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Persistent, mobile and toxic (PMT) and very persistent and very mobile (vPvM) substances pose an equivalent level of concern to persistent, bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative (vPvB) substances under REACH

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Abstract

Background: Under the EU chemicals regulation REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals EC 1907/2006), registrants are not obliged to provide information related to intrinsic substance properties for substances that pose a threat to the drinking water resources. In 2019, perfluorobutane sulfonic acid (PFBS) and 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)-propanoic acid (HFPO-DA trade name GenX) were demonstrated to have an equivalent level of concern (ELoC) to persistent, bioaccumulative and toxic or very persistent and very bioaccumulative (PBT/vPvB) substances owing to their persistent, mobile and toxic (PMT) substance properties and very persistent and very mobile (vPvM) substance properties, respectively. They were both subsequently identified as substances of very high concern (SVHC) applying Article 57(f) in REACH. This work follows up on this regulatory decision by presenting a science based, conceptual level comparison that all PMT/vPvM substances pose an ELoC to PBT/vPvB substances. Using the two cases named above, as well as 1,4-dioxane, 16 categories were developed to evaluate a) serious effects on human health, b) serious effects on the environment and c) additional effects. 1,4-dioxane has recently been proposed to be classified as Carcinogenic 1B by the Committee for Risk Assessment (RAC). The aim was to enable an objective and scientifically justified conclusion that these classes of substances have an equivalent level of concern for the environment and human health.

Results: In all of the categories related to human health, the environment and other effects, the PMT/vPvM case study substances exhibited comparable effects to PBT/vPvB substances. A difference in the human and environmental exposure pathways of PMT/vPvM and PBT/vPvB substances exists as they vary temporally and spatially. However, effects and impacts are similar, with PMT/vPvM substances potentially accumulating in (semi-)closed drinking water cycles and pristine aquatic environments, and PBT/vPvB substances accumulating in humans and the food chain. Both PMT/vPvM and PBT/vPvB substances share the common difficulty that long term and long-range transport and risk of exposure is very difficult to determine in advance and with sufficient accuracy.

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Conclusion: The registration process of substances under REACH should reflect that PMT/vPvM substances pose an equivalent level of concern to PBT/vPvB substances.

Keywords: Substance of very high concern, Regulation, Persistent, Mobile, Toxic, Article 57 (f), Per- and polyfluoroalkyl substances, Water, Bioaccumulative, Hazard

Background

Persistent, mobile and toxic (PMT) and very persistent and very mobile (vPvM) substances

For a chemical substance emitted into the environment to pose a threat to drinking water resources, it must be transported from the point of emission through natural barriers such as soils, riverbanks and aquifers, and in some cases through artificial barriers [1]. The time scales for this can vary from days, to weeks, to months and to years. Important factors controlling the overall threat are the scale of environmental emissions and whether the substance, or its transformation products, are sufficiently persistent in the environment and enough mobile in the aquatic environment to survive such a journey.

It is, therefore, clear that substances that are persistent in the environment, mobile in the aquatic environment as well as being toxic (PMT) or substances that are very persistent in the environment and very mobile in the aquatic environment (vPvM) have specific combinations of intrinsic substance properties that cause them to pose an inherent hazard to drinking water resources [2]. A persistent substance can be defined as one that remains in the same substance form in the environment over long periods of time. For regulatory standards, persistency is most often described as an inherent substance property: a degradation half-life in a given environmental media (e.g., air, water, soil, and/or sediment) under a specified set of environmental conditions (e.g., 12 °C [3]). A mobile compound is one that sorbs poorly to sediments and soils, resulting in a high potential to move and be transported through river banks, ground water and to drinking water extraction wells and remote aquatic ecosystems. Toxicity is a central consideration in chemical hazard and risk assessment and encompasses various modes of toxic action. It is most commonly described using hazard classification criteria and/or reported adverse human effects (e.g., carcinogenic, germ cell mutagenic, toxic for reproduction, etc.) [4].

There are many recent research developments and monitoring studies that have brought persistent and mobile substances to the forefront of worldwide scientific discussion [5–8]. As early as the 1990s, the scientific community realized the real hazard posed by persistent chemicals that are mobile in the aquatic environment [9–11]. These substance have previously gone by different acronyms: polar persistent pollutants (P³), polar

persistent organic pollutants (polar-POPs) [12] and persistent, mobile organic contaminants (PMOC) [11], but all terms describe the problematic intrinsic fate and hazard properties of persistence in combination with mobility. Neumann et al., [13] first presented the names persistent, mobile and toxic substances and very persistent and very mobile substances and the corresponding acronyms PMT and vPvM in 2015. Since then, the German Environment Agency has led efforts to establish criteria to identify PMT and vPvM substances under the EU chemicals regulation REACH (EC 1907/2006 Registration, Evaluation, Authorisation and Restriction of Chemicals) [2]. The similarity with the acronyms persistent, bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative (vPvB) is not accidental. It was designed to indicate from the outset the equivalency in the hazardous nature of these two sets of substances [2] and the necessity of the adoption of a hazard based regulation.

Many PMT/vPvM substances can breakthrough artificial barriers in waste water treatment plants (WWTP) [14] and drinking water treatment facilities, including through granular activated carbon (GAC) filtration, ultra-filtration, advanced oxidation processes (like ozonation) and reverse osmosis [15]. Stackelberg et al. [16] reported that even after clarification, disinfection (chlorination) and GAC filtration, many mobile substances were not effectively removed from WWTP. In their study, the removal of four mobile substances: *N,N*-Diethyl-metatoluamide, nonylphenol, camphor and bisphenol A varied between 25 and 76%. Substances that are even more persistent and mobile than these, would, by definition, more easily survive disinfection and breakthrough GAC filters in fewer bed volumes. This implies that in cases, where there are both ongoing emissions of PMT/vPvM substances and incomplete removal during water treatment, environmental concentrations will increase over time as these substances circulate in the water cycle [17] and potentially become irreversible [18, 19].

