Scientific Committee on Health, Environmental and Emerging Risks
SCHEER

Scientific Opinion on "Draft Environmental Quality Standards for Priority Substances under the Water Framework Directive"

PFAS

The SCHEER adopted this document
via written procedure on 18 August 2022

ACKNOWLEDGMENTS

Members of the Working Group are acknowledged for their valuable contribution to this opinion. The members of the Working Group are:

The SCHEER members
Marian Scott (Chair), Marco Vighi (Rapporteur), Thomas Backhaus, Teresa Borges, Peter Hoet, Pim de Voogt

The external Experts
Andrew Johnson, Jan Linders

Acknowledgements
Demosthenes Panagiotakos, Rodica Mariana Ion

All Declarations of Working Group members are available at the following webpage:
Register of Commission expert groups and other similar entities (europa.eu)

This Opinion has been subject to a commenting period of four weeks after its initial publication (from 5 April to 6 May 2022). Comments received during this period were considered by the SCHEER. For this Opinion, main changes were made in sections 3.1, 3.1.1, 3.2, 3.3 and the abstract.

Keywords: Per- and polyfluorinated alkylsubstances, PFAS, Water Framework Directive, environmental quality standards

Opinion to be cited as:
SCHEER (Scientific Committee on Health, Environmental and Emerging Risks), Final Opinion on Draft Environmental Quality Standards for Priority Substances under the Water Framework Directive - PFAS, 18 August 2022

Abstract

The SCHEER was asked to evaluate the proposed quality standards for per- and polyfluorinated alkyl substances (PFAS) presented in an EQS dossier drafted by the JRC. The SCHEER is of the opinion that the concern for human health due to PFAS should not only focus on biota and drinking water but also on consumption of vegetables and fruit.
The SCHEER considers the gap in the dossiers, due to missing ecotoxicity data for the period 2015-2021, a serious shortcoming and, therefore, recommends an update of the Draft EQS dossier.

The SCHEER endorses the use of Relative Potency Factors (RPFs) used in the derivation of quality standards for PFAS for humans. RPFs will, however, vary depending on the endpoint considered and therefore the SCHEER recommends monitoring the literature in order to signal possible new RPF data sets that may become available.

For five out of six PFAS, QSs could only be based on the deterministic approach. The SCHEER endorses the **$MAC\text{-}QS_{fw,eco}$** and **$MAC\text{-}QS_{sw,eco}$** values for **PFBA (1.1 and 0.11 $mg.L^{-1}$**, respectively), for **PFPeA (3.2 and 0.32 $mg.L^{-1}$**, respectively), for **PFHxA (0.86 and 0.086 $mg.L^{-1}$**, respectively) and **PFBS (3.7 and 0.37 $mg.L^{-1}$**, respectively). For PFOS the SCHEER endorses the **$MAC\text{-}QS_{fw,eco}$ of 0.025 $mg.L^{-1}$** but considers the value proposed for the **$MAC\text{-}QS_{sw,eco}$** to be incorrect and recommends that it should be changed into **0.0025 $mg.L^{-1}$**. For PFOA both the deterministic and the SSD approach could be applied. The deterministic approach resulted in the lowest $MAC\text{-}QS_{fw,eco}$ of 1.2 $mg.L^{-1}$, and the SCHEER cannot endorse this $MAC\text{-}QS_{fw,eco}$ because it was not clear why an AF of 10 instead of 100 was applied. For the **$MAC\text{-}QS_{sw,eco}$** a lowest value of **0.012 $mg.L^{-1}$** was proposed, which is endorsed by the SCHEER.

The SCHEER confirms that the $AA\text{-}QS_{fw,eco}$ and $AA\text{-}QS_{sw,eco}$ values for PFOA (0.03 and 0.003 $mg.L^{-1}$, respectively), PFBA ((0.11 and 0.011 $mg.L^{-1}$, respectively), PFPeA (0.032 and 0.0032 $mg.L^{-1}$, respectively), PFHxA (0.2 and 0.02 $mg.L^{-1}$, respectively), and PFBS (0.1 and 0.01 $mg.L^{-1}$, respectively) have been derived in agreement with the Technical Guidance. While this also holds for the $AA\text{-}QS_{fw,eco}$ for PFOS of 0.023 $\mu g.L^{-1}$, according to the SCHEER the $AA\text{-}QS_{sw,eco}$ value derived for PFOS is incorrect and the SCHEER proposes to set this value at 0.0023 $\mu g.L^{-1}$.

The SCHEER endorses the QS_{sed} of 13.5 $\mu g.kg^{-1}{}_{dw}$ derived for PFOS for a sediment with 5% organic carbon. The SCHEER cannot agree with the conclusions that no QS_{sed} is needed for PFOA, PFBS, PFBA, PFPeA and PFHxA, and recommends that more recent sediment studies should be evaluated in order to verify the correctness of current conclusions.
The SCHEER endorses the tentative **$QS_{biota,sec\ pois}$ of 22.3 $\mu g.kg_{ww}^{-1}$** for fish and **6.2 $\mu g.kg_{ww}^{-1}$** for bivalves (PFOA equivalents). The SCHEER also endorses the **$QS_{biota,hh}$ of 0.077 $\mu g.kg^{-1}{}_{biota\ ww}$** and the proposed **$QS_{dw,hh}$ of 4.4 $ng.L^{-1}$** (PFOA equivalents) and recommends to use this value also for protecting groundwater.

Although the majority of the MAC and AA values proposed for individual PFAS were derived in accordance with the TGD, the SCHEER is of the opinion that it would be more practical to embark upon a set of quality standards for the group of PFAS as soon as reliable RPFs for ecotoxicity are available, in line with the human health QS. Moreover, a discussion is lacking in the dossier on the relevance of the $AA\text{-}EQS_{fw}$ and $AA\text{-}EQS_{sw}$ for PFOS currently

in force in the EU, both of which are substantially stricter than the $AA\text{-}QS_{fw}$ and $AA\text{-}QS_{sw}$ proposed in the dossier.
Due to the different approaches used in deriving QS_{eco} and QS_{hh}, as well as the identified gap in recent data on ecotoxicity it is not possible for the SCHEER to assess whether the most critical EQSs (in terms of impact on environment/health) have been correctly identified. For PFOS the most critical AA-EQSs would be the ones currently in force in the EU (0.00065 $\mu g.L^{-1}$ for inland surface waters and 0.00013 $\mu g.L^{-1}$ for seawater).

About the Scientific Committees (2022-2026)

Two independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

These committees are the Scientific Committee on Consumer Safety (SCCS) and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER). The Scientific Committees review and evaluate relevant scientific data and assess potential risks. Each Committee has top independent scientists from all over the world who are committed to working in the public interest.

In addition, the Commission relies upon the work of other Union bodies, such as the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCHEER

This Committee, on request of Commission services, provides Opinions on questions concerning health, environmental and emerging risks. The Committees addresses questions on:

- health and environmental risks related to pollutants in the environmental media and other biological and physical factors in relation to air quality, water, waste and soils.
- complex or multidisciplinary issues requiring a comprehensive assessment of risks to consumer safety or public health, for example antimicrobial resistance, nanotechnologies, medical devices and physical hazards such as noise and electromagnetic fields.

