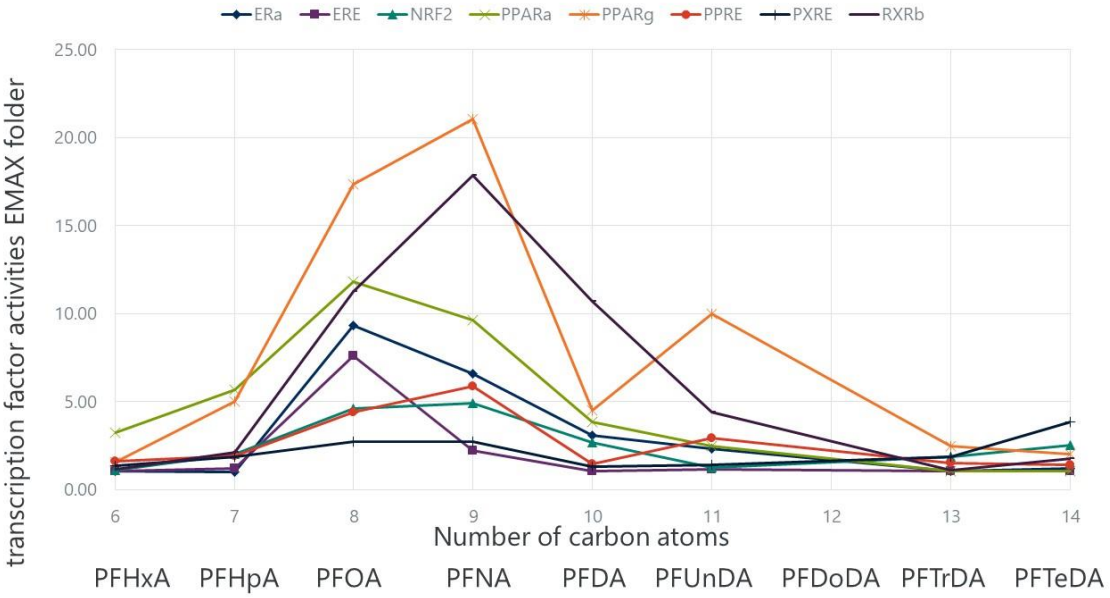


Kleszczynski, K., et al. (2007). "Analysis of structure-cytotoxicity in vitro relationship (SAR) for perfluorinated carboxylic acids." Toxicology in Vitro **21(6): 1206-1211.**

(3)-3 Carbon chain length and genetic analysis.

Researchers led by Houck at the Environmental Protection Agency (EPA) in 2021 embarked on a genetic analysis of 142 PFAS compounds to identify trends in their toxicity profiles. We conducted a comparative analysis of the activity of individual genes, gauging their frequency of activation relative to the Median values for maximum efficacy (EMAX) control. Specifically, we focused on genes that exhibited activity in response to PFOA and conducted a comparative assessment based on carbon chain length. Our findings, in light of PPARg (Peroxisome Proliferatoractivated Receptor-gamma) and Era (Estrogen receptor-Estrogen receptor-a), confirm that PFOA (C8) and PFNA (C9) exhibit pronounced activity against specific genes, with diminishing activity observed as the carbon number increases.

