Grouping strategies for assessing and managing persistent and mobile substances

Parviel Chirsir*[1], Emma H. Palm[1], Sivani Baskaran[2], Emma L. Schymanski*[1], Zhanyun Wang[3], Raoul Wolf[2], Sarah E. Hale[4] and Hans Peter H. Arp*[2,5]

[1] Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, 6 avenue du Swing, 4367, Belvaux, Luxembourg

[2] Department of Environmental Engineering, Norwegian Geotechnical Institute, NO-0806 Oslo, Norway

[3] Technology and Society Laboratory, Empa – Swiss Federal Laboratories for Materials Science and Technology, 9014 St. Gallen, Switzerland

[4] TZW: DVGW-Technologiezentrum Wasser (German Water Centre), Karlsruher Straße 84, 76139 Karlsruhe / Germany

[5] Department of Chemistry, Norwegian University of Science and Technology (NTNU), NO-7491 Trondheim, Norway

* Corresponding authors

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ORCIDs:

PC: 0000-0002-9932-8609, EHP: 0000-0001-7774-2510, SB: 0000-0001-6192-5072, ELS:0000-0001-6868-8145, ZW:0000-0001-9914-7659, RW: 0000-0001-5971-8525, SEH: 0000-0002-7743-9199, HPHA: 0000-0002-0747-8838

Abstract

Background: Persistent, Mobile and Toxic (PMT), or very Persistent and very Mobile (vPvM) substances are a wide class of chemicals that are recalcitrant to degradation, easily transported, and potentially harmful to humans and the environment. Due to their persistence and mobility, these substances are often widespread in the environment once emitted, particularly in water resources, causing increased challenges during water treatment processes. Some PMT/vPvM substances such as GenX and perfluorobutane sulfonic acid have been identified as substances of very high concern (SVHCs) under the European Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation. With hundreds to thousands of potential PMT/vPvM substances yet to be assessed and managed, effective and efficient approaches that avoid a case-by-case assessment and prevent regrettable substitution are necessary to achieve the European Union's zero-pollution goal for a non-toxic environment by 2050.

Main: Substance grouping has helped global regulation of some highly hazardous chemicals, *e.g.*, through the Montreal Protocol and the Stockholm Convention. This article explores the potential of grouping strategies for assessing and managing PMT/vPvM substances. It provides an overview of PMT/vPvM substances and reviews the definition of PMT/vPvM criteria and various lists of PMT/vPvM substances available. It covers the current definition of groups, compares the use of substance grouping for hazard assessment and regulation, and discusses the advantages and disadvantages of grouping substances for regulation. The article then explores strategies for grouping PMT/vPvM substances, including read-across, structural similarity and commonly retained moieties, as well as the potential application of these strategies using cheminformatics to predict P, M and T properties for selected examples.

Conclusion: Effective substance grouping can accelerate the assessment and management of PMT/vPvM substances, especially for substances that lack information. Advances to read-across methods and cheminformatics tools are needed to support efficient and effective chemical management, preventing broad entry of hazardous chemicals into the global market and favouring safer and more sustainable alternatives.

Background

In 2019 water pollution was estimated to cause 1.4 million premature deaths globally [1]. Improving water quality by reducing pollution is also defined as one of the tasks in the Sustainable Development Goals [2]. Meanwhile, the number of known chemicals that are in use is increasing dramatically. Over 350,000 chemicals and mixtures have been registered in the global market over the past 50 years [3], while the largest chemical databases contain over 100 million chemicals, with PubChem [4] and the Chemical Abstracts Service (CAS) registry containing 116 million [5] and 219 million [6] chemicals, respectively, as of January 2023. Chemical production and pollution are outpacing global assessment capacity, posing more risks to human health, wildlife, and the environment [7, 8]. In 2021, about 224.8 and 86.4 million tonnes of chemicals hazardous to human health and the environment, respectively, were consumed in the European Union (EU) [9]. Many of these hazardous chemicals are persistent, mobile and toxic (PMT) substances or very persistent and very mobile (vPvM) substances, collectively referred to as PMT/vPvM substances.

PMT/vPvM substances have been listed by the European Commission's Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) as one of the 14 emerging problems that could impact human health or the environment [10]. These substances do not degrade in the environment over an appreciable timescale and are easily transported through water and aquatic ecosystems due to poor sorption to soil and sediments [11–13]. PMT/vPvM substances can be found in a wide range of applications and sources, including in industrial processes, fire-fighting foams, and consumer products such as food, cosmetics and furniture [14]. They can cause long-term harm to humans and the environment and are also costly and difficult to remove from drinking water [15–18]. PMT/vPvM substances have been suggested to have an equivalent level of concern as persistent, bioaccumulative and toxic (PBT) substances or very persistent and very bioaccumulative (vPvB) substances. GenX and perfluorobutane sulfonic acid (PFBS), both PMT/vPvM substances, have been identified as substances of very high concern (SVHCs) under the European Registration, Evaluation, Authorisation and Restriction of Chemicals REACH regulation (EC 1907/2006) [11]. Furthermore, due to the high mobility of PMT/vPvM substances, many of them can break through artificial barriers in wastewater treatment plants, including granular activated carbon filtration and ultrafiltration systems, posing challenges for removal and remediation [11, 19]. These substances can be further transported through natural media such as soils, riverbanks, aquifers and groundwater, making them hard to contain and remove from the

environment. As such, these substances are problematic in drinking water, and many are detected frequently in European surface waters [11]. For example, 1,4-dioxin was found in Bavarian surface waters [20] and melamine in the Netherlands, France and Belgium [21].

Developing and applying substance grouping strategies is one way to manage and regulate PMT/vPvM substances more effectively. There are two main motivations for a substance grouping approach. The first is to expedite hazard assessments related to the large number of substances being introduced to the global chemical market. The second is to avoid regrettable substitution caused by drop-in substitution [22], where one substance is replaced by another with similar hazardous properties and effects [23]. Thus, this paper aims to explore grouping strategies to manage PMT/vPvM substances. It provides an overview of PMT/vPvM substances, including scoping the numbers of substances covered by existing definitions, reviewing previous successful grouping strategies, and determining the relevance of grouping strategies in the context of PMT/vPvM substances while exploring the future efforts required to achieve this effectively.

Definition of key terms

The International Union of Pure and Applied Chemistry (IUPAC) defines a chemical substance as "*matter of constant composition best characterized by the entities (molecules, formula, units, atoms) it is composed of. Physical properties such as density, refractive index, electric conductivity, melting point etc. characterize the chemical substance*" [24]. The term "substance" in this article is used in this context. Databases also refer to chemical entities as compounds and substances, but the context may be different. PubChem, for instance, define these as "*a substance is a chemical sample description provided by a single source and a compound is a normalized chemical structure representation found in one or more contributed substances*" [25]. Since this article later refers to calculations performed on PubChem queries, "compound" in this article refers to a chemical that fulfils the definition of a compound according to PubChem with a unique PubChem Compound Identifier (CID). A mixture, according to IUPAC, is a "*portion of matter consisting of two or more chemical substances called constituents*" [26]. Mixtures can be simple (*e.g.*, xylene is a mixture of three isomers, *o*-xylene, *m*-xylene and *p*-xylene) or complex (*e.g.*, C_9-C_{14} alcohols, or mineral oils). The latter are often referred to as "substances of Unknown or Variable composition, Complex reaction products or Biological origin" (UVCBs) [27].