SCHEER members

Thomas Backhaus, Roberto Bertollini, Teresa Borges, Wim de Jong, Pim de Voogt, Raquel Duarte-Davidson, Peter Hoet, Rodica Mariana Ion, Renate Kraetke, Demosthenes Panagiotakos, Ana Proykova, Theo Samaras, Marian Scott, Emanuela Testai, Marco Vighi, Sergey Zacharov

Contact

European Commission
DG Health and Food Safety
Directorate C: Public Health
Unit C2: Health information and integration in all policies
L-2920 Luxembourg
SANTE-C2-SCHEER@ec.europa.eu

PDF ISSN 2467-4559 ISBN 978-92-68-06287-6 doi:10.2875/97550 EW-CA-23-014-EN-N

http://ec.europa.eu/health/scientific_committees/policy/index_en.htm

TABLE OF CONTENTS

1. Background

Article 16 of the Water Framework Directive (WFD, 2000/60/EC) requires the Commission to identify Priority Substances among those presenting significant risk to or via the aquatic environment, and to set EU Environmental Quality Standards (EQS) for those substances in water, sediment and/or biota. In 2001 a first list of 33 Priority Substances was adopted (Decision 2455/2001) and in 2008 the EQS for those substances were established (Directive 2008/105/EC or EQS Directive, EQSD). WFD Article 16 requires the Commission to periodically review the list. The first review led to a Commission proposal in 2011, resulting in the adoption of a revised list in 2013 containing an additional 12 Priority Substances. Technical work to support a second review has been underway for some time, and several substances have been identified as possible candidate Priority Substances. The Commission will be drafting a legislative proposal, with the aim of presenting it to the Council and the Parliament around the middle of 2022.

The technical work has been supported by the Working Group (WG) Chemicals under the Common Implementation Strategy for the WFD. The WG is chaired inter alia by DG Environment and consists of experts from Member States, EFTA countries, candidate countries and several European umbrella organisations representing a wide range of interests (industry, agriculture, water, environment, etc.).

Experts nominated by WG Members (operating as individual substance Expert Groups and through the Sub-Group on Review of Priority Substances, SG-R) have been deriving EQS for the possible candidate substances and have produced draft EQS for most of them. In some cases, a consensus has been reached, but in some others, there is disagreement about one or other component of the draft dossier. EQS for a number of existing priority substances are currently also being revised.

The EQS derivation has been carried out in accordance with the Technical Guidance Document on Deriving EQS (TGD-EQS) reviewed by the SCHEER.

2. Terms of Reference[1]

DG Environment now seeks the opinion of the SCHEER on the draft EQS for the proposed Priority Substances and the revised EQS for a number of existing Priority Substances. The SCHEER is asked to provide an opinion for each substance. We ask that the SCHEER focus on:

1. whether the EQS have been correctly and appropriately derived, in the light of the available information and the TGD-EQS;

2. whether the most critical EQS (in terms of impact on environment/health) has been correctly identified.

Additional questions to the SCHEER

- **The EFSA' TWI (EFSA,2020), the relevant study for derivation of the provisional QS values $QS_{biota,hh}$ and QS for water($QS_{dw,\ hh}$)**

Following four meetings and three rounds of comments, the majority of the expert group agreed that the EFSA TWI should be used as the key study. However, the stakeholders expressed their disagreement over the relevance of the epidemiological data as they commented that the TWI was solely based on observations from a small cross-sectional epidemiological study by Abraham et al. (Arch Toxicol 2020, 94(6):2131-2147. doi: 10.1007/s00204-020-02715-4).
The JRC and other experts support the EFSA TWI because of reliability on the peer-reviewed assessment made by EFSA, where epidemiological data were assessed and used for risk assessment.
The derived TWI aims to protect all population groups including infants. The task of this expert group is to perform the hazard/risk assessment of substances by establishing a limit value to ensure the protection of all population.

- **The Relative Potency Factor Approach (RPF)**

The RPF is extensively described in the sub-chapter 7.5, of the draft dossier it is proposed as combination with the EFSA TWI. The RPF approach is based on the paper Bil et al (2021). The combination of TWI and RPF is implemented by RIVM (2021).
The experts agreed on this approach however the stakeholders expressed their concern for the uncertainty since they are not study for the relative potency on immune effects and for the reference supporting RPFs (Bil et al.), related to a single endpoint and recently published. In the comments, stakeholders wrote that
"*More validation is needed, as stated by the authors themselves. In particular, as the draft EQS proposal notes, extension of the RPFs to other toxicological endpoints, or ecological endpoints, has not been validated*".

[1] Text of the terms of reference is copied from the mandate given to the SCHEER

To the best of our knowledge, it is true that immune effects are not available/are unknown for some of the PFAS reported in the dossier. However, it does not impair the consideration that the considered PFAS are not equipotent with regard to immune effects either. Similar potency differences were observed for endpoints other than liver toxicity, such as different organ weights, hormone levels, clinical chemistry, white blood cell parameters and pathology endpoints (RIVM, 2021). Therefore, this might also be applicable to immune effects.
Re the RPF, the implementation of this methodology, would allow to measure PFAS quantities, resulting in the sum of PFOA equivalents in a mixture, so far, this would include 24 PFAS. It has been already implemented for other substances in the legal framework.

- **Proposals for the PFAS Risk Assessment**

SCHEER should pay attention to the proposals for the PFAS risk assessment, shown in the table 2 (proposal 1 and 2 are similar) and described in the section 7.8.2 and Table 7.9.1.

3. Opinion

The SCHEER will first address some general aspects of the ecotoxicity and human health of PFAS, in the light of the terms of reference and the dossiers received. Thereafter the quality standards proposed will be evaluated and discussed.

3.1 Introduction

For the preparation of the current Opinion, the SCHEER used the Draft EQS Dossier on PFAS provided by DG ENV in August 2021. Originally five separate dossiers of Italian EQS derivations from 2015 were provided in May 2021 to the SCHEER: for PFBA, PFBS, PFPeA, PFHxA and PFOA, respectively (IT, 2015). These dossiers are dated January 7th, 2015, while for PFOA an additional, updated dossier dated May 1st, 2015 was also provided by DG ENV in June 2021, together with a JRC report from May 2021 on PFAS (JRC, 2021).

The Draft EQS Dossier on PFAS considers 24 different PFAS, including the five mentioned above, and PFOS, and is based on three key pillars, i) relative toxicity approach using relative potency factors (RPF); ii) a key study by the European Food Safety Authority (EFSA) (2020) establishing a Tolerable Weekly Intake (TWI) for a combination of four PFAS, and iii) criteria for selection of the 24 PFAS.