The unknown extent of PMT/vPvM substances in our water resources

The EU drinking water directive (98/83/EC, amended 2015/1787) has the objective "*to protect human health from the adverse effects of any contamination of water [...] by ensuring that it is wholesome and clean*". The EU's

groundwater directive (2006/118/EC) states, "*groundwater is a valuable natural resource and as such should be protected from [...] chemical pollution*". Moreover, the EU's water framework directive (2000/60/EC) states that "*member States shall ensure the necessary protection for the bodies of water identified with the aim of avoiding deterioration in their quality to reduce the level of purification treatment required in the production of drinking water*". Thus, ensuring that the sources of our drinking water are secure from any threats caused by chemicals is of the utmost importance.

The wider environmental problem related to PMT/vPvM substances is likely larger than it appears at first glance. There are many examples of substances that are ubiquitously detected in the water cycle that can be considered as PMT/vPvM substances [1], such as melamine [20], sulfanilic acid [21] and trifluoroacetic acid [22], but owing to their differences in terms of structure and sources, they are not conceptually linked in this way. An important concern for the most mobile substances are the so-called "analytical gap" and "monitoring gap" that exist. Current analytical measurements for the most mobile substances are not widely available (the "analytical gap") and thus many go unnoticed and undetected in the water cycle ("the monitoring gap"). However, progress has been made to address this analytical gap and methods such as hydrophilic interaction liquid chromatography [23], supercritical fluid chromatography [24], mixed-mode liquid chromatography [25] and capillary electrophoresis [26] have now made it possible to analyse some of the most mobile substances. This progress also contributes to closing the monitoring gap as more of the most mobile substances can be detected. However, a recent series of studies has demonstrated that the monitoring gap is still very prevalent. In the studies, the first ranked industrial substances based on their properties of persistency and mobility, [27] second selected some of the top 57 ranked PM substances based on high emissions likelihood and for which analytical methods were rare but could be developed, and third conducted monitoring in surface and groundwater samples throughout Europe [28]. Out of these 57 substances chosen based on these considerations, 43 PM substances were detected in environmental waters, 23 of which had never been reported previously (including near ubiquitous ones, like methyl sulfate, 2-acrylamino-2-methylpropane sulfonate, benzyltrimethylammonium, benzyltrimethylamine, trifluoromethanesulfonic acid, and 1,3-di-o-tolylguanidine [28]). These studies both directly demonstrated the ubiquity of PM substances and that the "monitoring gap" is a real issue. As a consequence of these two gaps the most mobile substances in the aquatic environment remain undetected, unmonitored and consequently unregulated

[23, 28]. It becomes clear that a more holistic approach is needed to protect water quality and monitor, assess and manage chemical pollution of European surface waters [29].

Recent regulatory advances of PMT/vPvM substances in Europe

In the 2017 report, "Study for the strategy for a non-toxic environment of the 7th Environment Action Programme", prepared by Directorate-General for Environment (European Commission) strong concerns were raised about persistent substances that are hydrophilic, and thus mobile in water, meaning they pose particular threats to the quality of water resources [30]. The report emphasized that mobility could be considered of equivalent concern to bioaccumulation. Regulatory advances for PMT/vPvM substances have also been taken into REACH. REACH aims to *ensure a high level of protection of human health and the environment*" (Article 1,1) and is *"underpinned by the precautionary principle"* (Article 1,3). REACH provides a legislative basis to investigate hazardous properties of chemicals before market [31, 32] Through REACH, it becomes the responsibility of registrants to characterize the intrinsic hazard of substances and the risk of each of their uses over the complete life cycle. Based on this input, the European Member States and the European Chemicals Agency (ECHA) can then assess whether registered substances fulfil the criteria to be identified as substances of very high concern (SVHC) following Article 57 of REACH. Listing a substance as a SVHC is one possible pathway for authorisation or restriction under REACH.

In 2019, two substances were identified as SVHC based on their equivalent level of concern (ELoC) to persistent, bioaccumulative and toxic and/or very persistent and very bioaccumulative (PBT/vPvB) substances. One of these substances, perfluorobutane sulfonic acid (and its salts, PFBS) was identified as a SVHC owing to "*very high persistence, high mobility in water and soil, high potential for long-range transport, and difficulty of remediation and water purification as well as moderate bioaccumulation in humans*". These properties combined led the Member State Committee (MSC) under REACH to conclude that there is a very high potential for irreversible effects [33, 34]. The second substance HFPO-DA, commonly referred to as Gen-X, was acknowledged by the MSC to have a high potential to cause effects on wildlife and humans due to its very high persistence, mobility in water, potential for long-range transport, accumulation in plants and previously observed effects on human health and the environment [35]. In this case, the MSC unanimously agreed that in isolation, these factors are not enough to give rise to ELoC, however, that

in combination, they show that there is scientific evidence of probable serious effects to the environment and humans. The same year, the organization ChemSec published an update of the SIN list (Substitute It Now list) and added a new category for PMT/vPvM substances [36]. This list is designed to flag substances they encourage industry to substitute for others and now includes 16 PMT/vPvM substances.

Methods

Based on the aforementioned identification of these two PMT/vPvM substances, this work investigated whether a general case could be made to show that all PMT/vPvM substances can be considered as ELoC to PBT/vPvB substances and as such identified as SHVC under REACH. To achieve this, categories were developed based on previous recommendations to identify SVHC under the 'equivalent level of concern' route (for example as has been done for skin sensitizers [37] and neurotoxics and immunotoxicants [38]).