A group of substances may be defined as substances that are similar in structure, have similar physicochemical properties, toxicological properties, applications, or environmental fate, or follow a consistent pattern (*e.g.*, common precursors and/or degradation products) [28, 29]. For example, PMT substances are groups of chemicals that have similar properties of persistence and mobility and are toxic to human health and the environment. One group can already contain a large variety or a combination of chemical structures and properties. Two widely regulated groups of substances are dioxins (polychlorinated dibenzo-p-dioxins and polychlorinated dibenzo-furans) [30] and polychlorinated biphenyls (PCBs) [31], which are composed of about 210 [32] and 209 individual congeners, respectively [33].

Overview of PMT/vPvM Substances

Assessment of the number of substances being introduced to the global chemical market that may be PMT/vPvM substances requires a clear set of criteria and the ability to scale the application of these criteria to large numbers. The EU Chemicals, Labelling and Packaging (CLP) regulation (EC 1272/2008) criteria for PMT/vPvM substances [34] are displayed in Figure 1. The ***mobility*** (M) aspect (see Figure 1A) is defined based on the organic-carbon-water partition coefficient (K_{OC}, with units of L/kg) of a chemical which is then log transformed to log K_{OC} values. Since experimental log K_{OC} data are rare, it was suggested that the logarithmic octanol-water partition coefficient (log K_{OW} or log P) or the pH-adjusted log D_{OW} (or log D) could be used as a screening parameter where high-quality log K_{OC} data are not available [35, 36]. As such they are often used in a complementary fashion, where log K_{OW} and log D_{OW} data are used when log K_{OC} data are unavailable. ***Persistence*** (P) is defined based on the half-lives of a chemical in different environmental water and sediment systems (see Figure 1B), and ***toxicity*** (T) is defined based on multiple endpoints such as carcinogenicity, mutagenicity, and reproductive toxicity, shown in Figure 1C.

A compound that meets each of the persistence, mobility and toxicity criteria may be classified as PMT, or vPvM if both the very persistent (vP, see Figure 1B) and very mobile (vM, see Figure 1A) criteria are met. Some examples of PMT/vPvM substances are shown in Figure 2.

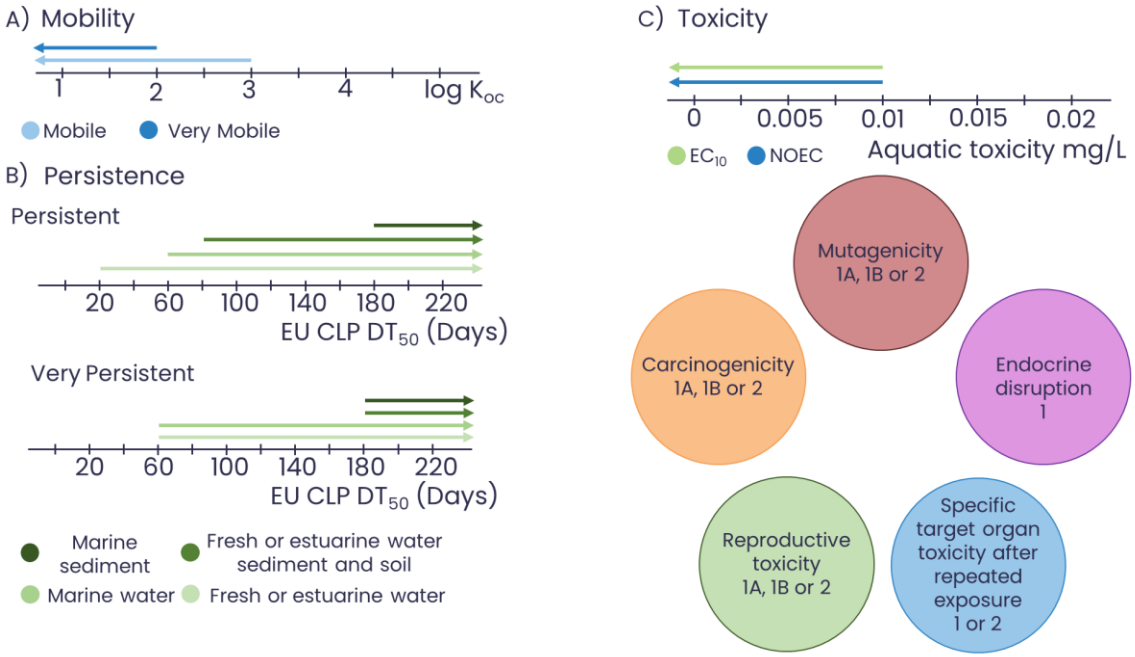

Figure 1: EU CLP criteria [34] for PMT/vPvM substances. *A) Mobility criteria based on log K_{OC} (blue). B) Persistence criteria, with persistent in green and C) Toxicity criteria, including carcinogenicity, mutagenicity, endocrine disruption, specific target toxicity and reproductive toxicity (1A, 1B, 1 and 2 refer to the categories for that criterion) as well as concentrations, where no observable effect concentration (NOEC) and effect concentration at 10% (EC_{10}) refer to marine and freshwater organisms.*

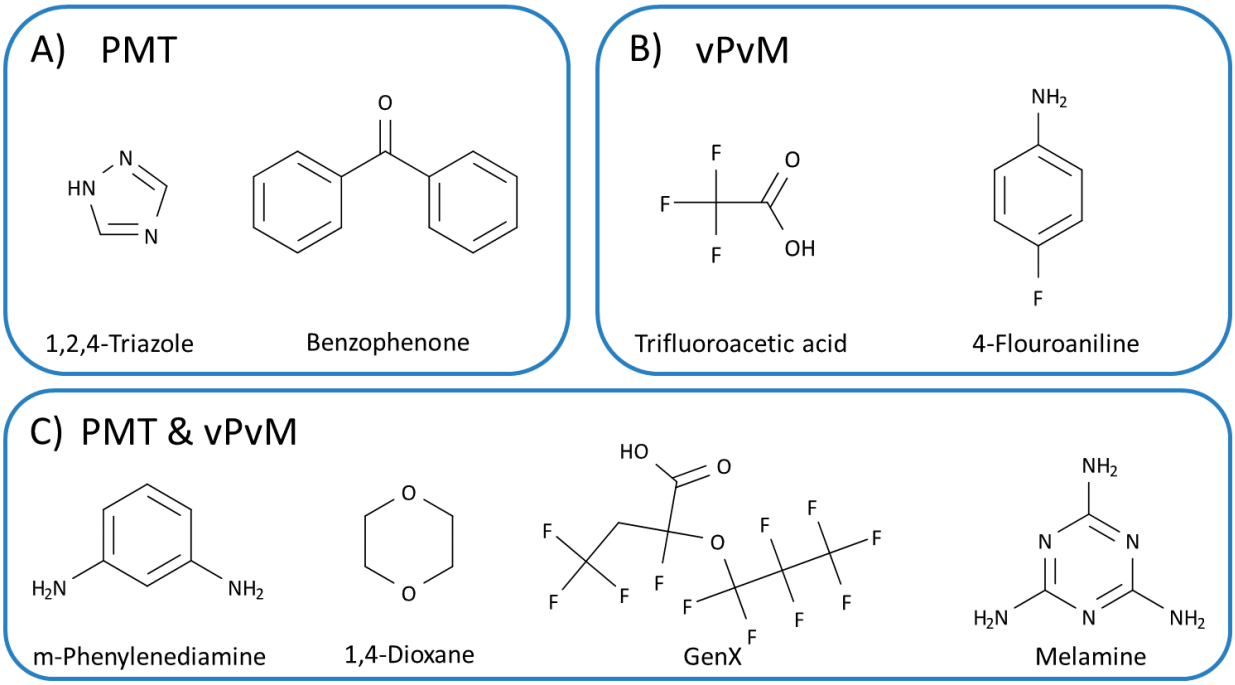

Figure 2: Selected examples of PMT/vPvM substances from Arp and Hale (2022) [36]. *A) PMT substances; B) vPvM substances; C) both PMT and vPvM substances.*