The Draft EQS dossier presents two possible proposals for PFAS risk assessment. The first one makes use of the RPF approach with a tentative $QS_{biota,hh}$ expressed as the sum of 24 PFOA equivalents and a QS in water based on a threshold level for the sum of four PFAS (PFOA, PFNA, PFHxS, PFOS) taken from the TWI and expressed in PFOA equivalents. The second proposal would be based on a separation of PFAS into two groups: bioaccumulative PFAS and mobile PFAS. In this proposal the QS for bioaccumulative PFAS should again be based on the RPF approach, while no further details are provided for the derivation of a QS in water for the mobile PFAS. The Draft EQS dossier notes that an agreement on the best way forward needs to be reached among the Sub-Group experts, and/or that otherwise, SCHEER's Opinion will be requested in this regard.

The SCHEER has thus far not received a mandate referring specifically to these two proposals. The SCHEER is of the opinion, however, that the suggestion put forward in the second proposal to separate into two groups should not be adopted because there is currently a lack of data and understanding of the behaviour and bioaccumulation of mobile PFAS.

Given the nature of PFAS production processes and the applications and uses of PFAS, it is inevitable that ecological receptors as well as humans are - or will be - exposed to PFAS mixtures. The SCHEER considers the RPF approach as the currently best available means for deriving EQSs. EFSA (2013) was the first to introduce the concept of RPFs without the prerequisite of grouping chemicals based on a common mode of action but rather based on the same target organ because information on mode of action is often lacking. One should, however, realise that different sets of RPFs are available (Gomis et al., 2018; Bil et al., 2020) and that each set will obviously lead to different outcomes.

With regard to the TWI (EFSA, 2020), which is based on decreased response of the immune system to vaccination, as a result of exposure to PFAS, the SCHEER agrees with the use of the TWI for deriving QSs for human health. For ecosystem health, however, there are currently no data sets available that would allow a proper calculation of pertaining 'ecotoxicological' RPFs.

As for the selection of PFAS, the SCHEER notes that, apart from 22 per- and polyfluorinated acids, two precursors are included in the list of 24 PFAS assessed in the draft EQS dossier. PF acids are stable compounds that can be introduced in the environment as such or that can be formed by transformation of so-called precursors. PF acids persist in the environment and in living organisms. The motivation to select the two precursors is based on "..*in environments such as low anthropogenic impacted area, these substances may be persistent for long time and travel for many kilometers distant from the sources. The two selected precursors are the most commonly found telomer precursors*..".
The motivation for including both precursors would be equally valid for many other precursors (e.g., telomer sulfonates, PF sulfonamides, etcetera), and therefore the reasons for selecting the current ones should be more clearly explained.

Referring to the mandate given to the SCHEER (see section 2. of this Opinion), the SCHEER will only evaluate the derivation of EQSs and will not comment in detail to the other sections in the Draft EQS dossier. A general comment to these sections is given in the preamble to the consolidated Opinion, which will be produced when all dossiers have been evaluated.

The Draft EQS dossier proposes two "generic" EQSs based on the RPF approach and expressed in PFOA equivalents. These include an AA-EQS for human health of 0.077 $\mu g.kg^{-1}{}_{biota\ ww}$ and an AA-EQS in water of 4.4 $ng.L^{-1}$. In addition to these, specific QS are presented for six individual PFAS: PFBA, PFPeA, PFHxA, PFOA, PFBS and PFOS, which are based on either the deterministic approach (i.e., using assessment factors) or on the probabilistic approach using Species Sensitivity Distributions (when enough taxa are represented in the toxicity data set).

3.1.1 Ecotoxicity

The Draft EQS dossier notes that 'Regarding the ecotoxicological assessment, it relied on past evaluations performed by Italy and The Netherlands for some available PFAS, and no additional data searches and ecotoxicological assessments were performed in the present EQS dossier[2]. Section 7 of the Draft EQS dossier presents ecotoxicity data on acute effects for six PFAS (PFBA, PFPeA, PFHxA, PFOA, PFBS, PFOS) and on chronic effects for 4 PFAS (PFHxA, PFOA, PFBS, PFOS). Additional clarification was sought from JRC, who explained, for ecotoxicity little

[2] Although, no additional data searches were performed, the EQS dossier was supplemented with additional information from the JRC Technical Report: 'Per- and polyfluoroalkyl substances (PFAS) of possible concern in the aquatic environment' from May 2021.

additional data were included in the search because QS_{eco} is not the critical QS. The JRC motivated this as follows: "*From existing evaluations, it is known that PFOS, PFOA and other PFAS have a relatively low toxicity to water organisms, but they may pose a problem when entering the food chain via fish. Therefore, the analysis was mainly focused on deriving human health-based quality standards for fish consumption. In general, no further evaluation of the studies was carried out, and the MAC- and AA-QS were derived following the evaluations performed by Italy (Valsecchi et al., 2017) and RIVM (2017). Ecotoxicity data on PFOS were collected from the EQS dossier of 2011, revised by the JRC in 2017. Sediment ecotoxicity data were however retrieved from the Swiss EQS_{sed} dossier prepared in 2020. Apart from this, no additional ecotoxicological data searches were performed in the EQS dossier.*"

Indeed, whereas the toxicity data used for deriving human health EQS for PFAS appear to be up to date, the ecotoxicity data collected in the draft EQS dossier (Tables 7.1 to 7.10) appear to cover a period up to 2015, except for PFBS, for which three chronic effects studies from 2018 and 2019 were listed. As a consequence, the recent scientific literature has not been included in the derivation of the EQSs. In particular for PFAS, new data have become available on occurrence and (eco)toxicity of PFAS in the period 2015-2021. This creates an unnecessary knowledge gap that should preferably be closed. A recent overview of ecotox data for PFAS can be found in the Supplemental Information of Ankley et al. (2020), who extracted data from the USEPA ECOTOX Knowledgebase. Although, the Ankley et al. (2020) paper is cited in the Draft EQS dossier, it is unclear why more recent data from that reference have not been evaluated or why they were disregarded; this preferably needs further clarification. While the current mandate does not request the SCHEER to systematically collect and review all recent literature on PFAS, the SCHEER is aware of several studies that may have been overlooked because of the apparent deadline used for ecotoxicity data collection. For example, mounting evidence suggests that immunotoxicity can occur at serum concentrations below, within, or just above the reported range both for highly exposed humans and wildlife (Corsini et al., 2014; DeWitt et al., 2020; Dalsager et al., 2021), that there is a significant health impact of low-dose PFASs (Liu et al., 2020) and that alternatives to legacy PFAAs could likely be intrinsically as potent as their predecessors (Gomis et al., 2018; Vogs et al., 2019). The SCHEER considers this gap in the dossiers a serious shortcoming and recommends updating the Draft EQS dossier regarding ecotoxicity data.

A recent workshop on the state-of-the-science supporting risk assessment of PFAS held in Durham, USA, in 2019 concluded that "…*currently there is insufficient knowledge to adequately assess the potential ecological effects of all PFAS that occur or could potentially enter the environment. Given the number of substances involved, the need to consider both single chemicals and mixtures, and the diversity of ecosystems/species that might be exposed and impacted, this knowledge cannot realistically be attained using conventional chemical-by-chemical testing approaches employing in vivo assays and apical responses*" (Ankley et al. 2020; Johnson et al., 2021). In the view of SCHEER, it is therefore practical to embark upon a set of quality standards for the group of PFAS. It should be kept in mind, however, that even when 24 single compounds are combined in an RPF approach, the contribution of substances outside the 24 selected may in some cases be relevant for the evaluation of the environmental risk due to PFAS exposure. It is recommended to develop more comprehensive monitoring programmes to support exposure assessment, including methods to efficiently assess biological effects for potentially sensitive species/endpoints[3].