These recommendations introduce four human health effect categories (i. possible serious health effects, ii. irreversibility of health effects, iii. delay of health effects, and iv. quality of life impacted), as well as two other effect factors (i. societal concern, and ii. is derivation of a safe concentration possible). To compare the ELoC of PMT/vPvM substances to PBT/vPvB substances, the assessment categories for human health were used directly; however, the other factor categories were altered and new categories were added. The other factors categories were changed to the following: (i. increased societal costs, (ii) negative effect on resources, and (iii) do emissions need to be minimized. Nine "environmental effect" categories were developed as follows: (i) irreversible exposure, (ii) irreversible effect, (iii) intergenerational exposure and effect, (iv) unknown/uncertain spatial scale, (v) disparity between point of release and point of effect, (vi) unknown/uncertain temporal scale, (vii) uncertain/difficult to predict long term fate and toxic effects, (viii) harmful to the aquatic environment, and, (ix) potential to reach remote pristine areas.

The development of these 16 categories covering health effects (4 categories), environment effects (9 categories) and other effects (3 categories) was aided by discussions and written consultations with a broad group of stakeholders during scientific and regulatory meetings and workshops. The following were of significance for the dialogue: the 16th meeting of ECHA's PBT expert group in September 2017, the Risk Management Expert Meeting in October 2017, the Society of Environmental Toxicology and Chemistry Europe Conferences in 2015, 2016, 2017, 2018 and 2020 and several workshops organised by the German Environmental Agency.

These 16 categories were then applied to three case study substances: PFBS, HFPO-DA and 1,4-dioxane. The first two substances were chosen due to their recent identification as SHVC and 1,4-dioxane owing to its listing in the public activities coordination tool (PACT) in 2019 for regulation under REACH. Following this, a general conceptual comparison using the defined categories was carried out to assess the ELoC between PMT/vPvM substances and PBT/vPvB substances.

Results and discussion

Case study I: Perfluorobutanesulfonic acid (PFBS) and its salts

PFBS belongs to the compound class of per- and polyfluoroalkyl substances (PFAS) that have a hydrophobic, alkylated, fluorine-saturated carbon-chain with a hydrophilic head attached at a terminal end [39]. A recent report has stated that over 4600 CAS registry numbers are associated with PFAS that may have been on the global market, including many that have at least one perfluoroalkyl moiety but were not commonly recognised as PFASs previously [40]. The use of PFAS has become more stringent in recent years, and currently C₁₁₋₁₄ perfluoroalkyl carboxylic acids (PFCAs), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorohexane sulfonic acid and its salts (PFHxS) are all under some form of regulation. As a result of this, long chain PFAS have been replaced with short chain PFAS. Short chain PFAS [41] are less bioaccumulative, but their high persistence, aquatic mobility [42] and unknown ecotoxicological effects renders them of concern. PFBS contains 4 carbon atoms and was introduced to market following the phase out of perfluorooctanesulfonic acid (PFOS) [43]. In water, PFBS is a strong acid which is predominantly dissociated as an anion.

In December 2019, PFBS and its salts were identified as SVHC in accordance with Article 57(f) based on scientific evidence of probable serious effects to the environment and human health which give rise to an ELoC to substances listed in Articles 57 (d) and (e) of REACH. Table 1 presents a summary of the argumentation agreed upon by the MSC [33, 34] to show that PFBS and its salts present an ELoC to PBT/vPvB substances.

REACH dossiers were used to prepare the table, and literature references to support statements can be found within these dossiers [33, 34]. Both the neutral and potassium salt forms have been registered under REACH (EC numbers 206–793-1 and 249–616-3, respectively).

Case study II: HFPO-DA (3:

2,3,3,3-tetrafluoro-2-(heptafluoropropoxy)propanoic acid) its salts and its acyl halides (tradename GenX)

HFPO-DA also belongs to the PFAS compound class and is used as a processing aid for producing fluoropolymers

Table 1 ELoC of PFBS (IUPAC name (1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-sulfonic acid) compared to PBT/vPvB substances

