Archives of Toxicology
https://doi.org/10.1007/s00204-023-03597-y

GUEST EDITORIAL

PFASs–restriction proposal commentary on ECHA's Annex XV restriction report, proposal for a restriction, March 2023

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Received: 24 August 2023 / Accepted: 29 August 2023

Abstract
PFASs are defined as substances that contain at least one fully fluorinated methyl (CF_3–) or methylene (–CF_2–) carbon atom. The excellent technical properties of members of the PFAS group have led to their use in a wide range of applications. The substance group comprises more than 10,000 individual compounds. A variety of adverse effects has been described for single substances. For the majority of the PFASs, neither toxicokinetic data nor effect data is available. Hence, because of the small number of PFASs for which a full toxicological profile is available, grouping based on the existing data is not feasible. A critical problem of PFASs and their degradation products is the very high persistence, which clearly fulfils the criterion for the substance property *Very Persistent* (vP) according to Annex XIII of the REACH Regulation. Because of this property the European Commission is planning to take action. Defining suitable subgroups appears to be a scientifically based approach. However, to reach this goal, large data gaps would have to be closed which would take up to centuries, a time-frame, which is not defendable with respect to potential irreversible harm. Because of the time pressure resulting from the potential irreversible harm, the precautionary principle has been selected as an appropriate tool to handle PFASs and in the restriction proposal PFASs are treated as one group. This approach is justified in the view of the advisory committee of the German Society for Toxicology. ECHA's proposal received a lot of attention in the public. However, communication so far has obviously led to the misunderstanding of a proven health hazard for all PFASs. Communication should explain the justification of the broad inclusion of substances as being based on the precautionary principle. Data gaps versus current knowledge need to be clearly communicated; communication should also include the possibility for derogation of essential use. It should address the issue of suitable substitutes to avoid unintended health consequences; and it should mention that existing persistent environmental contamination calls for developing innovation in remediation techniques.

Introduction

The European Commission (EC) is planning to phase out most uses of per- and polyfluoroalkyl substances (PFASs) in the EU as a part of its Chemicals Strategy for Sustainability (CSS) (European Commission 2020a). In this context, the European Chemicals Agency (ECHA) has recently published a proposal under the EU chemicals regulation REACH to restrict the manufacture, use and placing on the market (including import) of PFASs. The proposal, published in late March 2023, obtained considerable attention in public media, mostly with the notion of PFASs as "forever chemicals" (ECHA 2023). The Advisory Committee of the German Society for Toxicology would like to contribute to the discussion, seeing the importance of precautionary strategies in risk management under conditions of uncertainty. The currently available knowledge on PFASs indicates a possibility of harm to human health and the environment. In order to balance opportunities to solve problems of society by using PFASs versus any irreversible impact of PFASs on health and environment, a normative risk evaluation is needed. To accomplish this goal, it is decisive how the communication evolves between all interested groups and how criteria can be set that will guide policy making.

In fact, a critical problem of PFASs and their degradation products is the very high persistence, which very clearly

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Published online: 06 October 2023

fulfils the criterion for the substance property *Very Persistent* (vP) according to Annex XIII of the REACH Regulation. PFASs parent compounds and their degradation products[1] may persist for extended periods of time contaminating the environment non-reversibly. This is due to the property of the uniquely strong covalent bond between carbon and fluorine atom.

PFAS properties and toxicology

The OECD defines PFASs as fluorinated substances that contain at least one fully fluorinated methyl or methylene carbon atom (without any H/Cl/Br/I atom attached to it), i.e., with a few noted exceptions, any chemical with at least a perfluorinated methyl group ($–CF_3$) or a perfluorinated methylene group ($–CF_2–$) is a PFAS (OECD, Environment Directorate Chemicals and Biotechnology Committees 2021). By this definition, on which the restriction proposal is based, the substance group of PFASs comprises more than 10,000 individual substances.