3.1.2 Human health

The analysis provided in the Draft EQS dossier uses EFSA's conclusion that the relevance of the effects on the immune system observed at the lowest serum PFAS levels in both animals and humans is critical for risk assessment. Therefore, the combined exposure to four PFAS (PFOA, PFNA, PFHxS and PFOS) resulted in a group tolerable weekly intake (TWI) of 7 x 0.63 = 4.4 ng/kg $_{bw}$ per week, based on decreased response of the immune system to vaccination (EFSA, 2020). This value was used to derive the human-health based QSs in the Draft EQS dossier.

Overall, the SCHEER recognizes that epidemiological studies revealed associations between exposure to specific PFAS and a variety of health effects, including altered immune function, liver disease, lipid and insulin dysregulation, kidney disease, adverse reproductive and developmental outcomes and cancer, and that concordance exists with experimental animal data for many of these effects. However, the SCHEER also considers that there are differences in PFAS toxicokinetic properties in humans and animals that must be accounted for in order to understand differences in responses between sexes, across species and life stages. In this sense, extrapolation to humans should be done with caution and additional scientific evidence raised, making use of more contemporary and high-throughput approaches such as read-across, molecular dynamics, and protein modeling to accelerate the development of toxicity information on emerging and legacy PFAS, individually and as mixtures (Fenton et al, 2021).

The SCHEER endorses the approach taken in the EQS dossier and considers that although additional evidence is still missing to conclude that the RPF approach can be applied to immune effects, the fact that differences in potency were observed for PFAS for other endpoints like liver toxicity, organ weights, hormone levels, clinical chemistry, white blood cell parameters and pathology endpoints (RIVM, 2021), corroborates that the RPF approach may also be used for immune effects. Ultimately, using the RPF approach that relies on liver toxicity effects, where PFOA is the sole index compound (Bil et al., 2021), makes it possible to measure PFAS quantities, resulting in the sum of PFOA equivalents in a mixture, therefore including 24 PFAS. Recently, Rietjens et al. (2021) commented that "the RPF values proposed by Bil et al. (2021) are in themselves not robust enough for direct application in risk assessment". Bil et al. (2022) in a response to this critique, replied that "it is important to take into account combined exposure to PFAS as much as possible at this very moment", a view that is endorsed by the SCHEER.

[3] Assessing the Ecological Risks of Per- and Polyfluoroalkyl Substances: Current State-of-the Science and a Proposed Path Forward: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7984443/

The Draft EQS dossier notes that '… *PFAS pose a concern for human health through the drinking water and aquatic food consumption'*. The SCHEER is aware that, in addition, the risk for human health could also result from the consumption of vegetables and fruit due to the potential for bioaccumulation of short-chain PFAS (Jiao et al., 2020; Felizeter et al., 2021). Also, indoor air and dust can be a source of human exposure to short chain PFAS, in particular for toddlers (Zheng et al., 2020). However, the SCHEER appreciates that only the derivation of the $QS_{hh\ food,\ water}$ (consumption of fishery products) and the derivation of the $QS_{dw,water}$ (drinking water) should be considered in the dossier, according to the TGD for EQS derivation.

The RPFs used in the derivation of $AA\text{-}QS_{biota,\ hh}$ are based on benchmark doses of liver toxicity in rat, a phenomenon commonly observed after exposure to PFAS, albeit at different potencies. The SCHEER agrees with the observation that the assumptions for application of the RPF approach, set by EFSA (2020), are met and therefore the SCHEER endorses the use of RPFs for the derivation of quality standards for humans, such as the $AA\text{-}QS_{biota,\ hh}$ for fish consumption, $AA\text{-}QS_{dw,hh}$ for drinking water and $AA\text{-}QS_{sec\ pois,biota.}$ for secondary poisoning.

3.2 MAC-QS and AA-QS

The ecotoxicity data and the hazard assessment performed in the Italian EQS dossiers (IT,2015) drafted for PFOA, PFBA, PFBS, PFHxA, and PFPeA formed the basis for the derivation of QSs for freshwater, marine water and sediment. For PFOA, the Dutch EQS dossier (Verbruggen et al., 2017) was also taken into account. For PFOS, data were collected from the EQS dossier of 2011 revised by the JRC in 2017 (JRC, 2021). For PFOS, sediment ecotoxicity data for PFOS were retrieved from the Swiss EQS_{sed} dossier prepared in 2020 (Casado-Martinez, 2020). MAC- and AA-QS were derived following the evaluations performed by Italy (Valsecchi et al., 2017) and RIVM (2017).

Where sufficient data were available, an SSD approach was used to derive the quality standards. This was the case for PFOA only ($MAC_{fw,eco}$ and $MAC_{sw,eco}$). For PFOS, data were available for a number of species but the range of taxonomic groups covered was deemed insufficient by the JRC. When there is insufficient data for an SSD approach, the Assessment Factor (AF) approach is used, in agreement with the TGD. The reliability of the ecotoxicity studies obtained in the searches was also evaluated and several test data were excluded because the relevant studies were considered unreliable.

For PFOA, the MACs for freshwater and saltwater were derived using the HC5 of the SSD, and AFs of 10 (FW) ($MAC\text{-}QS_{fw,eco}$ = 2.8 $mg.L^{-1}$) or 100 ($MAC\text{-}QS_{sw,eco}$ = 0.28 $mg.L^{-1}$), respectively, were applied. The MACs presented are appropriately calculated, but as indicated in the preceding text, they are based on data published before 2015. In addition, a deterministic approach, applying an AF of 10 and 1000, respectively, was also presented, which resulted in a $MAC\text{-}QS_{fw,eco}$ of 1.2 $mg.L^{-1}$

and a $MAC_{sw,eco}$ of 0.012 mg.L^{-1}. It is not clear to the SCHEER why an AF of 10 instead of 100 was applied for the MAC-$QS_{fw,eco}$; the SCHEER assumes that the scatter in the data results in a standard deviation below the critical factor of 3, but this is not explicitly stated in the draft EQS dossier.

For PFBA, the MAC-$QS_{fw,eco}$ was derived from the lowest observed acute toxicity (LC50 = 110 mg.L^{-1}). An AF of 100 was applied for freshwater and 10x100 for saltwater, resulting in values of 1.1 mg.L^{-1} (MAC-$QS_{fw,eco}$) and 0.11 mg.L^{-1} (MAC-$QS_{sw,eco}$), respectively. The SCHEER endorses these values.

For PFPeA, the $MAC_{fw,eco}$ was derived from the lowest observed EC_{50} applying an AF of 10, which resulted in a value of 3.2 (3.18) mg.L^{-1}. Applying an additional AF for marine water, the resulting MAC-$QS_{sw,eco}$ was calculated at 0.32 mg.L^{-1}. The SCHEER endorses these values.