There are several published lists containing PMT/vPvM substances, five of which are hosted on the NORMAN Suspect List Exchange (NORMAN-SLE) [37, 38]. The UBAPMT suspect list is an extract of substances currently registered under REACH that meet the proposed PMT/vPvM criteria set by UBA in 2019. The original list has 254 substances, while the 2022 revised version has 340 substances due to an increase in chemicals registered in REACH and updated chemical information [39]. The EAWAGPMT list contains 1,156 compounds identified in groundwater by Kiefer *et al*. [40, 41], while the UFZHSFPMT list includes 1,063 potential persistent mobile compounds as described by Neuwald and Muschket *et al*. [42–44]. The ZEROPMBOX1 contains 38 compounds, including representative per- and poly-fluoroalkyl substances (PFAS), triazines and triazoles used to start the H2020 ZeroPM project [45]. Finally, the PMTPFAS list contains 180 fluorinated compounds extracted from the UBAPMT, EAWAGPMT and UFZHSFPMT lists [46]. In combination, the five lists contain 2,081 unique compounds, but this does not represent all PMT/vPvM substances in the global market.

Grouping and Regulations

Assessing and regulating individual PMT/vPvM substances that fall within a PMT/vPvM substance group is inefficient and more time-consuming than assessing an entire group. Past strategies have led to drop-in replacements, subsequently referred to as regrettable substitution [22]. Assessing chemicals individually also ignores cumulative exposures and risks of groups of substances [47]. Considering primarily the structural similarity and similar properties of PMT/vPvM substances, it may be more feasible and prudent to regulate these substances as a group. The idea of substance grouping based on the relationship between hazard and structural similarity is not new, since many of the very first organic substances to be regulated were groups sharing a similar structure. The successes of regulation in managing substances as groups such as ozone-depleting substances (ODS) under the Montreal Protocol [48, 49] and specific groups of persistent organic pollutants (POPs) under the Stockholm Convention [50] are discussed below. Moreover, successfully grouping substances for regulation not only accelerates but also prevents and reduces inconsistencies in the regulatory process [51]. Grouping substances can enhance chemical safety management, facilitating the identification of regulated substances and potential substitutes for harmful ones [51].

While there may be several legislations about grouping substances globally, this section focuses on the use of grouping in EU legislation. In the EU, the European Chemical Agency (ECHA)

coordinates the REACH regulation for the restriction, evaluation and authorization of substances based on hazard classifications and the CLP regulation for labelling based on hazard classifications. REACH Annex XI section 1.5 specifies how groups or categories of substances can be defined and which regulatory actions can be applied [28]. It states that "*substances whose physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity may be considered as a group, or 'category' of substances*" [28]. The toxicological or hazard properties referred to are described in the CLP regulation shown in Figure 1.

According to Article 36 of the CLP regulation, certain substances, including those with respiratory sensitizing properties (category 1), germ cell mutagenicity, carcinogenicity, and reproductive toxicity (category 1A, 1B and 2), are considered hazardous and are subject to harmonized classification. This also applies to active substances listed in Directive 91/414/EEC (the Plant Protection Product Directive) or Directive 98/8/EC (the Biocide Directive). Moreover, Article 57 includes substances that are hazardous to the environment and are also subject to harmonized classification. A list of these hazardous substances for which harmonized classification and labelling has been established at the EU level can be found in Part 3 of Annex VI of the CLP regulation.

Under REACH, UVCBs are regulated based on the structural similarity of the constituents identified and can also be regulated as part of a different group. This means that certain components of these substances may be identified and registered as part of a different group. Annex XI section 1.5 of REACH provides more information on the regulation of UVCBs [28, 52].

Existing grouping legislation and impacts

The Montreal Protocol on Ozone-Depleting Substances

The Montreal Protocol, established in 1987 and enforced in 1989, belongs to the multilateral environmental agreement, the Vienna Convention for the Protection of the Ozone Layer, to regulate the manufacturing and consumption of ODS [48, 53]. This is a group of over 100 substances including chlorofluorocarbons (CFCs), methyl chloroform, hydrochlorofluorocarbons (HCFCs) and hydrobromofluorocarbons (HBFCs) that release chlorine and bromine into the stratosphere, damaging the ozone layer [48, 54]. This can lead to increased global warming, skin

cancer and damage to marine ecosystems [55]. The Montreal Protocol is considered to have drastically decreased relative consumption (total of production and imports - total of exports and destroyed) of ODS in the EU (100% to 0.36%) and globally (100% to 1.35%) between 1986 and 2021 [53, 56], as shown in Figure 3. The success of the Montreal Protocol is attributed to universal participation and strict regulation. Since these substances were regulated based on their ozone-depleting properties [57], this is an example of a property-based regulatory effort that has been successful [53, 58]. However, the Montreal Protocol has also been criticized for shifting the burden by transitioning from ODS to greenhouse gases and PMT/vPvM precursors, as discussed further below.

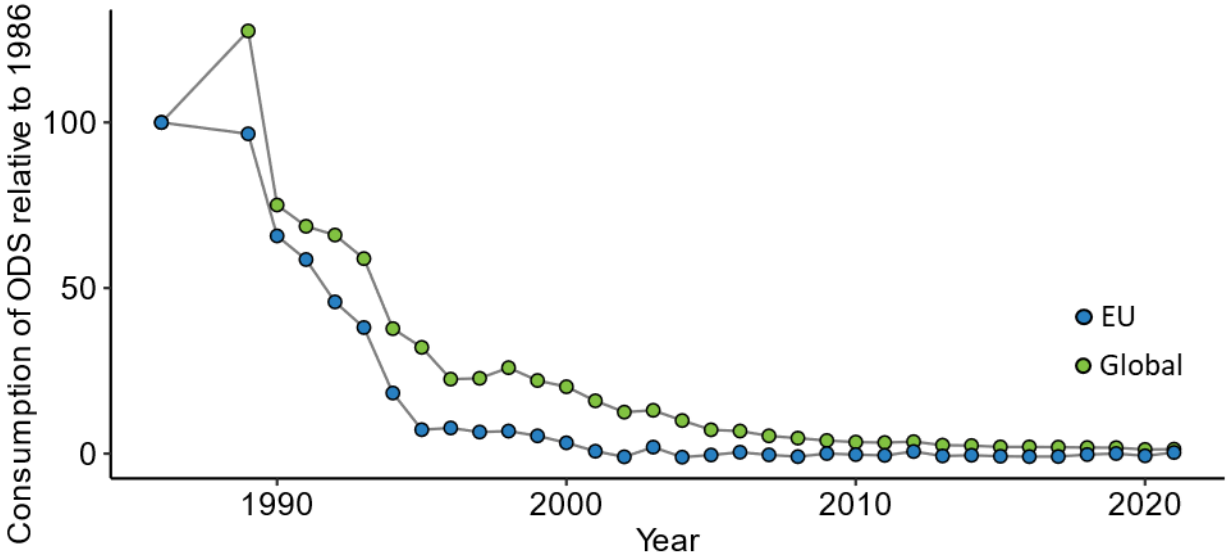

Figure 3*: EU and global relative consumption of ODS since 1986* [56] *showing the reduction of the consumption of ODS due to the Montreal Protocol.*