PFASs are chemicals of anthropogenic origin that are widely used in consumer products, technical applications such as medical devices, and in industrial processes owing to chemical inertness and water-, grease- and dirt-repellent properties. PFASs can enter the environment during phases of manufacture, use, and waste disposal. They have been detected as ubiquitous pollutants in the environment, for example in soil, groundwater, and drinking water, and in human biomonitoring studies. Human exposure occurs via food and drinking water as well as other routes including dusts and gases in indoor and ambient air. It is to be expected that without limiting PFASs emissions, humans will be exposed to steadily increasing levels of PFASs up to exposures exceeding human health thresholds. For some PFASs, adverse health effects have been observed in experimental animals and humans.

Currently, toxicity data are available only for few PFASs, primarily legacy PFASs such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). So far, a harmonized classification and labelling according to the CLP regulation is available for six PFASs, perfluorooctanoic acid (PFOA), ammoniumpentadeca- fluorooctanoate (APFO), perfluorononan-1-oic acid (PFNA), nonadecafluorodecanoic acid (PFDA), perfluorooctane sulfonic acid (PFOS), and perfluoroheptanoic acid (PFHpA).

The currently available toxicokinetic data clearly show large differences. Striking substance specific, but also interspecies and strain specific differences in toxicokinetics have been found for rats in which seven PFASs were investigated (PFBA, PFHxA, PFHpA, PFNA, PFDA, PFBS, PFHxS) and for mice in which eight PFASs were studied (PFBA, PFHpA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA) (Schrenk et al. 2020). In humans, the kinetics of 12 PFASs were studied from which the half-life of PFBA was the shortest (2.5 days, range 1.6 to 6.3 days) and PFHxS the longest (25 years, range 1.6 to 182 years). In cases where clearance data are available, the values differed widely, ranging between 4.33 mL/kg per day for PfHxA and 0.027 mL/kg per day for PFHxS (Schrenk et al. 2020). Thus, large differences in their potential to accumulate were observed for the limited number of investigated PFASs. These wide inter-species, inter-strain, and substance-specific variations pose a significant challenge for risk assessment.

Epidemiological studies have suggested associations without clear causal relationships between exposure to specific PFASs and a variety of health effects. Concordance with experimental animal data exists for some of the effects (Fenton et al. 2020).

In experimental animals, alterations in immunological parameters and liver (non-alcoholic fatty liver disease (NAFLD)) represent the most sensitive adverse effects (Brunn et al. 2023; Jin et al. 2020; Schrenk et al. 2020). Additionally, developmental toxicity has been discussed for some PFASs. In contrast, a prospective human observational study on birth weight and development through the first two years of life showed no effect of PFOA, PFOS, PFNA, and PFHxS (Shoaff et al. 2018).

Until now, only a few PFASs (PFOA, PFOS, PFDA, and PFNA) have been harmonized classified as suspected human carcinogens according to the CLP classification system mandatory in the EU (Hazard category "Carc. 2", hazard statement H351). No mutagenic effect was demonstrated for PFOS and PFOA, despite their potential to induce oxidative stress. However, in EFSA's assessment (Schrenk et al. 2020) it is stated that structurally similar PFNA and PFDA have been tumour promoting in a trout liver model with questionable relevance for humans, whereas a long-term rat study with PFHxA did not give any evidence for carcinogenic effects.

A variety of adverse effects has been described for single substances. For the majority of PFASs neither toxicokinetic nor effect data are availble and hence because of the small number of PFASs with a full toxicological profile, grouping based on the existing data is not feasible. For the communication of the state of the knowledge a differentiated description of the health effects of PFASs is required, which will resolve the biased public perception unfortunately triggered by misunderstandings. The challenge for risk assessment arising from the actual combination of unique covalent bond strength and resulting persistence, vast data gaps on hazard endpoints across the group as well as seemingly

[1] Sometimes named as 'arrowhead substances', if terminal degradation products of precursors are obtained.

contradictory findings, and last but not least a ubiquitous occurrence in the environment and humans, can be adressed by applying the precautionary principle.

The proposal

Arguing that PFASs have a non-negligible potential to harm the environment and human health, the European Chemicals Agency has identified the need to follow the precautionary principle as a state objective of environmental protection laid down in Article 191 of the Treaty of the Functioning of the European Union. The submitted proposal cannot apply classical hazard and risk assessment strategies because for most of the PFASs necessary data on harmful properties are not available nor are expected to become available in the near future.