For PFHxA, the MAC-QS for freshwater and saltwater were derived from the second lowest LC_{50} value available, discarding the lowest reported value because of the unreliability of that study. Using AFs of 100 and 1000, respectively, the $MAC_{fw,eco}$ amounted to 0.86 mg.L^{-1} and the $MAC_{sw,eco}$ to 0.086 mg.L^{-1}. The SCHEER endorses these values.

For PFBS, the lowest available EC_{50} was used and AFs of 100 and 1000, respectively, were applied to obtain the MAC-$QS_{fw,eco}$ (3.7 mg.L^{-1}) and the MAC-$QS_{sw,eco}$ (0.37 mg.L^{-1}). The SCHEER endorses these values.

For the MAC-$QS_{fw,eco}$ for PFOS, the lowest available LC50 was used and an AF of 100 was correctly applied. This resulted in a value of 0.025 mg.L^{-1}. For the MAC-$QS_{sw,eco,}$ an additional factor of 10 was said to be applied (because only one marine species was available in the data set, this additional AF of 10 would be correct), but the published value of 0.025 mg.$L^{-1}$is the same as the MAC-$QS_{fw,eco}$. Therefore the SCHEER considers the value proposed for the MAC-$QS_{sw,eco}$ to be incorrect and recommends that it should be changed to 0.0025 mg.L^{-1}.

AA-QS

For PFOA, the AA-QS values were derived from a single freshwater mesocosm study and applying AFs of 10 leading to an AA-$QS_{fw,eco}$ of 0.03 mg.L^{-1}, and 100 leading to an AA-$QS_{sw,eco}$ of 0.003 mg.L^{-1}, respectively. The SCHEER agrees with the AFs applied that are in agreement with the TGD.

For PFBA, no chronic data were available and the same (i.e. acute) test data were used as for deriving the MACs, applying AFs of 1000 and 10,000, respectively, leading to an AA-$QS_{fw,eco}$.of 0.11 mg.L^{-1} and an AA-$QS_{sw,eco}$ of 0.011 mg.L^{-1}. The SCHEER agrees with the AFs applied that are in agreement with the TGD.

For PFPeA, no chronic data were available and the same (i.e. acute) test data were used as for deriving the MACs, applying AFs of 1000 and 10,000, respectively, leading to an AA-$QS_{fw,eco}$.of 0.032 mg.$L^{-1}$and an AA-$QS_{sw,eco}$ of 0.0032 mg.L^{-1}. The SCHEER agrees with the AFs applied that are in agreement with the TGD.

For PFHxA, a lowest chronic effect value was available (9.96 mg.L^{-1}) and an AF of 50 was applied since two long-term data sets were available. This resulted in an

$AA\text{-}QS_{fw,eco}$.of 0.20 mg.L^{-1} and an $AA\text{-}QS_{sw,eco}$ of 0.02 mg.L^{-1} by applying an additional AF of 10 for marine water. The SCHEER agrees with the AFs applied that are in agreement with the TGD.

Additionally, the SCHEER notes that table 7.10 of the draft dossier has the wrong header. It currently reads “acute ecotoxicity data”, while it should read “chronic ecotoxicity data”.

For PFBS, the listed lowest chronic toxicity value is 1 µg.L^{-1}. Three trophic levels are represented in the chronic data set and hence an AF of 10 is used to derive $AA\text{-}QS_{fw,eco}$, resulting in a value of 0.1 µg.L^{-1} An additional AF of 10 was used to derive the $AA\text{-}QS_{sw,eco}$, leading to a value of 0.01 µg.L^{-1}. The SCHEER agrees with the AFs applied that are in agreement with the TGD.

For PFOS, in the chronic dataset there are several LOECs that are far below the lowest No observed effect concentration (NOEC), and consequently, applying an assessment factor of 10 on the lowest NOEC would lead to a highly under-protective AA-QS. Therefore, an assessment factor of 100 was applied to the lowest LOEC, leading to a $AA\text{-}QS_{fw,eco}$ of 0.023 µg.L^{-1}. The SCHEER agrees with using this AF and concludes that the $AA\text{-}QS_{fw,eco}$ has been correctly derived on the basis of these data. However, the SCHEER is aware that for PFOS an $AA\text{-}EQS_{fw}$ of 0.00065 µg.L^{-1} in inland surface waters currently applies. A discussion of the proposed $AA\text{-}QS_{fw}$ in the light of the existing $AA\text{-}EQS_{fw}$ should have been provided in the dossier.

For the $AA\text{-}QS_{sw,eco}$, an additional AF of 5 (rather than 10) was applied because of the presence of an additional marine taxon in the data set, resulting in the $AA\text{-}QS_{sw,eco}$ of 0.0046 µg.L^{-1}. The SCHEER does not agree with this AF or with the resulting value for the $AA\text{-}QS_{sw,eco}$ because the value of “>3 mg.L^{-1}” for the EC50 doesn’t seem to indicate that shell deposition is a “very sensitive” parameter, and any further justification for using this AF is lacking. The SCHEER therefore suggests to use the AF of 10 which would result in an $AA\text{-}QS_{sw,eco}$ of 0.0023 µg.L^{-1}. However, the SCHEER is aware that for PFOS an $AA\text{-}EQS_{sw}$ of 0.00013 µg.L^{-1} in seawater currently applies. A discussion of the proposed $AA\text{-}Qs_{fw}$ in the light of the existing $AA\text{-}EQS_{sw}$ should have been provided in the dossier.

The SCHEER notes that in the current draft EQS dossier from the JRC, no QSs for groundwater (GW) are presented for compounds PFBA, PFBS, PFPeA, PFHxA and PFOA, contrary to the QS_{gw} presented in the original Italian dossiers. The reason why such values are no longer presented was originally unclear to the SCHEER, but following upon request, the JRC clarified that the QS derivation was done for all matrices including the one for drinking water (DW) but not for GW as this is part of a separate mandate. For the latter the SCHEER adopted a preliminary opinion on 7 January 2022[4].

[4] https://ec.europa.eu/health/publications/groundwater-quality-standards-proposed-additional-pollutants-annexes-groundwater-directive-2006118ec_en

$QS_{sediment}$

According to the TGD, QS_{sed} values should be derived: (i) if K_{oc} or log K_{ow} exceed trigger values, (ii) if there is evidence for toxicity to benthic organisms and (iii) if there is evidence for accumulation in sediments. For PFBA, PFPeA, PFHxA, PFOA, and PFBS, the Draft EQS dossier relies entirely on the Italian dossiers which concluded that for sediment-dwelling organisms, insufficient information on toxicity of PFOA, and no information on toxicity of PFBA, PFPeA, PFHxA or PFBS, is available to support a decision to derive a QS_{sed} for any of these PFAS. For PFOS, a separate dossier was available on the derivation of a QS_{sed} (Casado-Martinez, 2020).