Criteria to assess	Case study 1: PFBS
Serious effects to human health Poses a threat to human health?	PFBS can easily pass through drinking water treatment facilities due to its low adsorption potential. This means that PFBS can enter and not be removed from the drinking water production chain and will pose a threat to human health via a permanent exposure through drinking water. PFBS has shown a high propensity to transfer and enrich in plants due to its high mobility in plant xylem and can, therefore, enter the human food chain. PFBS has been detected in blood samples from citizens from Italy, Sweden and China. In addition, it has been detected in tissue samples from lungs and kidneys from Spanish citizens. The observed probable serious effects for human health and the environment include thyroid hormonal disturbances and reproductive toxicity, and effects on liver, kidney and haematological system, hormonal disturbances and effects on reproduction and effects on expression of hormone receptors
Irreversible health effects?	Together the threats above lead to a very high potential for irreversible effects
Delayed health effects?	Long-term, low dose exposure may potentially lead to currently unexpected or even still unknown effects over longer time periods
Impaired quality of life?	Drinking water quality is compromised and the toxic effects mentioned above will impair quality of life
Serious effects to the environment Irreversible exposure?	PFBS has high potential for irreversible exposure. Based on experimental and quantitative structure–activity relationship (QSAR) results, the degradation of PFBS is very low or negligible. Exposures are not expected to decrease upon cessation of releases because of the high persistence of the substance. Degradation of other PFAS precursors constitutes a secondary source of PFBS which results in continued exposure. PFBS is also mobile in the aquatic environment. Thus, the very high persistence, together with low adsorption potential and high mobility, imply a very high potential for increasing environmental concentrations and potential irreversible exposures of wildlife and of humans via the environment
Irreversible effect?	Based on predicted continuous exposure, there will be an increasing and poorly reversible environmental background concentration which will accumulate in organisms until reaching an equilibrium. The permanent and irreversible exposure to organisms can lead to irreversible effects. Half-lives in the environment exceed half-lives in organisms
Intergenerational exposure and effect?	PFBS has been found to transfer from mother to offspring in humans, whales and in birds and may disturb development at sensitive life stages and in vulnerable populations. Thus, intergenerational effects can be assumed via a transport with breast milk from mother to child over generations
Unknown/uncertain spatial scale?	The high potential to cause very long-term exposures means it is difficult to quantify exposures with sufficient certainty. PFBS is very mobile and can spread to other environmental compartments rapidly, confirmed by its environmental distribution. PFBS has been frequently detected in fresh water, snow, ice and surface water close to point source releases and far from point source releases in marine water
Disparity between point of release and point of effect?	Prior to 2012, the majority of studies on arctic marine biota did not report PFBS above detection limits. However, in these earlier studies it is likely that the analytical detection limits were inferior to those today. Thus, in more recent studies this observation has been reversed showing that PFBS can migrate to areas far from the point of release and cause effects there. Future concentration levels are uncertain
Unknown/uncertain temporal scale?	The high global transport potential (characteristic travel distance (CTD) = 17,616 km, $P_{OV} = 220$ days), is demonstrated by detection of PFBS in samples of surface water, snow, ice, air and marine water from remote areas such as the Arctic and the Antarctic
Uncertain/difficult to predict long term fate and toxic effects?	Long-term, low dose exposure may potentially lead to currently unexpected or even still unknown effects
Harmful to the aquatic environment?	PFBS has been detected in marine (arctic and non-arctic) and freshwater biota throughout the world. PFBS meets the ecotoxicity threshold for the T criterion in Annex XIII of REACH (see above)

Table 1 (continued)

Criteria to assess	Case study 1: PFBS
Potential to reach remote pristine areas?	PFBS has a high global transport potential and is already globally distributed (oceans, soil, biota) including in remote pristine areas (arctic, Antarctic). PFBS has been reported in atmospheric samples at trace levels throughout the world, though mostly in rain. The tendency for PFBS to prefer water to air (based on the K_{aw} value), means that air emissions are likely prone to wet deposition by partitioning with clouds and rain droplets. This serves as a mechanism for transport from one area to another
Other effects	
Increased societal costs?	Short and long term negative effects on human health present costs for society. The cost of breaking the C-F bond in PFBS is high and requires a lot of energy. There are few technically feasible methods for the remediation of PFBS contaminated water. Drinking water analysed for PFBS in areas near and far removed from PFAS source zones report the ubiquitous presence of PFBS. The effects on human health above also result in an increased societal cost, for example through increased healthcare demands. These factors combined pose a high societal cost, currently estimated to be 100 s of millions of Euros for PFAS contaminated soil across Europe [44]
Negative effect on resources?	There are very few methods that can be used to treat water on the larger scale. PFBS accumulates in the food chain. These factors demonstrate negative effects on resources
Do emissions need to be minimized?	The consequences of an underestimation of adverse effects are not easily reversible by regulatory action. Even if there is immediate regulatory action to prevent further emission, the adverse effect will continue. Regulatory action can eliminate point source emissions, but they have no influence on what has already been emitted. Environmental redistribution will continue for decades and background levels will keep increasing

with many applications, such as fluoropolymer resins, wire cables and coatings. The production history and volumes of HFPO-DA are unknown, although it has been suggested that production began in 2009 [45]. HFPO-DA was first detected in environmental samples from the Cape Fear River, North Carolina in 2018, likely from a point source release from a production plant [46]. HFPO-DA has also been detected in other countries in relation to known local production and use. HFPO-DA has been detected in the Xiaoqing River System in China [47], in America [48], in the Lower Rhine River [47] and in rivers in close proximity to a production plant in the Netherlands [49].

QSAR modelling and ready or inherent biodegradability tests have shown that HFPO-DA does not exhibit any primary biodegradation, is not readily or inherently biodegradable and is not structurally transformed under the experimental test conditions. Experimental data is limited, and the bioaccumulation potential of HFPO-DA is uncertain. HFPO-DA has a very low adsorption potential to organic carbon and other solids and a low volatility meaning it has a highly mobility in the aquatic environment and can be transported to areas far from the point of release. According to the classification and labeling in accordance with the CLP Regulation (Regulation (EC) 1272/2008), HFPO-DA has the hazard classifications Acute Toxicity 4, Skin Corrosion/Irritation 1B, Eye

Damage/Irritation 1, and specific target organ toxicity – single exposure (STOT SE) 3.

In June 2019, HFPO-DA and its salts were identified as SVHC in accordance with Article 57(f). The MSC acknowledged that HFPO-DA has a high potential to cause effects in wildlife and in humans through the environment due to its very high persistence, mobility in water, potential for long-range transport, accumulation in plants and observed effects on human health and the environment. Table 2 presents the argumentation used by the MSC to show how HFPO-DA present an ELoC to PBT/vPvB substances [35].

REACH dossiers were used to prepare the table, and literature references to support statements can be found within these dossiers [35].