The Stockholm Convention on Persistent Organic Pollutants

The Stockholm Convention was signed in 2001 to protect humans and the environment from POPs [50]. An EU Legislation regulation (EC No 850/2004) was adopted later to implement the Convention in the EU [59, 60]. Initially, the Convention regulated 12 POPs or groups of POPs such as aldrin, chlordane and dichlorodiphenyltrichloroethane (DDT). Over time, the list expanded to include 39 substances and substance groups as of January 2024, with the regulation covering

the manufacturing, sales, use, and waste management of these chemicals, as well as unintentional releases in some cases [50, 61]. Structural similarity and the resulting similar compound properties played a major role in managing the grouping of substances under the Convention, for instance, polychlorinated biphenyls (PCBs), dioxins and DDT derivatives [62]. The Stockholm Convention has been successful in reducing the emission of regulated POPs since its enforcement. The emission levels of PCBs, for example, decreased by over 60% from 2001 to 2020, while dioxin levels also dropped by 50% from 2001 to 2020 (top of Figure 4). This reduction is also noticeable as the number of registered patents for 17 dioxins, 12 PCBs and hexachlorobenzene (HCB) dropped since the Convention (bottom of Figure 4).

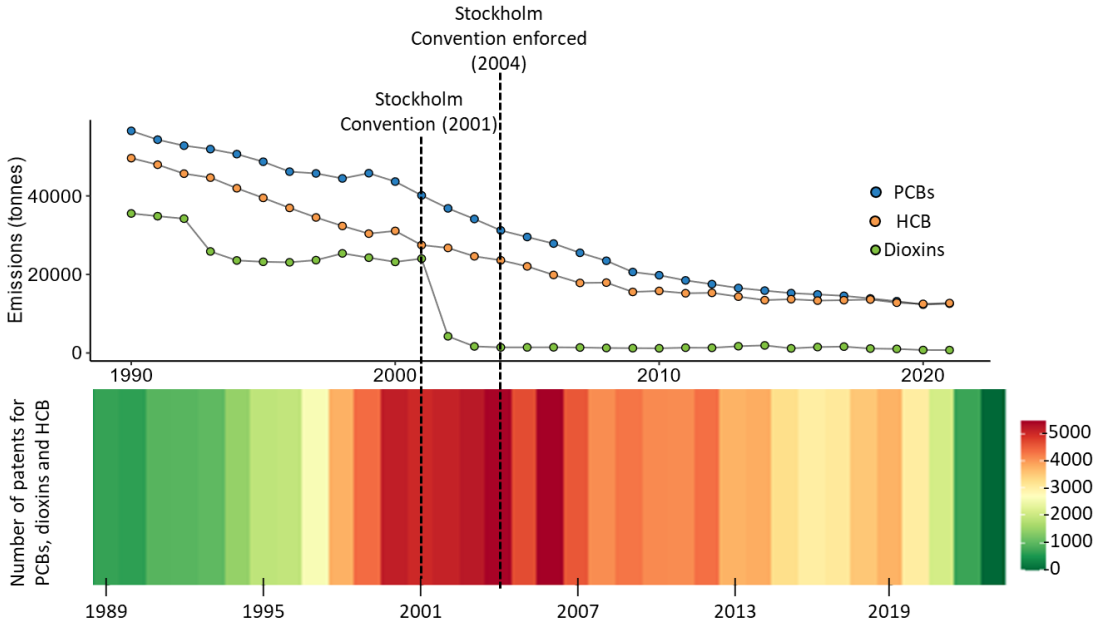

Figure 4*: Top: Emission tonnage of PCB, dioxins and HCB from regulation (EU) No 277/2012, between 1990 to 2020* [63]*. Bottom: The chemical stripes drawn using the chemical stripes package in R* [64] *show a decrease in the number of registered patents of PCB, dioxins and HCB in PubChem; the date range was chosen to match the emission data.*

Substitution of regulated substances with PMT/vPvM substances

The concept of regrettable substitution first appeared in the literature in 2011 [65]. There are many examples of regrettable substitution, which refers to the practice of replacing a hazardous substance with a structurally similar substance for a specific use or function, that is also hazardous or potentially more hazardous, or that has not been tested broadly enough for different hazards and other than those of the substance being replaced [66]. One well-known example is Bisphenol A, an endocrine-disrupting chemical (EDC) that was first discovered in 1891 [67]. Due to its harmful effects, it has since been replaced by various other EDCs with similar structures such as Bisphenol S and Bisphenol P. Currently, more than 30 bisphenols, including the ones mentioned above, are recommended for restriction by ECHA [68].

One of the reasons for the “drop-in” solution by companies after substance regulation (both as individual or as a group) is that structurally similar substances often have similar functions in the product being applied, and can be manufactured generally without requiring substantial changes in processes, infrastructure, or product testing [47]. Unfortunately, similar toxicological effects are likely to occur as well [23], and at other times “burden shifting” towards different hazards. A key example is the series of restrictions related to the Montreal Protocol that began with a global phase-out of CFCs [69, 70]. Later, hydrobromofluorocarbons (HBFCs) were introduced as replacements but were only briefly commercialized [71]. They were then replaced with hydrochlorofluorocarbons (HCFCs), which exhibited substantially less ozone-depleting potential, and exhibited the same commercial properties as CFCs [72]. HCFCs were eventually also included under the Montreal Protocol and were again replaced by chemicals with similar chemistry, hydrofluorocarbons (HFCs) [48]. Due to the removal of chlorine atoms from the molecules, HFCs no longer pose a threat to the stratospheric ozone layer [73], but they are still highly persistent and have high global warming potential. Therefore, in a subsequent amendment to the Montreal Protocol, the Kigali Amendment, HFCs themselves were listed [73, 74]. As a consequence of the Kigali amendment, the industry that manufactures fluorinated gases then sought to substitute HFCs with hydrofluoroolefins (HFOs), which have a short atmospheric lifetime of 6 days [75, 76]. However, these HFOs (almost) exclusively degrade to form trifluoroacetic acid (TFA), a vPvM substance that is ubiquitous in the environment, especially in drinking water systems, but the current understanding of its risk to human health and the environment is limited. While some research has argued that TFA has low health risks [77, 78], other studies have shown mild liver hypertrophy in rats, and eye and skin irritation [77, 79]. As the levels of TFA are rapidly increasing, some EU countries have proposed to ban HFOs as part of the broad PFAS restriction under REACH. In summary, although the Montreal Protocol is often considered the most

successful multilateral environmental agreement, this has led to burden shifting over time from ODS to the production of persistent, mobile substances such as TFA.