For two PFAS (PFPeA, PFHxA), the Draft EQS dossier concludes from the available monitoring data (see section 7.4 of the draft EQS dossier) that there is no need to derive a threshold based on the criterion: 'evidence of accumulation in sediments'. Several studies do show however that PFAS, including short-chain compounds, can be found at relatively high concentrations (e.g., sum of PFAS up to 30 $\mu g.kg^{-1}_{dw}$ in river sediments, Zhu et al., 2014) and that extraction methodologies may have significantly underestimated PFAS contamination in sediments (Harfmann et al, 2021). The Draft EQS dossier, despite noting that from the available monitoring data, accumulation of PFBA in sediment can be considered possible, concludes that there is no need for a QS_{sed} for PFBA. Given the general comments by the SCHEER on environmental measurements (see preamble), the omission of some recent studies, and the notion that PFOS along with other PFAA may be widespread in sediments with peak concentrations in the tens of $\mu g.kg^{-1}_{dw}$ range (Casado-Martinez 2021), the SCHEER cannot agree with these conclusions. Therefore, the SCHEER recommends that more recent sediment studies should be evaluated in order to verify the correctness of the current conclusions about the absence of the need to derive QS_{sed} for PFBS, PFBA, PFPeA and PFHxA.

The PFOA dossier does identify values for K_{oc} and (estimated) log K_{ow} that exceed the respective trigger values. For the K_{OC} value reported, the Italian dossiers state that the value is not representative of a riverbed sediment (without clarifying why), and because sorption of PFOA is said to depend on electrostatic interactions. However, several studies, also from before 2015, including those (Higgins and Luthy, 2007) in the ref list of the PFOA dossier, have demonstrated that sediment organic carbon is a dominant sediment parameter affecting sorption of PFAS. While it is true that sorption of PFAS cannot be predicted from a single sorbent bulk property (Krop et al., 2021), such as organic carbon (OC) content only, the SCHEER is of the opinion that as a first approximation K_{oc} values could have been used for the derivation of QS_{sed} and that the use of more recent literature (Sörengaard et al., 2020; Sima and Jaffé, 2020) on sorption of PFOA and other PFAS may well allow for a derivation of $QS_{sed.}$

For PFOS, a long-term value was available for one species. Data for a second species were classified as unreliable (Casado-Martinez, 2020) due to several limitations of the pertaining study. A QS_{sed} based on field or mesocosm data could not be derived as no studies were available. Based on the single species and a corresponding AF of 100, a QS_{sed} of 13.5 $\mu g.kg^{-1}_{dw}$ for a sediment with 5% OC was proposed for PFOS by the Swiss Centre for Applied Ecotoxicology (Casado-Martinez, 2020). The SCHEER endorses this value. According to the Swiss dossier, no field or mesocosm studies that provide effect concentrations of PFOS in sediment are available, thus, no QS_{sed} based on field data or mesocosm data has been derived.

The Swiss dossier also proposed a $QS_{sed,secpois}$ for PFOS of 1.85 $\mu g.kg^{-1}{}_{dw}$, derived from the available toxicity data. It was originally not clear to the SCHEER why this value was not adopted in the draft EQS dossier. The JRC informed the SCHEER in February 2022 that the value from the Swiss report ($QS_{sed,secpois}$ for PFOS of 1.85 $\mu g.kg^{-1}{}_{dw}$) was not included in the draft dossier because in the Swiss report it was mentioned that, for the calculation, "*BSAFs and TMFs for PFOS were those used in Babut (2018) but were not further assessed for reliability and relevance due to time constraints. Consequently, this value (BSAF) was considered quite uncertain due to the relatively small database available*". The SCHEER accepts this line of reasoning, but suggests that the reliability of the data from the Babut reference should be evaluated.

$QS_{B,SECPOIS}$

In the Draft EQS dossier, a secondary poisoning assessment was conducted for both fish and molluscs because both food items were identified as the critical ones for the food chain. The assessment is based on a methodology developed by RIVM, which was evaluated by the SCHEER in 2017 (SCHEER, 2017). The SCHEER then concluded "The SCHEER is in favour of new methodologies being developed for secondary poisoning such as the proposal to normalise contaminant concentrations to the calorific content of the food. However, the scientific evidence for the new methodology is very sparse compared with the documentation that is available for the diet- or dose-based methodologies that are being used by EFSA and ECHA in current risk assessments. The SCHEER concludes that uncertainties that may be introduced with the new methodology cannot yet properly be evaluated due to a lack of scientific information."

The RIVM also accounted for differences in food intake by stating that "*Hence higher food intake due to lower assimilation efficiency will not result in higher uptake of substances*". The SCHEER (2017) commented "that this may not hold for substances bound to proteins rather than lipids, such as some heavy metals (e.g., cadmium) and polar organics (e.g., perfluorinated alkylated substances)".

The latter comment is highly relevant for the current dossier and thus may require additional attention by the assessors. Indeed, the Draft EQS dossier acknowledges that normalisation of perfluorinated compounds is not straightforward because their accumulation behaviour is different from lipophilic substances. Yet, the procedure based on the energy content is correctly applied according to the TGD. The SCHEER endorses the specific AFs (of 3 and 10, respectively) that were used and agrees with the different BMFs of 4.5 and 15 for fish and molluscs, which were used for FW and SW, respectively, being aware that there is evidence in the literature that PFOA and PFOS biomagnify in the food chain. The SCHEER endorses the tentative $QS_{biota,sec\ pois}$ of 22.3 and 6.2 $\mu g.kg_{ww}^{-1}$ for fish and bivalves. respectively (PFOA equivalents).

Human Health

$QS_{B,HH}$

The overall evidence for bioaccumulation in the food chain for some PFAS triggered the inclusion of secondary poisoning in the present EQS derivation, where the relative potency factor (RPF) methodology was applied and the $QS_{biota,hh}$ for PFOA is calculated, using the EFSA's TWI as TL_{hh}. The SCHEER endorses the approach taken by the JRC.

In the EQS dossier, the calculation of the $QS_{sec\ pois,biota}$ was performed for the index compound PFOA, using the No Observed Adverse Effect Level (NOAEL) of 0.3 $mg.kg^{-1}_{bw}\ d^{-1}$ for litter loss and pup survival in mice (Abbott et al., 2007). However, the SCHEER doesn't endorse this approach and would recommend using the lowest NOAEL value of 0.06 $mg.kg^{-1}_{bw}\ d^{-1}$, based on rat liver toxicity obtained from Perkins et al. (2004), the same study used for the determination of the Benchmark Dose (BMD) for the RPF approach. As noted in section 3.1.2, the SCHEER recognises that there are differences in PFAS toxicokinetic properties in humans and animals that may lead to high levels of uncertainty in the QS derived.

SCHEER endorses using the EFSA's TWI of 4.4 $ng.kg^{-1}_{bw}\ wk^{-1}$, equivalent to 0.63 $ng.kg^{-1}_{bw}\ d^{-1}$, to calculate the $QS_{biota,hh}$ of 0.077 $\mu g.kg^{-1}_{biota\ ww}$ measured in fish for the sum of PFAS (expressed as PFOA-equivalents).

$QS_{DW,HH}$.