In the proposal, the vast number of PFASs (see above) is considered as one chemical group, comprising individual substances as well as homologues, oligomers and polymers. Among the possible regulatory risk management alternatives, a restriction with possible derogations was chosen as preferred approach. This *Restriction Option 2* (RO2) will lead to a phased restriction in some cases, with specific time-limited exemptions for certain uses. RO2 also provides some indefinite derogations for exceptional cases. The restriction covering all PFASs as an integrative group is aiming at to:

- limit as many uses as practically possible and thereby minimize emissions and human and environmental exposures to PFASs;
- include currently unknown PFASs and PFAS uses; and
- prevent regrettable substitution of restricted PFASs with other PFASs with similar concerns.

Restriction Option 2

In contrast to a complete ban as in Restriction Option 1 that reduces PFASs emissions most comprehensively after a transition period of 18 months, Restriction Option 2 as recommended by the proposal allows for derogations from the restriction. For certain PFASs uses derogations (*proposed* or *for reconsideration*) would be possible for up to 12 years (5 years and 12 years, respectively, after the end of a transition period of 18 months). Here, the availability of technically and economically feasible PFAS-free alternatives on the market is the most important criterion to be considered in proposing derogations. RO2 includes a few time-unlimited derogations, e.g., for PFASs used as active substances in Plant Protection Products (PPP), Biocidal Products (BP) and human and veterinary Medicinal Products (MP), as these are addressed under their respective regulations.

The proposed RO2 approach means that derogations can be established solely through the inventory of the most important uses and technical processes involved in the production of PFASs and the weighting of the existence or the non-existence of technically and economically feasible alternatives. RO2 has not yet addressed the issue of essential uses of PFASs. As early as 2020, the Commission recommended to develop a policy document on the concept of essential uses of PFASs (European Commission 2020b).

In our view, considering essential versus non-essential uses would lead to a stronger focus on specific substances in the huge class of PFASs, for which restriction is urgently needed. The EC should now adopt their policy document immediately in the context of PFASs restrictions.

Grouping

The grouping approach applied in the restriction proposal is substantially different from established practices under CLP and REACH for e.g. classification. PFASs in scope of the restriction proposal are handled as one group, because they share the persistency of the perfluorinated moieties as main concern. Thus, the group of PFASs encompasses a wide range of different chemical entities for which a common hazard and risk is supposed by the proposal. For the purpose of the restriction proposal, PFASs are defined as substances that contain at least one fully fluorinated methyl (CF_3–) or methylene (–CF_2–) carbon atom, without any hydrogen, chlorine, bromine, or iodine attached to it. This definition is used similarly to OECD's definition of PFASs (OECD, Environment Directorate Chemicals and Biotechnology Committees 2021) and in this respect determines the inclusion or else the exclusion of certain PFASs subcategories to be considered. This means that the persistence characteristic of an individual PFAS member structurally falling under the definition of the group might be sufficient to be regulated under the proposed restriction, e.g., unless derogation criteria are fulfilled.

In the view of the U.S. EPA and of Anderson and colleagues, persistence alone is not sufficient for grouping PFASs aiming to assess human health risk. Rather defining suitable subgroups appears to be a more appropriate approach (Anderson et al. 2022; U.S. Environmental Protection Agency, Office of Water and Office of Research and Development 2021).

Regulatory measures

The restriction proposal alone will not result in zero pollution for the postulated derogations and attenuation of existing contamination. Therefore, health-based guidance

values (HBGV) are required that should be derived for specific PFAS chemical subgroups. These HBGV are necessary for the monitoring of PFAS emissions, their control in consumer products as well as the planning for the remediation of already existing environmental contaminations.