Similar to the Montreal Protocol, increased regulatory pressure on PBT/vPvB substances in Europe and the USA was seen as a driver for the chemical industry to produce more hydrophilic, and hence mobile, substances [80]. Individual fluoropolymer manufacturers have developed their own structurally similar per- and polyfluoroalkylether carboxylic acids (PFECAs) as replacements for PFOA, which was used as a processing aid in fluoropolymer production. However, as mentioned above, some of these replacements, including GenX, are similarly problematic despite being less bioaccumulative [81]. To date, many monitoring programs have seen an increase in these replacements in water resources and fish due to increasing use and emissions [82]. GenX and PFBS were identified as SVHCs under the EU REACH regulation in 2019 and were some of the first SVHCs that were considered an equivalent level of concern to PBT/vPvB substances [11]. Thus, the phasing out of some PBT/vPvB substances such as the long-chain PFASs has led to burden shifting towards PMT/vPvM substances such as PFECAs [83].

Existing regulation of substances as groups based on structural similarity and/or intrinsic properties has been successful, as demonstrated in the Montreal Protocol of ODSs and the Stockholm Convention of POPs. Meanwhile, regrettable substitution with increasing production of PMT/vPvM substances such as TFA and GenX has been noted as a side-effect. This shows a limitation of the grouping approach under the Montreal Protocol and the Stockholm Convention: limiting the scope of intrinsic properties during grouping may lead to burden shifting to other hazards. This calls for a grouping strategy that can prevent regrettable substitution and improve the efficiency and effectiveness of chemical regulatory processes.

Grouping strategies

Read-across grouping

Read-across in substance grouping is a strategy that relies on the use of important information obtained from tests conducted on a reference substance known as the “source” substance within a group to predict the properties of another substance in the group known as the “target”

substance [84]. This method relies on justified similarities in structure, toxicokinetic, physicochemical and molecular properties, transformation process/endpoints and other similar data for interpolation of relevant information [85] and is recommended in Section 1.5 of Annex XI of the REACH regulation for groups of substances [52]. It can be applied from a single source substance to a single target substance (analogue approach) or from multiple source substances to multiple target substances within a group (category approach) [84, 86]. This method is commonly used to fill data gaps for chemical safety assessment in the regulatory process but has also been used to build grouping hypotheses for categories of chemicals [84, 85]. The Read-Across Assessment Framework (RAAF) by ECHA has been developed to guide systematic and consistent applications of read-across [87].

Read-across is advantageous because it reduces the number of experimental tests needed during an assessment by using existing experimental data for the source substance(s) to predict the properties of the untested substance(s) [88]. If a clear hypothesis and justification are provided, read-across can be used efficiently to predict the hazard properties of target substances and fill data gaps in the regulatory process, thereby facilitating and speeding up assessment and regulatory decisions [89]. However, read-across requires an adequate justification for use, and appropriate documentation covering all assumptions and conclusions [89, 90]. This can be complex and may require a certain level of expertise for interpretation [91]. Despite its limitations, read-across can be applied to the grouping of PMT/vPvM substances.

Grouping based on retained moieties from transformation reactions

Both biotic and abiotic transformations generally result in transformation products (TPs) with significantly higher mobility (lower log K_{OW}) than their parent compounds or precursors, making them more mobile in the environment. This seems intuitive as one of the "goals" of metabolism and wastewater treatment processes is to increase the polarity of the compounds. For metabolic processes, this allows the compounds to be expelled from the body with the urine. However, some persistent substructures may be retained during the transformation resulting in similar toxic properties between the parent compound and TPs. For example, decabromodiphenyl ethane forms 6 metabolites that were found to be carcinogenic like the parent compound [92]. In other cases, even small structural changes can result in large differences in toxicity such as for bis(pentabromophenyl) ether, which has low thyroid binding affinity itself but can form the TP

2,3,5,6-tetrabromo-4-(2,3,4,5,6-pentabromophenoxy)phenol with a strong thyroid binding affinity [92]. Therefore, it is of interest not only to identify parent compounds that may be PMT/vPvM, but also compounds that can form PMT/vPvM TPs, along with identifying the common moieties that were retained and not readily metabolized.

One way to do this identification is by utilizing the “transformations” section in PubChem, which links parent compounds to TPs with basic reaction information [93]. Of all the substances on the five suspect lists mentioned above, perfluorooctanoic acid (PFOA) has the highest number of recorded parent compounds (22) in the PubChem transformations section (from version 0.1.6 of the dataset archived on Zenodo) [94]. This is also one of several PMT/vPvM TPs where parent compounds are included in the legislation as part of the substance group. Specifically, the Stockholm Convention restricts the use of PFOA-related compounds, which include compounds that form PFOA after degradation [61]. TFA is also a known TP of several different compounds containing a CF_3– moiety. Since there are over 5 million compounds containing a CF_3– moiety are included in PubChem [95], many of which are also industrially relevant, there are a myriad of potential sources of TFA.

Triazoles are another example of moieties preserved from parent compounds to TPs. Out of the triazole compounds in PubChem, 62 have recorded TPs (12 Jan 2024) [94]. This corresponds to 233 unique reactions, out of which the triazole moiety is retained in 88% of the cases, showing its high stability. While usually not acutely toxic in low doses, triazoles may cause several severe chronic toxic effects such as endocrine disruption and neurotoxicity [96]. Triazole substances such as benzotriazoles are present in the environment at high levels [96]. Thus, the retention of this functional group and other PMT/vPvM moieties may be concerning from an exposure point of view, supporting the idea that grouping based on retained moieties or TPs is relevant to obtain comprehensive and inclusive groups for PMT/vPvM substances.

Grouping for hazard assessment

Grouping PMT/vPvM substances may consider which structural properties make certain substances inherently more persistent, mobile and toxic. For persistence in the environment, an important property is the readiness of the bonds to be broken down under ambient conditions, whether it be from radical reactions or through metabolic processes. For instance, the C-F bonds in PFAS (bond dissociation energy of 513.8 ± 10.0 kJ/mol), and aromatic-Cl bonds in PCBs or dioxins (394.9 ± 13.4 kJ/mol), are difficult to break down in the environment, making groups rich

in such bonds likely to be persistent [97]. Compounds with molecules containing high bond dissociation energies can be flagged for persistence assessment and subsequent inclusion as PMT/vPvM if each of the M and/or T criteria are met. Biodegradability models can be used to quickly provide relevant information about the persistence of many substances or the presence of many persistent substructures, pending further investigation and confirmation by experimental studies [98]. However, the applicability domain of available models is dependent on their training data, resulting in unreliable predictions for compound classes that may not be covered yet [98].

For mobility, the chemical substructures that are associated with low K_{OC} values are those that are highly polar or ionic, as this favours their water solubility over sorption to soil organic carbon [36, 99]. A 2022 review found that most ionic compounds with measured log K_{OC} values have log K_{OC} values <4.0 [36]. Thus, the presence of many hydrophilic substituents may be a predictor of mobility, and conversely, chemicals with largely hydrophobic substructures are unlikely to be mobile in the environment. However, an important limitation of mobility is size. Extremely large molecules that are highly polar and ionic may not be mobile if they have sufficient hydrophobic substructures to decrease their solubility, or (as in the case of water-soluble polymers) can aggregate for charge neutrality and therefore lose/reduce their mobility as an aggregate [100]. Quantitative structure-activity relationship (QSAR) models are available to predict the mobility of certain substances and can be applied effectively (within their respective applicability domains) to classify the mobility of substances.