Case Study III: 1,4-dioxane CAS No. 123–91–1

1,4-dioxane has a plethora of uses. It is a solvent in the production of lacquers, varnishes, cleaning and detergent preparations, dyes, antifreeze, adhesives, cosmetics, deodorant fumigants, shampoos, emulsions and polishing compositions, polyester manufacturing, pulping of wood, extraction medium for animal and vegetable oils, laboratory chemical (eluent in chromatography), cassettes, plastic and rubber, insecticides as well as a stabilizer for 1,1,1-trichloroethane [7, 50] 1,4-dioxane is prevalent in groundwater at industrial due to its historic use as a

Table 2 ELoC of HFPO-DA compared to PBT/vPvB substances

Criteria to assess	Case study 2: HFPO-DA
Serious effects to human health Poses a threat to human health?	There is evidence that the general population can be exposed to HFPO-DA via several routes including drinking water, locally emitted air, home grown fruits and vegetables, plants and fish. Removal from water is very difficult and current methods are likely insufficient to achieve removal. Observed effects in rodents' liver, kidney, haematological system, immune system and related to development can be a cause of concern for humans. Due to the positive response in a rodent carcinogenicity study (i.e., pancreatic-, liver- and testis tumours), HFPO-DA could be a possible human carcinogen
Irreversible health effects?	HFPO-DA adversely impacts human health at a daily intake that could be as low as 21 ng/kg bw/day (tTDI). HFPO-DA has been found in the serum of residents living close to a fluorochemical plant in China, and in the blood of employees from a fluorochemical production plant in the Netherlands
Delayed health effects?	The effect on human health may come with a possible delay between exposure and the onset of any observable adverse effect (i.e., cancer). In addition, health effects may also be relevant for short-term exposure (i.e., immune effects, haematological effects, liver effects, kidney effects)
Impaired quality of life?	The evidence above shows that there are serious health effects that can be felt based on already released HFPO-DA and future emissions. Water sources will be compromised, pollution must be remediated, and both affect quality of life
Serious effects to the environment	
Irreversible exposure?	The high persistence and chronic background concentrations of HFPO-DA implies that there is a continuous and irreversible exposure once chemicals are released in sufficient quantities to aquatic resources. Exposures are not expected to decrease upon cessation of releases because of the high persistence of the substance. Current lack of water treatment methods results in irreversible exposure
Irreversible effect?	The very persistent and very mobile nature of HFPO-DA means that a cessation of emissions will not necessarily result in a reduction in concentration. Observed adverse effects on humans and current information on toxicity shows that effects can be considered irreversible. Chronic background concentrations result in continuous exposure that may also lead to the irreversibility of adverse effects
Intergenerational exposure and effect?	Cessation of emissions will not necessarily result in a reduction in substance concentration and continuous exposure over very long times can lead to inter-generational effects that will impact the quality of life and are of high societal concern. Due to the high persistence and lack of biodegradation, exposure in aquatic media will remain over multiple generations. As such, effects of current emissions may be observed or only become apparent in next generations
Unknown/uncertain spatial scale?	The high persistency and the high mobility of HFPO-DA lead to long distance transport processes in the environment. HFPO-DA has been reported to have been transported over a distance of at least 1700 km after its emission from the Rhine Meuse delta into the North Sea. The high mobility in the aqueous environment means it can spread to other environmental compartments rapidly and is transported by sea currents and via air. Observed concentrations in disconnected water bodies, soil and ground water are linked to subsequent wet and dry deposition of HFPO-DA after emission to air
Disparity between point of release and point of effect?	Due to the potential for wide spread distribution and long-range transport of HFPO-DA, effects will not only occur at the point of release but also far away from its point of release
Unknown/uncertain temporal scale?	There is a current lack of information and thus uncertainty related to the temporal scale of effects of HFPO-DA based on its more recent introduction to the market
Uncertain/difficult to predict long term fate and toxic effects?	The very high persistency of the substance and the current uncertainties in bioaccumulation make long term fate and toxic effects difficult to predict and widely unknown
Harmful to the aquatic environment?	HFPO-DA has been observed in multiple water bodies around the world as it is highly mobile and spreads with water. It has been detected in surface water, raw water and drinking water. HFPO-DA has been observed in fish from China, the USA and the Netherlands. The co-exposure of HFPO-DA with other contaminants including other very persistent fluorochemicals such as PFOA, perfluorohexanoic acid (PFHxA) and PFBS present in the environment lead to possible combination effects. The demonstrated effects on humans and biota, combined with the compromised effect on water, render HFPO-DA harmful to the aquatic environment

Table 2 (continued)

Criteria to assess	Case study 2: HFPO-DA
Potential to reach remote pristine areas?	The potential for long range transport modelled using the Long-Range Transport Tool resulted in a characteristic travel distance of 8682 km. This indicates that HFPO-DA can reach any area in the world before any significant amount of substance degradation has occurred. Current fate modelling suggests the water compartment to be the main residence compartment
Other effects	
Increased societal costs?	The continuous long-term exposure of humans can impact quality of life and is of high societal concern. Irreversible concentrations in the environment will, furthermore, lead to inter-generational effects. Intrinsic chemical properties mean that there is a lack of drinking water treatment methods able to remove HFPO-DA which must be developed and paid for by society
Negative effect on resources?	There are few methods that can be used to treat water on the larger scale. This presents a negative effect on resources. No significant removal capacity was demonstrated in the different steps of the drinking water treatment process in a drinking water treatment plant. Water was sampled after each step in the purification process (raw water, ozonation, coagulation/flocculation/sedimentation, settled water ozonation, biological activated carbon filtration, and disinfection by medium-pressure UV lamps and free chlorine)
Do emissions need to be minimized?	The intrinsic properties mean that emission reduction mitigation measures are needed and current spreading and toxic effects on affected populations may be difficult to reverse

stabilizer [51] and in sewage water resulting from consumer use of surfactants.

1,4-dioxane is non-volatile with a very low Henry's Law constant (4.8×10^{-6} atm·m³/mol at 25 °C). However, 1,4-dioxane has a high water solubility (100 mg/mL), a low octanol–water partitioning coefficient (log Kow = −0.27) and adsorbs only weakly to organic matter with a log Koc of 0.42 [50]. 1,4-dioxane has a half life of 2 to 5 years in groundwater and 56 days in surface water highlighting the persistent nature of this substance [52]. Taken together these properties imply that 1,4-dioxane is readily leached into water systems and transport through even subsurface environment, which has been demonstrated by point-source releases of 1,4-dioxane causing plumes which have the potential to contaminate both nearfield and distal water bodies [53].