Currently, the regulation of PFASs in the EU is mainly carried out within the POP Regulation and REACH. The EU POP Regulation (European Union 2019) currently only covers PFOS and PFOA. Under REACH, PFASs restrictions (European Union 2021) and SVHC dossiers (Substances of Very High Concern) have been processed for 14 substances or substance groups so far. The PFOS and PFOA restrictions were transferred from REACH to the EU POP Regulation in 2006 and 2020, respectively. In ECHA's classification and labelling notifications database, human health endpoints considered of most concern following long-term exposure of humans (i.e., carcinogenicity, mutagenicity, reproductive toxicity including effects on or via lactation, and specific target organ toxicity), 357 PFASs are self-classified for at least one of these five endpoints; however, harmonized classifications are available for only 41 PFASs, as already pointed out above. (ECHA 2023).

PFASs are also subject to other regulations outside REACH and the EU POP Regulation with precise HBGV or limit values, e.g., in the field of water policy (PFOS), for water intended for human consumption (sum of PFAS [2]), under COMMISSION REGULATION (EU) No 10/2011 (European Union 2011) on plastic materials and food contact materials (PFOA). In addition, regulations on specific areas, such as soil protection, groundwater, surface water, already exist at national level in some member states.

As outlined in the restriction proposal, the approach is now different if compared to previous hazard and risk assessments. The derivation of DNELs/DMELs[3] is not considered relevant, since PFASs should be treated as non-threshold substances for the purposes of risk assessment like PBT/vPvB substances under REACH, although a science-based justification for this approach is not available (ECHA 2023). Therefore, any exposure to PFASs can be regarded as an unacceptable risk to human health. Since the non-threshold approach requires minimisation of exposures or releases, a quantitative comparison of the exposure values to effect thresholds (i.e., DNEL or DMEL values) is not necessary/feasible (ECHA 2023). To solve the seeming regulatory dilemma of an imperfect scientific basis and a pressing need for regulation due to the threat of irreversible harm applying the precautionary principle is an appropriate approach.

In the absence of the precautionary principle in US legistation, US EPA's PFAS Strategic Roadmap (2021) is a comprehensive approach addressing research, restriction and remediation. It shows a distinct way to assess health risks of PFASs. It includes the establishment of an evidence base on individual PFASs, defining categories of PFASs, improvement of the scientific understanding of the universe of PFAS, sources of environmental contamination, exposure pathways, and human health as well as ecological effects.

Compliance monitoring

The restriction option RO2 is intended to apply to products and applications unless otherwise specified (Chapter 2.5). Discrete *concentration limits* (named *limit values*) for products and applications are mentioned in the proposal as follows:

- 25 ppb for any PFAS (except polymeric PFASs) (equals to 25 µg/kg),
- 250 ppb for the sum of PFASs (equals to 250 µg/kg), optionally with prior degradation of precursors, and
- 50 ppm for PFASs, including polymeric PFASs (equals to 50 mg/kg).

The limit value of 250 ppb is intended to address the risk for combined effects of co-occurring PFASs that may need to be taken into consideration (without any single PFAS exceeding the limit value of 25 ppb). Whether an opening of the scope of application of the concentration limits to single substances and mixtures beyond products is intended (Chapter 4, Conclusion) is difficult to judge. The previously mentioned limit values to apply to products and applications are mentioned in the overall conclusion according to chapter 4 in the context of "PFASs on their own, in another substance, as a constituent, in mixtures or in articles placed on the market". Monitoring of PFASs will be a challenge.

The limit values proposed in Chapter 2.5 are not related to any health concern. With regard to the limit values mentioned in the restriction proposal, harmonization has to be considered with the existing regulations such as COMMISSION REGULATION (EU) 2021/1297 (European Union 2021).

[2] The following substances shall be analysed: Perfluorobutanoic acid (PFBA), Perfluoropentanoic acid (PFPA), Perfluorohexanoic acid (PFHxA), Perfluoroheptanoic acid (PFHpA), Perfluorooctanoic acid (PFOA), Perfluorononanoic acid (PFNA), Perfluorodecanoic acid (PFDA), Perfluoroundecanoic acid (PFUnDA), Perfluorododecanoic acid (PFDoDA), Perfluorotridecanoic acid (PFTrDA), Perfluorobutane sulfonic acid (PFBS), Perfluoropentane sulfonic acid (PFPS), Perfluorohexane sulfonic acid (PFHxS), Perfluoroheptane sulfonic acid (PFHpS), Perfluorooctane sulfonic acid (PFOS), Perfluorononane sulfonic acid (PFNS), Perfluorodecane sulfonic acid (PFDS), Perfluoroundecane sulfonic acid, Perfluorododecane sulfonic acid, and Perfluorotridecane sulfonic acid.