The toxicity of a substance is related to its chemical structure and determines the type of health effects it induces in the biological systems [101]. The interaction of a chemical with a biological system is determined by the functional groups, stereochemistry and other molecular features [102]. A change in the structure can lead to changes in toxicity, depending on how this change affects the toxicophore – the structural portion associated with the toxicity of the chemical [103]. Toxicity is also related to the absorption, distribution, metabolism and excretion ability of the body, which depends on the chemical structure of the substance. Increased hydrophobicity leads to increased absorption and increased potential toxic effects (due to potential bioaccumulation). A concern with PMT/vPvM substances is chronic exposure via water consumption, which can lead to elevated concentrations in humans and diverse biota [11, 104].

Considering the chemical features that make these substances P, M and T, and the provided criteria for classification, PMT/vPvM substances can be identified and grouped accordingly. Read-across can be applied to identify PMT substances on the basis that they have similar

(sub)structures, similar properties and available toxicological data. This can be done through a fragment-based approach, which relies on the identification of small similar fragments or functional groups with similar properties [105]. Substance grouping approaches take the fragment models one step further. Substances can have similar properties due to the similarity in structures – this includes functional groups, common precursors or reaction products, and a constant pattern in the changing of the potency of the properties across the group [28, 87]. The substance grouping approach is used in read-across techniques and alternative assessments [87]. This has largely been supported by using models such as the KOCWIN model. This is a fragment-based model that relates substructures and mobility (K_{OC}) based on appropriate training data [106, 107]. The mobility (K_{OC}) of new chemicals can be predicted using the established relationship (when they are within the applicability domain). Similarly, the ReadyBiodegradable model in OPERA [90] and MS2Tox [108] can be used to predict the biodegradability and toxicity, respectively, of many new PMT/vPvM substances.

Substances that produce TPs that are persistent, mobile and/or toxic could be grouped and regulated as PMT/vPvM substances. An example of these are several aromatic amines registered under REACH that are PMT/vPvM substances, such as 4,4'-methylenedianiline, 4,4'-oxydianiline, 4-chloroaniline, 3,3'-dichlorobenzidine, 4,4'-methylenebis(2-chloroaniline), 4,4'-methylenedianiline, and 2-methoxy-5-methylaniline [28, 39, 42]. However, some aromatic amines have multiple known precursors listed in the PubChem transformations library (e.g. 4-aminophenol and aniline). As such, regulating aromatic amines and precursor substances as a group based on PMT/vPvM substances warrants further investigation and consideration.

The strategies mentioned above regarding grouping can be matched to substance regulation in various ways. Firstly, substances falling within a PMT/vPvM group with little known data could be flagged for follow-up to see if persistence and mobility measurements have been conducted, and if read-across methods (based on patterns with other substances) could be used to fill data gaps. This could help prioritise filling data gaps and would help develop read-across approaches for further substances within the group. If any other substance with a similar structure exists in the group and is hazardous (source substance), this could be seen as a reason to investigate for similar toxicological hazards for this substance (target substance). If several members within a group are shown to be PMT/vPvM substances, then a precautionary approach would be to assume all group members with no assessments are similarly hazardous, until there is sufficient scientific data to show otherwise.

Cheminformatics challenges in grouping PMT/vPvM substances

Estimating the number of individuals and groups of chemicals that fit the PMT/vPvM classification is a challenging task. Firstly, most substances lack readily available persistence, mobility and toxicity data. Due to the limited data availability, the prediction models of these properties are also limited in their accuracy and applicability domains. However, some suitable data and models are available as a starting point, especially for log K_{OW} for mobility prediction. For example, both XlogP and the newer XlogP3 [109, 110] and the KOWWIN [106] module in EPISuite [111] use a multivariate regression approach to K_{OW} prediction. While K_{OC} data is more limited than K_{OW} data, there are also several models which attempt to predict K_{OC}, including KOCWIN from EPISuite [112] and the K_{OC} module of OPERA [90], which both utilise the training data from the PHYSPROP database [90, 112]. For persistence, OPERA also contains three modules for predicting biodegradability (BiodegHL, ReadyBiodegradable and Km) as well as one module predicting rate constants for gas-phase reactions with hydroxyl-radicals, though with more limited applicability domains compared to the K_{OC} module [90]. The prediction of toxicity is even more challenging due to the limited available training data. However, models still exist for several toxicological endpoints such as LC_{50}, mutagenicity and developmental toxicity for many possible structures [108, 113, 114]. One example is MS2Tox, which predicts LC_{50} values for fish [108].

The PubChemLite for Exposomics [115] dataset was used to give a preliminary estimate of the number of potential environmental contaminants that are predicted to meet the CLP definition of mobility. PubChemLite is a subset of ~350,000 compounds from PubChem with environmentally relevant annotation content [115]. Predicted log K_{OW} (from the XlogP3 values present in the PubChemLite dataset [116]) and log K_{OC} (calculated with EPISuite KOCWIN) were used. In total, 350,492 compounds (97.3 %) had XlogP3 values available from PubChem and K_{OC} values were predicted for 346,133 (96.0 %) using KOCWIN [112]. The results of the K_{OW} and log K_{OC} distribution are shown in Figure 5. Based on these predicted values, between 39% and 64 % of the substances in PubChemLite (136,440 and 233,040 substances, respectively) would be classified as mobile or very mobile using the XlogP3 and KOCWIN models, respectively.

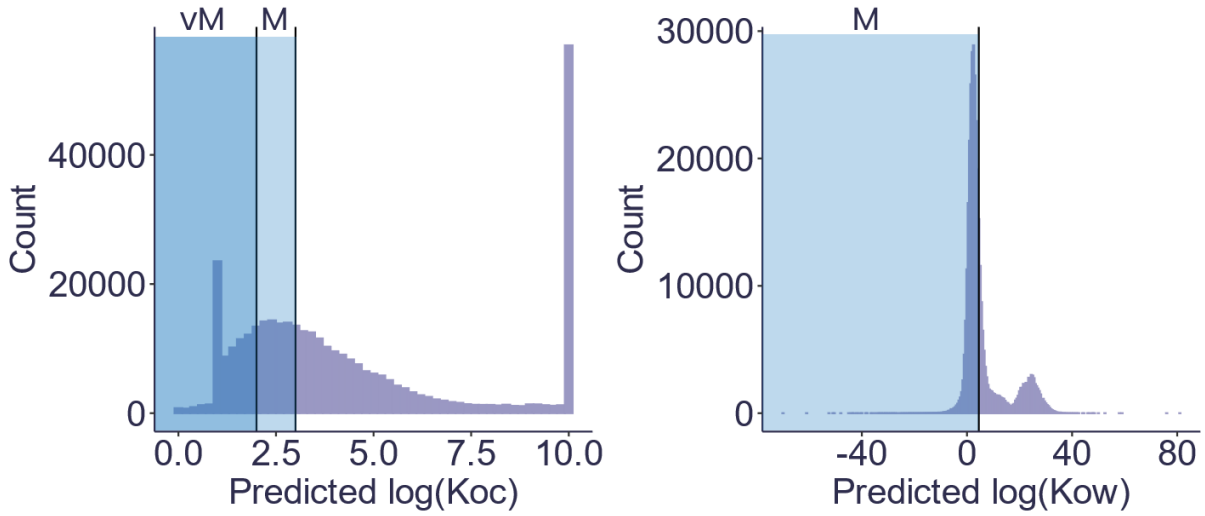

Figure 5: Predicted log K_{OC} (KOCWIN, 346,133 compounds total) and log K_{OW} (XlogP3, 350,492 compounds total) values for PubChemLite [115, 116]. Some of the K_{OC} predictions may fall outside the applicability domain of the model. The "*count*" *is the number of compounds inside each bin. Bin-widths are 0.2 and 0.5 for log K_{oc} and log K_{ow} respectively.*