For all five PFAS, the Italian dossiers state that simple treatments for removal of PFAS in the production of drinking water are not efficient. However, a definition of 'simple' was not provided. As a consequence of the lack of removal efficiency, a treatment factor, defined by the TGD in order that $QS_{DW,HH}$ reflects a true environmental raw water threshold, was not applied. The SCHEER notes that in the past decade several studies have demonstrated that PFAS removal is possible by applying advanced filtration techniques, e.g., membrane filtration (Albergamo et al., 2020).

As the contribution of drinking water accounts for 2-17% of intake of PFAS (RIVM, 2021), a risk of exposure through drinking water intake exists and therefore a provisional drinking water QS has been calculated. If considering surface water as a source for drinking water use, the SCHEER agrees that an AA-QS for water ($QS_{dw,hh}$) should be derived using the EFSA's TWI as TL_{hh}, which would correspond to a provisional $QS_{dw,\ hh}$ of 4.4 $ng.L^{-1}$(0.0044 $\mu g.L^{-1}$). This value would be the provisional QS for the sum of PFOA-equivalents. It would protect water organisms from secondary poisoning since the TL_{hh} based on EFSA's TWI would result in a $QS_{dw,\ hh}$ that has a value lower than the back-calculated water-based $QS_{biota,hh}$.

The SCHEER endorses the approach taken in the EQS dossier, also noting that this $QS_{dw,\ hh}$ value is lower than the existing drinking water standards of 0.1 and 0.5 $\mu g.L^{-1}$ identified for the sum of PFAS, and for total PFAS (EU Directive 2020/2184).

For comparison: the Swedish National Food Agency has recently recommended new limits for drinking water of 4 $ng.L^{-1}$ for four PFAS, also based on the EFSA opinion on the TWI intake of PFAS. Additionally, the proposal for a new Swedish drinking water law includes a monitoring of 21 PFAS substances[5]. The Danish Environmental Protection Agency already in June 2021 lowered the Danish threshold value of PFAS in drinking water to 2 $ng.L^{-1}$ for a set of four PFAS (PFOA, PFNA, PFHxS and PFOS)[6]. This threshold value is also based on the EFSA opinion on TWI. These are the strictest limits in the EU currently known to the SCHEER. The SCHEER notes that very recently the US-EPA has published much lower Lifetime Drinking Water Health Advisories for PFOA and PFOS: 0.004 $ng.L^{-1}$ for PFOA, 0.02 $ng.L^{-1}$ for PFOS (US-EPA, 2022).
For the time being the SCHEER endorses the proposed $QS_{hh,dw}$ of 0.0044 $\mu g.L^{-1}$ and also recommends using this value for protecting groundwater. A further assessment of the underlying data that led to the new US-EPA advisories seems warranted, however.

3.3. Critical EQS

Due to the different approaches used in deriving QS_{eco} and QS_{hh}, as well as the identified gap in recent data on ecotoxicity and the incongruity between the existing AA-EQS and proposed AA-QS values for PFOS, it is not possible for the SCHEER to assess whether the most critical EQSs (in terms of impact on environment/health) have been correctly identified.

4. Minority opinion

None

5. Abbreviations

AA	Annual average
AF	Assessment factor
BMF	Biomagnification factor
BMD	Benchmark dose
BSAF	Biota sediment accumulation factor
dw	dry weight
EC50	Effect concentration affecting 50% of population tested
EFSA	European Food Safety Authority
EQS	Environmental quality standard
FW	Freshwater

[5] https://www.livsmedelsverket.se/foretagande-regler-kontroll/regler-for-livsmedelsforetag/dricksvattenproduktion/riskhantering-pfas-i-dricksvatten-egenfangad-fisk#Nya_gr%C3%A4nsv%C3%A4rden_f%C3%B6r_PFAS_i_dricksvatten
[6] https://tox.dhi.dk/en/news/news/article/danish-epa-more-tough-on-pfas-in-drinking-water/

HC5	Hazardous concentration for 5% of species
K_{oc}	Partition coefficient between organic carbon and water
K_{ow}	Partition coefficient between n-octanol and water
LC50	Lethal concentration affecting 50% of population tested
LOEC	Lowest observed effect concentration
MAC	Maximum allowable concentration
NOAEL	No observed adverse effect level
NOEC	No observed effect concentration
OC	Organic carbon
PF	Per- and polyfluoro-
PFAA	Per- and polyfluorinated alkyl acids
PFAS	Per- and polyfluorinated alkyl substances
PFBA	Perfluorobutanoic acid
PFBS	Perfluorobutane sulfonic acid
PFHxA	Perfluorohexanoic acid
PFNA	Perfluorononanoic acid
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctane sulfonic acid
PFPeA	Perfluoropentanoic acid
QS	Quality standard
RPF	Relative potency factor
SSD	Species sensitivity distribution
SW	Saltwater
TGD	Technical guidance document (on deriving EQS)
TL	Threshold limit
TMF	Trophic magnification factor
TWI	Tolerable weekly intake
US-EPA	Environmental Protection Agency of the United States
WFD	Water Framework Directive
WG	Working Group

6. References

Abbott BD, Wolf CJ, Schmid JE, Das KP, Zehr RD, Helfant L, Nakayama S, Lindstrom AB, Strynar MJ and Lau C (2007). Perfluorooctanoic acid induced developmental toxicity in the mouse is dependent on expression of peroxisome proliferator activated receptor-alpha. Toxicological Sciences, 98, 571–581.

Albergamo V, Blankert B, Van der Meer WGJ, Voogt P, Cornelissen ER (2020) Removal of polar organic micropollutants by mixed-matrix reverse osmosis membranes. Desalination 497, 114337.

Ankley GT, Cureton P, Hoke RA, Houde M, Kumar A, Kurias J, Lanno R, McCarthy C, Newsted J, Salice CJ (2020) Assessing the ecological risks of per-and polyfluoroalkyl substances: Current state-of-the science and a proposed path forward. Environmental Toxicology and Chemistry 40:564–605.

Babut, M. (2018). Essai de transposition des NQEbiote en concentrations seuil pour les sédiments. Programme 2016/2018 – Thème « Risques liés à la contamination chimique des milieux aquatiques » - Action n° 45. Rapport final. https://www.documentation.eauetbiodiversite.fr/notice/00000000016d869a14fd54da6c76fbd8

Bil W, Zeilmaker M, Fragki S, Lijzen J, Verbruggen E, Bokkers B (2020) Risk assessment of per- and polyfluoroalkyl substance mixtures: a relative potency factor approach. Environmental Toxicology and Chemistry 40, 859–870.

Bil W, Zeilmaker M, Fragki S, Lijzen J, Verbruggen E, Bokkers B (2022) Response to Letter to the Editor on Bil et al. 2021 "Risk Assessment of Per- and Polyfluoroalkyl Substance Mixtures: A Relative Potency Factor Approach"Environmental Toxicology and Chemistry, 41 (1), 13–18.

Casado-Martinez C (2020) EQSsed – Proposal by the Ecotox Centre for: Perfluorooctane Sulfonate (PFOS). Swiss Centre for Applied Ecotoxicology, Duebendorf.

Casado-Martinez C, Pascariello S, PolesselloS , Valsecchi S, Babut M, Ferrari BJD (2021) Sediment quality assessment framework for per- and polyfluoroalkyl substances: Results from a preparatory study and regulatory implications. Integrated Environmental Assessment and Management 17, 716-725.