1,4-dioxane is currently listed with the hazard classes under the Classification and labelling in accordance with the CLP Regulation: "Flammable liquids 2", "Carcinogenic 2", "Eye Damage/Irritation 2", and "STOT SE 3". In addition, a recent opinion from the Committee for Risk Assessment (RAC) has proposed that 1,4-dioxane should be classified as Carcinogenic 1B [50]. The properties suspected of causing cancer, may cause respiratory inhalation and causes serious eye irritation are properties of ecotoxicological concern. Table 3 shows the ELoC of 1,4-dioxane to PBT/vPvB substances.

PBT/vPvB substances as precedent for the identification of PMT/vPvM substances under REACH

When concerns were raised about the identification and unintended ecotoxicological effects of DDT [66] and the detection of PCBs in top predators [67] it became clear that such PBT/vPvB substances can reach threshold concentrations at which (eco)toxic effects occur, unless emissions are controlled or minimized. Since then, PBT/vPvB substances have been included in a large amount of regulation [4] including REACH. Annex XIII provides criteria to be used to identify PBT/vPvB substances and these should be applied to all substances manufactured or produced at 10 or more tonnes per year and for all constituents present greater than 0.1% (though certain substances are exempted, such as isolated intermediates, as described in Article 14(2)). In ECHA's PBT/vPvB guidance it is stated that: "*PBT or vPvB substances may have the potential to contaminate remote areas that should be protected from further contamination by hazardous substances resulting from human activity because the intrinsic value of pristine environments should be protected*" [...] "*the effects of such accumulation are unpredictable in the long-term*" [...] "*such accumulation is in practice difficult to reverse as cessation of emission will not necessarily result in a reduction in substance concentration*" [68]. PBT/vPvB substances have also been acknowledged to present a planetary boundary threat if released in substantial quantities, as their removal from the environment can be irreversible [69].

The same is true for PMT/vPvM substances; however, there is a regulatory gap in REACH to address

Table 3 ELoC of 1,4-dioxane compared to PBT/vPvB substances

Category to assess	Case study III: 1,4-dioxane
Serious effects to human health Poses a threat to human health?	Exposure to 1,4-dioxane occurs through ingestion of contaminated water and food, dermal contact or inhalation of vapours. Mobility of 1,4-dioxane means reaching drinking water sources is highly likely. Ingestion of 1,4-dioxane through drinking water is the dominant pathway of exposure [54, 55]. Previously reported that over 25% of the American population received drinking water with concentrations of 1,4-dioxane that were above the recommended guideline value for human ingestion [52]. In addition, 1,4-dioxane has been proposed as Carcinogenic 1B [50]
Irreversible health effects?	1,4-Dioxane is classified for carcinogenicity in Annex VI of regulation (EC) No 1272/2008 as follows: Carc 2 (suspected human carcinogen; H351: suspected of causing cancer). CLP classification as Eye Irrit. 2 (causes serious eye irritation) and STOT SE 3 (may cause respiratory irritation after a single exposure) and Carc 2. The suspected human carcinogen is based on evidence from experimental animal studies. Organ systems primarily affected by 1,4-dioxane include the liver and kidneys. Adverse nasal and ocular effects have also been reported [56, 57]. Taken together, these various concerns can lead to a high potential of irreversible effects
Delayed health effects? Impaired quality of life?	Chronic exposure is reported leading to effects that are felt long after the release [58] Drinking water quality compromised in addition to aforementioned health effects
Serious effects to the environment Irreversible exposure?	Recognized as a recalcitrant to biodegradation, based on the evidence " No significant biodegradation in 301F test" and QSARs that consistently predict persistence [1, 59]. Dioxane is considered to have been an emerging compound for the last 40 years [58]
Irreversible effect?	Chronic background concentrations result in continuous exposure that may also lead to the irreversibility of adverse effects. Mixture effects are likely [51]
Intergenerational exposure and effect?	Half-lives of 2–5 years have been reported for ground water and 56 days reported for surface water, implying long releases from ground water plumes long after the time of release could occur [52]
Unknown/uncertain spatial scale?	1,4-dioxane has a high solubility (100 mg/mL), low octanol–water partitioning coefficient ($\log K_{ow} = -0.27$) and weak adsorption into mineral phases and onto organic matter [50]. These intrinsic properties result in a high mobility and rapid spreading to different environmental compartments and from soil to water. This is highlighted by the ubiquitous presence of 1,4-dioxane in groundwater [60], drinking water, wastewater effluents, river water [61], oceans [62] surface water [54] and bank filtrate [63]. 1,4-dioxane has been detected in Japanese, Canadian, American and European waters
Disparity between point of release and point of effect?	As observed from monitoring studies, chronic background concentrations result in continuous exposure that may also lead to the irreversibility of adverse effects
Unknown/uncertain temporal scale?	High quality groundwater and surface models to predict advective–dispersive transport and reactions that transform and immobilize contaminants over large temporal and spatial domains have not yet been used for 1,4-dioxane in groundwater due to the absence of data required to accurately quantify mass transfer and complex transformations diverse types of subsurfaces [64]
Uncertain/difficult to predict long term fate and toxic effects?	Long-term, low dose exposure through ground water and drinking water, which has been documented, may potentially lead to unexpected or even still unknown effects
Harmful to the aquatic environment?	Does not appear to meet the ecotoxicity threshold of Annex XIII of REACH. However, co-occurrence with other chlorinated solvents is very often reported, and therefore, mixture toxicity effects cannot be ruled out [52]. Furthermore, treatment by chlorination can lead to the formation of the chlorinated byproducts that are more toxic than the parent 1,4-dioxane [64]
Potential to reach remote pristine areas?	Half lives of 2 to 5 years have been reported for ground water and 56 days reported for surface water [52]. This combined with a $\log K_{oc}$ of 0.5 implies that in ground water it moves just as quickly ground water itself, particularly if there is little organic carbon content. Therefore, dioxane can be transported for several decades at the speed of groundwater or bank filtrate before degrading to trace amounts from original emissions
Other effects Increased societal costs?	The ubiquitous occurrence of 1,4-dioxane in water and the intrinsic hazardous properties of this substance mean that society will bear a cost of healthcare that is needed following exposure. The mobility and difficulty of removing 1,4-dioxane from drinking water also implies costs