[3] DNEL: Derived No-Effect Level; DMEL: Derived Minimal Effect Level.

We agree that it will not be possible to set a safe level for the PFASs group overall, given the vast number of substances covered. The literature which has been published is addressing the health effects particularly of perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkane sulfonic acids (PFSAs), especially PFOA and PFOS. Other PFASs are less well researched, but scientific attention and available information on hazards is increasing (ECHA 2023).

Recently, a tolerable weekly intake (TWI) of 4.4 ng/kg bw per week was established for PFOA, PFNA, PFHxS and PFOS (Schrenk et al. 2020), which is lower compared to the CONTAM Panel's TWI of 13 ng/kg body weight (bw) per week for PFOS and 6 ng/kg bw per week for PFOA from 2018. However, a constellation in which some well-studied PFASs show effects at lower levels than previously assumed and that existing limit values are exceeded is not sufficient to justify a non-threshold approach. It should be considered that the non-threshold approach ultimately means that any exposure to a PFAS, even at very low doses, is associated with a health risk. This is certainly not true for all compounds of the PFAS substance group. A basic principle of regulatory practice is that in the case of non-genotoxic carcinogens the risks can be quantified. In addition, latest knowledge is used to demonstrate that quantitative considerations can also be applied to the assessment of genotoxic substances which are currently treated as non-threshold substances (Menz et al. 2023).

Aspects of (bio)chemical analytics–the question of measurability of PFASs

Effective compliance monitoring depends on comprehensive quantitative analytical methods. The quantification of PFASs in biological/environmental matrices is complex and labour-intensive. Following liquid–liquid or solid phase (micro) extraction, PFASs are separated using gas or liquid chromatography and analytes are typically detected and quantified by mass spectroscopy or tandem mass spectroscopy (Jalili et al. 2023). With regard to structural diversity of the various PFASs for a given methodology, the lower limit of quantification (LLOQ) may vary considerably by up to several orders of magnitude ranging from 0.35 up to 26 ng/L for aqueous environmental samples (Coggan et al. 2019) and more pronouncedly from 0.086 ng/L up to 260,000 ng/L for human serum and placental tissue (Kaiser et al. 2021). At present, quantification is not possible for every single substance. Targeted PFASs analysis currently covers about 40 different PFASs (limited by the availability of reference standards) (ECHA 2023). It seems unlikely that for a chemical group such as that of PFASs, with more than 10,000 compounds, sufficiently sensitive analytical methods will be available for each individual substance in the short term. In such cases, non-targeted analysis using high resolution mass spectroscopy for the screening of unknown PFASs offers the possibility to estimate the 'total' PFASs concentration (Li et al. 2023). The PFAS sum parameter analysis measuring total fluorine (TF), extractable organic fluorine (EOF), and adsorbable organic fluorine (AOF) are other methods. A targeted analysis, however, should be the preferred method whenever possible.

Communication

ECHA's comprehensive technical proposal received a lot of attention in the public discussion, which led to misunderstandings with regard to the justification of the broad inclusion of substances. This is not because of a proven health hazard but is based on strategic measures of the precautionary principle. It is necessary to explain that the proposal is based on the precautionary principle and the justification for this should be disclosed. Meaning and impact of the precautionary principle have been clarified in a Communication of the European Commission in 2000 by the use of several criteria, which have essentially been confirmed by the European Court (Commission of the European Communities 2000).