Corsini E, Luebke RW, Germolec DR, DeWitt JC (2014) Perfluorinated compounds: Emerging POPs with potential immunotoxicity. Toxicology Letters 230, 263–270.

Dalsager L, Christensen N, Halekoh U, Gade Timmermann CA, Nielsen F, Boye Kyhl H, Husby S, Grandjean P, Kold Jensen T, Raun Andersen H (2021) Exposure to perfluoroalkyl substances during fetal life and hospitalization for infectious disease in childhood: A study among 1,503 children from the Odense Child Cohort. Environ International 149, 106395.

DeWitt JC, Brown P, Carignan C, Kasper S, Schaider L, Osimo C, Fitzstevens M (2020) Op-ed: PFAS chemicals—the other immune system threat. Environmental Health News (6 July 2020).

EFSA (2013) International Frameworks Dealing with Human Risk Assessment of Combined Exposure to Multiple Chemicals. EFSA Journal 2013, 11(7), 3313.

EFSA (2020). Risk to human health related to the presence of perfluoroalkyl substances in food. European Food Safety Authority, Scientific Opinion. doi: 10.2903/j.efsa.2020.6223

EU Directive 2020/2184. On the quality of water intended for human consumption (recast). http://data.europa.eu/eli/dir/2020/2184/oj

Felizeter S, Jürling H, Kotthoff M, de Voogt P, McLachlan MS (2021) Uptake of perfluorinated alkyl acids by crops: results from a field study. Environmental Science Processes and Impacts, 23, 1158 -1170.

Fenton SE, Ducatman A, Boobis A, DeWitt JC, Lau C, Ng C, Smith JS, Roberts SM (2021) Per- and Polyfluoroalkyl Substance Toxicity and Human Health Review: Current State of Knowledge and Strategies for Informing Future Research. Environmental Toxicology and Chemistry 40, 606–630.

Gomis MI, Vestergren R, Borg D, Cousins IT (2018) Comparing the toxic potency in vivo of long-chain perfluoroalkyl acids and fluorinated alternatives. Environment International 113, 1-9.

Harfmann JL, Tito K, Kieber RJ, Avery GB, Mead RN, Shimizu MS, Skrabal SA (2021) Sorption of hexafluoropropylene oxide dimer acid to sediments: biogeochemical implications and analytical considerations. ACS Earth and Space Chemistry 5, 580-587.

Higgins and Luthy (2007) Modeling sorption of anionic surfactants onto sediment materials: an a priori approach for perfluoroalkyl surfactants and linear alkylbenzene sulfonates, Environmental Science and Technology, 41, 3254-3261.

IT (2015) Italian EQS Working Group. PFOA, PFBA, PFBS, PFHxA, PFPeA Dossiers. 07-01-2015.

Jiao X, Shi Q, Gan J (2020), Uptake, accumulation and metabolism of PFASs in plants and health perspectives: a critical review, Critical Reviews in Environmental Science and Technology.

Johnson MS, Buck RC, Cousins IT, Weis CP, Fenton SE. (2021). Estimating environmental hazard and risks from exposure to per- and polyfluoroalkyl substances (PFAS): Outcome of a SETAC focused topic meeting. Environ Toxicol Chem 40, 543-549.

JRC (2021) Draft EQS dossier on PFAS. EC Joint Research Centre, Ispra.

Krop HB, Eschauzier C, van der Roest E, Parsons JR, de Voogt P (2021) Independent mode sorption of perfluoroalkyl acids by single and multiple adsorbents. Environmental Science: Processes and Impacts 23, 1997.

Liu S, Yang R, Yin N, Faiola F (2020). The short-chain perfluorinated compounds PFBS, PFHxS, PFBA and PFHxA, disrupt human mesenchymal stem cell self-renewal and adipogenic differentiation. Journal of Environmental Sciences, 88, 187-199.

Perkins RG, Butenhoff JL, Kennedy GL Jr, Palazzolo MJ. 2004. 13-week dietary toxicity study of ammonium perfluorooctanoate (APFO) in male rats. Drug Chem Toxicol. Nov;27(4):361-78.

Rietjens, I. M. C. M., Schriks, M., Houtman, C. J., Dingemans, M. M. L., van Wezel, A. P. (2022). Letter to the editor on Bil et al. 2021 "Risk assessment of per- and polyfluoroalkyl substance mixtures: A relative potency factor approach". Environmental Toxicology and Chemistry, 41(1), 7–12.

RIVM (2017) Moermond CTA, Verbruggen EMJ, Smit CE. Environmental risk limits for PFOS: A proposal for water quality standards in accordance with the Water Framework Directive. RIVM rapport 601714013, Bilthoven.

RIVM. 2021. Notitie implementatie van de EFSA som-TWI PFAS. RIVM – Finaal 7 april 2021, Bilthoven. In Dutch.

SCHEER (2017). Scientific Advice on Environmental Quality Standards, Luxemburg, 15 September 2017.

Sima MW, Jaffé PR (2020), A critical review of modeling Poly-and Perfluoroalkyl Substances (PFAS) in the soil-water environment, Science of the Total Environment, 757, 143793.

Sörengård M, Östblom E, Köhler S, Ahrens L (2020) Adsorption behavior of per-and polyfluoralkyl substances (PFASs) to 44 inorganic and organic sorbents and use of dyes as proxies for PFAS sorption, Journal of Environmental Chemical Engineering 8, 103744.

Valsecchi S, Conti D, Crebelli R, Polesello S, Rusconi M, Mazzoni M., Elisabetta Preziosi, Carere M, Lucentini L, Ferretti E, Balzamo S, Simeone MG, Aste F (2017). Deriving environmental quality standards for perfluorooctanoic acid (PFOA) and related short chain perfluorinated alkyl acids. Journal of Hazardous Materials, 323, 84-98.

Verbruggen EMJ, Wassenaar PNH, Smit CE (2017). Water quality standards for PFOA. A proposal in accordance with the methodology of the Water Framework Directive. RIVM Letter report 2017-0044, Bilthoven.

Vogs C, Johanson G, Näslund M, Wulff S, Sjödin M, Hellstrandh M, Lindberg J, Wincent E (2019) Toxicokinetics of Perfluorinated Alkyl Acids Influences Their Toxic Potency in the Zebrafish Embryo (Danio rerio) Environmental Science and Technology 53,3898–3907.

US-EPA (2022) Lifetime Drinking Water Health Advisories for four Perfluoroalkyl Substances. Federal Register / Vol. 87, No. 118 / Tuesday, June 21, 2022 [FRL 9855–01–OW].

Zheng G, Boor BE, Schreder E, Salamova A (2020) Indoor exposure to per- and polyfluoroalkyl substances (PFAS) in the childcare environment. Environmental Pollution 258, 113714.

Zhu Z, Wang T, Wang P, Lu Y, Giesy JP (2014) Perfluoroalkyl and polyfluoroalkyl substances in sediments from South Bohai coastal watersheds, China. Marine Pollution Bulletin 85, 619-627.