To investigate this in more detail on slightly smaller subsets, four compound classes: triazines, aromatic amines, PFAS and triazoles were selected based on the five suspect lists mentioned previously (UBAPMT, EAWAGPMT, UFZHSFPMT, PMTPFAS and ZEROPMBOX1) [39, 40, 42, 45, 46]. The substructure search function of PubChem was then used to estimate the number of compounds that belong to these compound classes. An overview of these search queries can be found in Table 1. As can be seen in the first three rows, relatively unspecific substructures can generate very large query results. For the 1,2,3-triazole substructure over 1 million substances were found, which corresponded to a search of only 87% of the database as the search results are capped at 1 million substances. Similarly, the aromatic amines (with aniline as the searched substructure) resulted in over 1 million substances with only 2% of the database searched. The 1,3,5-triazine query resulted in 718,119 substances. The compounds classified within the OECD definition of PFAS in the PubChem PFAS tree were used to source PFAS, which contained 6,604,017 compounds at the time the queries were performed (Dec. 17, 2023) [95]. It is unlikely that all compounds containing these substructures would meet the PMT/vPvM criteria outlined in the CLP. For example, only 250,873 of the 718,199 triazines meet the CLP criteria for mobility based on the predicted log K_{OW} from XlogP3. As such the substructures used when discussing PMT/vPvM compound grouping for regulation purposes should be more specific.

More specific substructure queries were used to interrogate these results further according to the PMT/vPvM criteria, shown in the remaining rows of Table 1 and Figure 6, using the structures of melamine, benzotriazole and benzidine as well as the “larger PFAS parts” definition (contains –CF_2CF_{2-}) from the PubChem PFAS tree [95]. The search was then progressively restricted to exclude the searched substructures from being part of larger ring systems and substances with molecular weights greater than 300 g/mol. The results of this search were also used to perform persistence and toxicity prediction as discussed above. The top two rows of Figure 6 show these substructure query results. Like their less specific triazine counterpart, they seem too broad to capture only PMT/vPvM substances. However, when restricting the search to only compounds below 300 g/mol, between 87 and 99% of the compounds would meet the CLP definition of mobility. The most restricted PubChem search results were also used for biodegradability and LC50 predictions using the ReadyBiodegradable model from OPERA and MS2Tox (compounds which fell outside the applicability domain of the ReadyBiodegradable model were excluded in the biodegradability results; this information is not given by MS2Tox). As can be seen in Figure 6, almost all compounds inside the applicability domain were classified as non-biodegradable. This indicates that in addition to their mobility, most compounds within these classes are potentially persistent.

Table 1: Overview of the PubChem substructure searches (queries performed 19/12/2023). Default settings for all queries were (1) single or double bonds match aromatic bonds (2) chain bonds in the query may match rings in hits and (3) remove any explicit hydrogens before searching. Extra settings "Ring" (rings may not be embedded in a larger system) and the filter "MW<300" (Molecular weight < 300 g/mol) are indicated in the respective column. Query URLs are embedded into the substructure column. The first three rows in italics are generic queries, the latter rows are the queries used to generate Figure 6 and are coloured accordingly. The OECD PFAS results were obtained via the PubChem classification browser. DB = database, values in brackets indicate the % of the database searched (queries are capped at 1 M results).

Substructure	Substructure SMARTS	Extra Settings	Number of Structures
1,3,5-Triazine	*C1=NC=NC=N1*	*None*	*718,134*
Aromatic amine	*C1=CC=C(C=C1)N*	*None*	*>1 M (2 % of DB)*
1,2,3-Triazole	*C1=NNN=C1*	*None*	*>1 M (87 % of DB)*
Melamine	C1(=NC(=NC(=N1)N)N)N	None	96,660
Melamine	C1(=NC(=NC(=N1)N)N)N	Ring	47,519
Melamine	C1(=NC(=NC(=N1)N)N)N	Ring, MW<300	10,528
Benzotriazole	C1=CC2=NNN=C2C=C1	None	165,361
Benzotriazole	C1=CC2=NNN=C2C=C1	Ring	158,766
Benzotriazole	C1=CC2=NNN=C2C=C1	Ring, MW<300	30,945
Benzidine	C1=CC(=CC=C1C2=CC=C(C=C2)N)N	None	208,934
Benzidine	C1=CC(=CC=C1C2=CC=C(C=C2)N)N	Ring	48,123
Benzidine	C1=CC(=CC=C1C2=CC=C(C=C2)N)N	Ring, MW<300	1,618
OECD PFAS	PFAS Tree - OECD PFAS definition	None	6,604,017
OECD PFAS	PFAS Tree - OECD PFAS definition	Larger PFAS Parts	222,174
OECD PFAS	PFAS Tree - OECD PFAS definition	Larger PFAS Parts, MW<300	29,521