Figure -3: Relationship between carbon number and gene activity

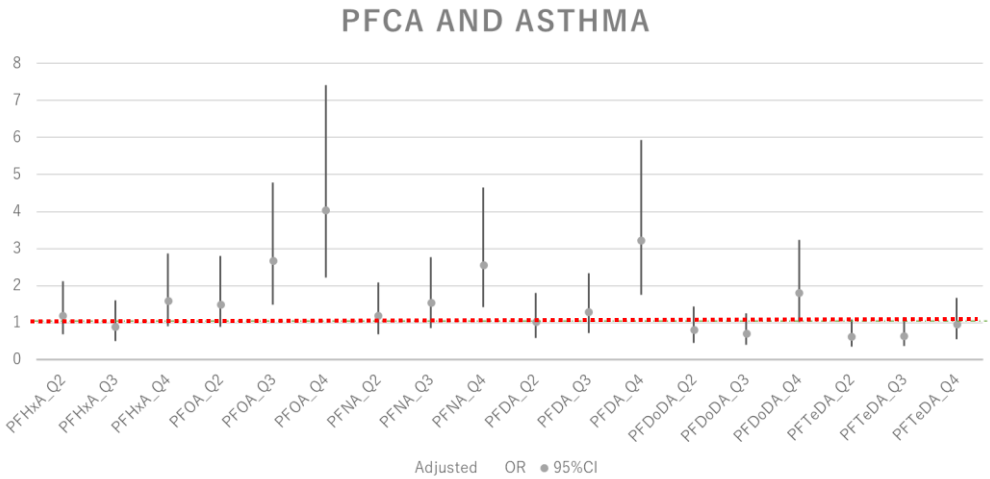


Houck, K. A., et al. (2021).
"Bioactivity profiling of per- and polyfluoroalkyl substances (PFAS) identifies potential toxicity pathways related to molecular structure."
Toxicology **457**: 152789.

(3)-4 Carbon numbers and epidemiological studies.

In a 2021 epidemiological study led by Shearer, J. J., et al. exploring human kidney cancer, the odds ratio analysis revealed a significant association , as the 95% confidence interval for PFOA (C8) alone does not encompass the value of 1. Conversely, intentional differences were not discerned in the cases of PFNA (C9), PFDA (C10), and PFUnDA (C11), as their respective 95% confidence intervals spanned across the value of 1. Similarly, another epidemiological study conducted by Dong, G. H., et al. in 2013, investigating asthma in children. Their analysis of odds ratios revealed a significant distinction for PFOA (C8), whilst no significant distinction in odds ratios for PFHxA (C6), characterised by a lower carbon number, and PFTeDA (C14), featuring a higher carbon number.

Figure -4: Odds ratio between carbon counts and epidemiological studies



- Shearer, J. J., et al. (2021). "Serum Concentrations of Per- and Polyfluoroalkyl Substances and Risk of Renal Cell Carcinoma." Journal of the National Cancer Institute **113(5): 580-587.**

Dong, G. H., et al. (2013). "Serum polyfluoroalkyl concentrations, asthma outcomes, and immunological markers in a case-control study of Taiwanese children." Environmental Health Perspectives **121(4): 507-513.**

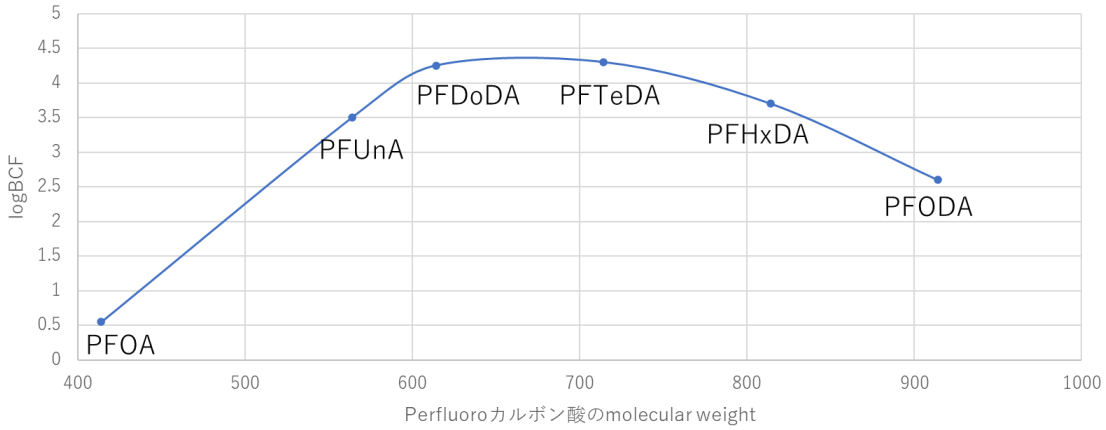
(4) Correlation between carbon chain length and carboxylic acid concentration (LogBCF)

In the context of evaluating carboxylic acid concentration in fish, an analysis of carbon chain length reveals that PFDoDA (C12) and PFTeDA (C14) exhibit the highest bioconcentration factors (BCFs). Notably, as the carbon chain length increases, there is a corresponding decrease in BCF. This trend is indicative of a reduced tendency of bioaccumulation. It is important to note that when the molecular weight of a substance exceeds 700, it tends to exhibit limited bioaccumulation potential. In simpler terms, molecules with a molecular weight exceeding 700 are less likely to bioaccumulate. This effect is particularly pronounced in comparison to PFTeDA (C14), which possesses a molecular weight of 714. Larger molecular weights hinder the passage of substances through cell membranes, reducing their ability to enter the body.