Table 3 (continued)

Category to assess	Case study III: 1,4-dioxane
Negative effect on resources?	There are few methods that can be used to treat water on the larger scale. This presents a negative effect on resources. Even expensive techniques, such as air stripping or adsorption by activated carbon, are unsuitable. Removal by membrane filtration is also ineffective; even reverse osmosis fails to reach higher than 70% rejection due to its small size and neutrality [65]. These physical removal processes, even if they are effective, simply transfer 1,4-dioxane from one phase to another, wherein it is more concentrated and requires subsequent treatment
Do emissions need to be minimized?	The intrinsic properties mean that emission reduction mitigation measures are needed and current spreading and toxic effects on affected populations may be difficult to reverse

Details shown are based on a literature review and the CLP classification of 1,4-dioxane [50]

these substances. The case studies above show that PMT/vPvM substances have an ELoC to PBT/vPvB substances due to the scientific evidence of probable serious effects to human health or the environment. The difference between these substance groups is their exposure route. In cases, where emissions are continuous, mobile substances can accumulate in (semi-) closed drinking water cycles as waste water is recycled to drinking water and as well as in pristine remote environments, far from the site of release, via surface water and groundwater transport. Similarly, under prolonged emissions, bioaccumulative substances are able to accumulate in the food chain and also in pristine remote environments via migrating biota and in some cases atmospheric transport [70]. For both PMT/vPvM and PBT/vPvB substances, the long term and long-range transport and risk of exposure is very difficult to determine in advance and with sufficient accuracy. Owing to the complex nature of water systems and food chains as well as a lack of modelling tools, risks posed by these substances are most often identified retrospectively. In addition, reversing emissions (and, therefore, effects) is difficult due to the high persistence of these substances. Reservoirs of emitted substances in commercial products, landfills, polluted soil and aquifers, for instance, can act as continuous sinks to the environment over long time scales. Thus, there is the potential for risks to persist over multiple generations. In extreme cases, where exposure of either PMT/vPvM or PBT/vPvB substances reaches harmful levels, such as chronic toxicity, they would pose irreversible health and environmental effects that could result in impaired quality of life or ecosystem function. Releases of both PMT/vPvM and PBT/vPvB substances places pressure on society from an economic and resource point of view, since a cessation of emissions does not necessarily lead to a reduction in

concentrations in the long term. Based on this, Table 4 provides a summary of the criteria that can be used to demonstrate that all PMT/vPvM substances can be considered an ELoC as PBT/vPvB substances, and as such should be identified as SVHC under Article 57(f).

Conclusion

The conceptual comparison using the 16 categories developed here supports the assumption that PMT/vPvM substances cause an equivalent level of concern as PBT/vPvB substances and as such should be regulated under Article 57 in REACH. Currently this can be done using Article 57 (f) as shown above, or it could be achieved via the introduction of two new articles: Article 57 (g) for PMT substances and Article 57 (h) for vPvM substances. At the time of writing, a Motion for Resolution has been put forward by the European Parliament for such an inclusion [71]. For practical guidance towards this inclusion, the German Environment Agency has recently published criteria and an assessment procedure that can be used under REACH to identify PMT/vPvM substances [2]. These criteria could be added to Annex XIII of REACH and used by ECHA to publish a Guidance on Information Requirements and Chemical Safety Assessment for a PMT/vPvM assessment. Using these established PMT/vPvM substance criteria in Article 57 and Annex XIII would allow the distinct and unambiguous identification of PMT/vPvM substances as SVHCs. This would provide the chemical industry with a defined framework to follow, as for PBT/vPvB substances, and would allow the substitution of hazardous substances and uses under REACH.

Abbreviations

B: Bioaccumulative; BAF: Bioaccumulation factor; BCF: Bioconcentration factors; CLP: Classification, labelling and packaging regulation; CMR: Carcinogens, mutagens and/or reproductive toxicants; CTD: Characteristic travel distance;

Table 4 Conceptual comparison showing that PMT/vPvM substances pose an equivalent level of concern as PBT/vPvB substances