It is important to have in mind that the precautionary principle is designed with a re-evaluation

follow-up loop when precautionary actions are planned by identifying suitable risk management tools. This begins with a science-based evaluation of the cause of concern, followed by an analysis of the cause of concern against benefits, which finally enables a tentative normative assessment. Here, cost–benefit analysis, availability of alternatives, public acceptance of remaining risks and risk context is weighed against substance related effects. So measures are to be checked for the putative impact with emphasis on proportionality, non-discrimination, transparency and coherence of proposed regulatory actions and are open for adaptations (German Advisory Council on the Environment 2011).

Furthermore, communication should consider aspects as follows:

Data gaps versus current knowledge need to be clearly communicated to allow for an informed risk perception as the basis of sound decisions;

In addition, communication should also include:

Essential use cases, such as respirators, dialysis machines, seals and gaskets in high-risk chemical plants (e. g. phosgene), and electronic devices, which may require continuing the use.

Communication should also consider:

to address the issue of suitable substitutes to avoid unintended health consequences;

And lastly, it should be mentioned that.

already existing persistent environmental contamination calls for continuing risk prioritisation and innovation in remediation techniques.

Recent reporting on PFASs' health hazards may have distorted public risk perception. Because risk perception has significant impact on the ongoing societal decision-making process, we feel the need to provide a more data-driven, balanced view and communication to the public.

Conclusion

PFASs comprise non-polymeric and polymeric compounds used as such or as constituents in mixtures and products for consumer, professional, and industrial uses. The excellent technical properties of many members of the PFASs group have led to their use in a wide range of applications over a long period of time. PFASs are very persistent themselves or can form very persistent PFASs degradations products in the environment because of the unique bond strength between carbon and fluorine. This is the key hazardous property common to all PFASs considered by ECHA in the restriction proposal. The persistence of PFASs, underlined by their ubiquitous occurrence in the environment and humans, is the basis of the grouping approach used in the restriction proposal. Adverse health effects are only known for a relatively small number of substances from the PFAS group. The extrapolation of these known adverse health effects as a common property of the whole group goes beyond established regulatory practices and sets a precedence.

Risks arising from the production, marketing, and use of PFASs are currently not adequately managed. ECHA´s proposal to restrict the manufacture, use and placing on the market (including via import) of PFASs is commendable and challenging in every aspect. For a variety of the essential uses of the tremendous number of PFASs, realistic time periods for the development of alternatives must be available. At the same time, appropriate decontamination strategies need to be developed in dealing with existing environmental contaminations. Both aspects, the temporary continuation of PFAS production and application in the cases of essential uses and the remediation of existing contaminations of the environment, would be subject of established risk assessment methods and requires detailed knowledge of data on toxicologically relevant endpoints. Closing data gaps for derogated substances, particularly on toxicological effects, is therefore of high public interest.

In view of the far-reaching use of PFASs in consumer products, adequate public information is required on the impact of the planned restriction by ECHA and its rationale. Public discussions have often led to oversimplified statements on adverse health aspects of PFASs. Therefore, we ask all stakeholders to improve the communication to foster a balanced and broad acceptance of the proposal, without eliciting exaggerated fears on the risks of the substance group.

Declarations

Conflict of interest This commentary has been compiled by the Advisory Committee (AC) of the German Society of Toxicology. The AC is elected by the members of the German Society of Toxicology and consists of representatives from academia, industry and administration to guarantee a broad range of toxicological competence. Opinions expressed are that of the AC and do not represent official statements of members' affiliations. The AC presents and justifies its activities to the members of the German Society of Toxicology, for example at the yearly plenary meeting. The German Society of Toxicology is the largest scientific toxicological organization in Europe, with more than 1300 members. In the past 15 years, the Advisory Committee has already published review articles about the EU chemicals strategy (Batke et al. 2022), bromate in swimming pool water (Röhl et al. 2022), hydraulic fracturing (Wollin et al. 2020), lead in agricultural soils (Schupp et al. 2020), inorganic arsenic in food (Gundert-Remy et al. 2015), nanotoxicology (Gebel et al. 2014), bisphenol A (Hengstler et al. 2011), alternative methods to animal experiments (Lilienblum et al. 2008) and REACH (Hengstler et al. 2006). Commentaries to PFAS have not yet been published by the AC.

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