As an illustrative example within the realm of PFAS substances, fluoropolymers are known for their inertness to the human body, boasting molecular weights well in exceeds of 100,000 Daltons (Da). Consequently, they are recognisedd as incapable of being absorbed by the human body. PTFE, a prominent fluoropolymer, has been employed in over 40 million cases spanning more than four decades as a permanent cardiovascular medical device. Extensive clinical and preclinical data, along with chemical extractables and migration studies, have

conclusively established that fluoropolymers do not present any discernible health risks or bioavailability concerns. (*4, 5)

Figure -5: Number of carbons and LogBCF



Inoue, Y., et al. (2011). "Unique Physicochemical Properties of Perfluorinated Compounds and Their Bioconcentration in Common Carp Cyprinus carpio L." Arch Environ Contam Toxicol.

(5) Conclusion

Based on the comprehensive analysis conducted in sections (3)-1 to (3)-4 above, the following important findings regarding carbon chain length and toxicity

1. **Certain PFAS compounds, such as PFOA (C8), PFNA (C9), and PFDA (C10), tend to be more toxic, while shorter PFAS compounds below C6 and longer PFASs above C13 generally exhibit lower toxic.**
2. **According to SDA theory, short-chain PFAS compounds (up to PFHxA (C6)) exist as a single molecule and are quickly removed from cells. In contrast, PFOA (C8) and similar compounds having longer carbon chains start to form molecular aggregates, which can increase their toxicity.**
3. **As the longer carbon chain length (C13 and above), these compounds also form aggregates, but their ability to dissolve in water decreases. Consequently, the likelihood of them of entering the water environment or the body is reduced.**

The proposed restriction highlights the potential health risks associated with the persistence of certain substances in the human body, and it is assumed that the increase in carbon chain length of these substances will increase the accumulation potential and increase the toxicity. However, the above results indicate that the relationship between carbon chain length and toxicity is complex and cannot be explained by simple proportionality. One possible reason for this complexity is that self-aggregation of PFAS (becoming a

polymer) can reduce the occurrence of toxicity and inactivates it. In other words, we postulate that the SDA theory provides a theoretical framework to elucidate this observed behaviour.

Consequently, it is advisable to differentiate between PFAS existing in their individual monomolecular state and PFAS forming molecular aggregates when discussing their accumulation in the human body. The latter should be treated as if they were polymerised PFAS. Additionally, it is worth noting that molecular aggregates of PFAS with a carbon chain length of C14 or higher exhibit different water solubility characteristics compared to those with a molecular chain length falling between C8 and C14. Therefore, distinctions based on chain length are essential when considering these molecular self-aggregation of PFASs.

While the assessment method for PFAS proposed by the SDA theory is of significant importance, it should be subject to further verification in future research. Nonetheless, we believe that these theoretical underpinnings offer valuable insights for understanding the physical properties of PFASs and should be taken into serious consideration when re-evaluating the proposed PFAS restriction.

Reference:

1: Prof. Takeshi Hasegawa, Physicochemical Nature of Perfluoroalkyl Compounds Induced by Fluorine, The Chemical Society of Japan and Wiley-VCH GmbH, Weinheim
Physicochemical Nature of Perfluoroalkyl Compounds Induced by Fluorine - Hasegawa - 2017 - The Chemical Record - Wiley Online Library

2: Takeshi Hasegawa ,Shoji Nakayama, PFAS science and regulation should be reconsidered using fluorine-specific physical chemistry, 05 July 2023, Version 1
PFAS science and regulation should be reconsidered using fluorine-specific physical chemistry | Earth, Space, and Environmental Chemistry | ChemRxiv | Cambridge Open Engage

3: Korzeniowski, S. H., et al. (2023). "A critical review of the application of polymer of low concern regulatory criteria to fluoropolymers II: Fluoroplastics and fluoroelastomers." Integrated Environmental Assessment and Management 19(2): 326-354.
A critical review of the application of polymer of low concern regulatory criteria to fluoropolymers II: Fluoroplastics and fluoroelastomers - PubMed (nih.gov)

4: Henry, B. J., et al. (2018). "A critical review of the application of polymer of low concern and regulatory criteria to fluoropolymers." Integrated Environmental Assessment and Management **14**(3): 316-334.
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