Criteria to assess	PBT/vPvB	PMT/vPvM
Serious effects to human health	Yes	Yes
Poses a threat to human health?	Accumulation in the food chain (exposure route)	Accumulation in the water cycle (exposure route)
Irreversible health effects?	Yes Substances can bioaccumulate in humans; chronic and acute effects possible	Yes The continuous human exposure through drinking water intake and continuous remote aquatic ecosystem exposure due to mobility and over long time scales means chronic and acute effects are possible
Delayed health effects?	Yes Substances can continue to accumulate in humans long after emissions have ceased, causing chronic exposure effects to become more evident with time/age	Yes Exposure may occur even long after emissions have ceased, causing chronic exposure effects to become more evident with time/age
Impaired quality of life?	Yes Health effects (chronic or not) can impair quality of life	Yes Health effects (chronic or not) can impair quality of life, including fouling of drinking water (taste, odour, etc.)
Serious effects to the environment	Yes	Yes
Irreversible exposure?	Once the contamination is in the environment it cannot be removed and impacts cannot be mitigated by reducing pollution levels. Emissions from contaminated areas can be ongoing long after phase-out	Once the contamination is in the environment it cannot be removed, particularly due to the lack of water treatment facilities. Emissions from contaminated areas can be ongoing long after phase-out
Irreversible effect?	Yes Both chronic and acute irreversible effects possible, depending on toxic profile	Yes Both chronic and acute irreversible effects possible, depending on toxic profile
Intergenerational exposure and effect?	Yes Effects are long term and felt over more than one generation due to persistency, such as exposure through lactation and food chain uptake	Yes Effects are long term and felt over more than one generation due to persistency, such exposure through lactation and exposure to the same aquatic media
Unknown/uncertain spatial scale?	Yes Bioaccumulation within the trophic food chain in an environmental compartment has complex dynamics	Yes Able to spread within aquatic compartments (such as ground water or surface water) to other environmental aquatic compartments relatively rapidly or over long distances
Disparity between point of release and point of effect?	Yes Release occurs at one point and effects are felt at different trophic food chain levels	Yes Release occurs at one point and effects are felt following transport to a new aquatic environmental compartment
Unknown/uncertain temporal scale?	Yes Long term effects unknown	Yes Long term effects unknown
Uncertain/difficult to predict long term fate and toxic effects?	Yes Long term fate unknown Long term toxic effect unknown Quantitative environmental risk assessment and a safe environmental concentration cannot be performed or defined	Yes Long term fate unknown Long term toxic effect unknown Quantitative environmental risk assessment and a safe environmental concentration cannot be performed or defined

Table 4 (continued)

Criteria to assess	PBT/vPvB	PMT/vPvM
Harmful to the aquatic environment?	<p>Yes</p> <p>Far reaching effects (spread with aquatic biota and long-range transport)</p> <p>Effects on top predators of particular concern</p> <p>Low effect concentrations to aquatic organisms possible</p> <p>Mixture toxicities effects with other stressors cannot be ruled out</p>	<p>Yes</p> <p>Far reaching effects (spread directly via water)</p> <p>Can affect all aquatic trophic levels due to similar exposure</p> <p>Low effect concentrations to aquatic organisms possible</p> <p>Mixture toxicities effects with other stressors cannot be ruled out</p>
Potential to reach remote pristine areas?	<p>Yes</p> <p>Particulate and biota assisted transport within water bodies and atmosphere</p>	<p>Yes</p> <p>Transport across water bodies to pristine oceans, ground water or pristine lakes and watersheds</p>
Additional effects	<p>Yes</p> <p>Cost implications for society in terms of healthcare</p> <p>Cost implications for society in terms of harm to wider environment, e.g., contaminated land and sediment remediations</p>	<p>Yes</p> <p>Cost implications for society in terms of healthcare</p> <p>Cost implications for society in terms of harm to wider environment, e.g., contaminated soil and groundwater remediation</p> <p>Cost implications for drinking water treatment</p>
Increased societal costs?	<p>Yes</p> <p>Food resources impaired via uptake in the food chain</p> <p>Land and sediment polluted by such substances comprised</p> <p>Potential impact on product recycling and the circular economy due to such substances impacting food resources</p>	<p>Yes</p> <p>Drinking water quality impaired (including taste, odour, resources for remediation having unfavourable outcomes)</p> <p>Makes recycling wastewater more problematic and expensive</p> <p>Land, ecosystem services and groundwater polluted by such substances and compromised</p> <p>Potential impact on product recycling and the circular economy, due to products with such substances contaminating water resources-</p>
Negative effect on resources?	<p>Yes</p> <p>Mitigation measures must be put into place</p> <p>Accumulation in biota and toxic effects difficult to reverse</p>	<p>Yes</p> <p>Mitigation measures must be put into place</p> <p>Impacts on the drinking water sources and pristine ecosystems difficult to reverse</p>
Do emissions need to be minimized?		

ECHA: European Chemicals Agency; EDC: Endocrine disrupting compounds; ELoC: Equivalent level of concern; EU: European Union; GAC: Granular activated carbon; GC: Gas chromatography; HFPO-DA: 2,3,3,3-Tetrafluoro-2-(heptafluoropropoxy)-propanoic acid; LOEC: Lowest observed effects concentration; M: Mobile; MTBE: Methyl tert-butyl ether; MSC: Member State Committee; NOEC: No observed effects concentration; P: Persistent; PBT: Persistent, bioaccumulative and toxic; PFAS: Per- and polyfluoroalkyl substances; PFBS: Perfluorobutane sulfonic acid; PFCA: Perfluoroalkyl carboxylic acid; PFHxA: Perfluorohexanoic acid; PFOA: Perfluorooctanoic acid; PFOS: Perfluorooctanesulfonic acid; PFNA: Perfluorononanoic acid; PMT: Persistent, mobile and toxic; REACH: Registration, Evaluation, Authorization and Restriction of Chemicals; RPLC: Reverse phase liquid chromatography; STOT RE: Specific target organ toxicity—repeat exposure; STOT SE: Specific target organ toxicity (single exposure); SVHC: Substance of very high concern; T: Toxicity; vB: Very bioaccumulative; vP: Very persistent; vPvB: Very persistent and very bioaccumulative; vPvM: Very persistent and very mobile; WWTP: Wastewater treatment plant; QSAR: Quantitative structure activity relationship.

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Authors' contributions

SH and MN conceived the idea. SH, HPHA, MN, IS all contributed to the writing. All authors read and approved the final manuscript.

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Competing interests

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