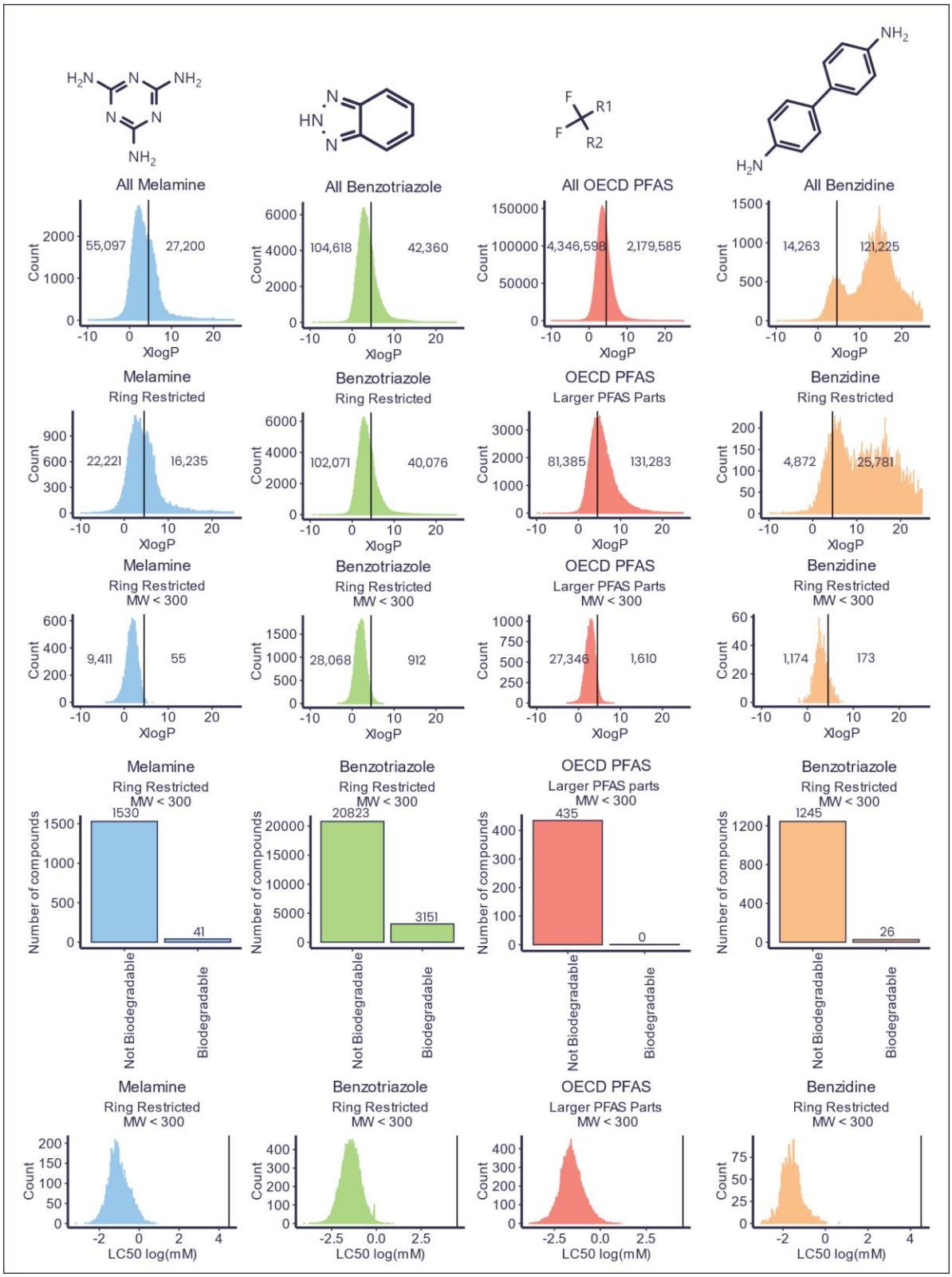

Figure 6: *Distribution of PubChem XlogP3 values for four searches with varying restrictions (top three rows), plus predicted biodegradability from the OPERA ReadyBiodegradable model and LC50 values predicted from MS2Tox for the most restricted search queries (last two rows). Search settings and total numbers are given in Table 1.*

Perspectives for grouping strategies

Challenges for assessing and managing PMT/vPvM substances

Based on the criteria for persistence, mobility and toxicity, many chemicals may be PMT/vPvM substances, warranting further assessments and management (see Table 1). One of the major challenges of dealing with PMT/vPvM substances is the lack of high-quality data. As shown above, there is a growing need for computational modelling to complement experimental approaches as the number of substances to be tested increases, yet efficient computational methods rely on high quality and sufficient experimental data availability, which is a major limiting factor. Structurally diverse substances with multiple functional groups and stereochemistry can lead to unexpected behaviour, posing a critical challenge [117]. However, developing high-throughput screening (HTS) methods for toxicity testing may be difficult for these diverse substances and toxicological endpoints, which produce large amounts of data, and require expert knowledge to interpret and manage [118].

Identification, monitoring and removal are other challenges to managing PMT/vPvM substances. Targeted identification and monitoring approaches will not be sufficient to detect all PMT/vPvM substances, hence it is crucial to ensure wider availability of analytical methods and reference standards to properly identify, quantify and assess potential PMT/vPvM substances. Targeted analysis could be complemented with non-targeted analytical approaches, yet regulatory acceptance of non-targeted monitoring is still lacking [119]. Moreover, the lack of data on persistence, mobility, toxicity, TPs, complex mixtures and appropriate suspect lists for broader suspect screening poses identification and monitoring challenges [20].

Prioritization strategies for testing and assessment

Considering many potential PMT/vPvM substances, and the possible challenges outlined, it is necessary to develop other strategies that could be used in combination with the proposed grouping strategies above to prioritize chemicals for assessing their PMT/vPvM properties. Exposure and emission information could serve in the prioritization of chemicals for testing.

Utilising exposure information such as mode of exposure (chemicals in food or drinking water) [120, 121] or Occupational Exposure Banding strategy for categorization of airborne substances lacking defined limits [122], could help identify chemicals with high exposure potential. Additionally, emission levels can be used as another criterion, where specific substances with higher emission levels can be targeted for testing.

The use of *in vitro*, *in vivo*, and *in silico* approaches can aid the grouping and prioritization of chemicals for testing or assessments by regulatory bodies. This can be done by generating grouping hypotheses and justification for inclusion or exclusion criteria for substances in groups [122]. In particular, novel approaches may generate huge amounts of toxicological and high-throughput "omics" data including metabolomics, transcriptomics, and exposomics to support the validation and establishment of grouping hypotheses needed by regulatory authorities [123]. An example of a grouping hypothesis is the mode of action (MOA) hypothesis, which states that all chemicals that share a common mode of action are candidates for grouping [124]. Additionally, concepts such as adverse outcome pathways and toxicity pathways can be translated into prioritization hypotheses that can target specific substances, hence advancing prioritization for hazard assessment [125, 126]. These can facilitate regulator efforts to restrict hazardous substances.

It is important to acknowledge that although some strategies for prioritizing substances may seem effective, they mainly depend on the availability of data including hazard, exposure, and toxicological data. Therefore, there is a need for collective efforts such as high-quality data generation, community-level data collection, Open Science, FAIR data and improved data-sharing policies that can improve the generation and availability of relevant data. The data can then be used to improve the prioritization, identification and regulation of PMT/vPvM substances.

Conclusion

To achieve the EU's zero pollution ambition of a non-toxic environment by 2050, regulating the production, use and disposal of PMT/vPvM substances is necessary. As shown in Table 1, scaling PMT/vPvM criteria to big substance collections reveals that there are potentially thousands of PMT/vPvM substances that could cause harm to human health and the environment, especially concerning water quality and drinking water treatment.

The Montreal Protocol and the Stockholm Convention have demonstrated that grouping substances can be an effective strategy to expedite the elimination of the production, use, and emission of toxic substances such as ozone-depleting substances (ODSs) and persistent organic pollutants (POPs). This approach can also accelerate the identification and regulatory processes for substances that lack hazard information. Grouping can prevent the introduction of new hazardous substances into the global market. However, it is important to ensure that grouping is done in a way that is feasible and promotes the use of safer and more sustainable alternatives. Otherwise, it could result in the production of regrettable substitutes, as was the case with ODSs and POPs, which led to the creation of some PMT/vPvM substances.

Read-across based on structural or substructural similarity is one of the strategies that could be used to group PMT/vPvM substances, which relies on the idea that substances with similar structures have similar properties. Commonly retained moieties from transformation reactions could also be a grouping strategy for PMT/vPvM substances. Substances that are structurally similar to PMT/vPvM according to read-across, or form persistent, mobile TPs could be flagged for subsequent assessment and/or regulatory actions.

Cheminformatics may be used for substance grouping based on predictive models for properties such as biodegradability, mobility, and toxicity. PubChemLite predictions suggest that between 39% (136,440 compounds) and 64% (233,040 compounds) of potentially environmentally relevant compounds are mobile or very mobile. Certain compound classes, such as triazines, aromatic amines, triazoles and PFAS, are likely to be persistent, non-biodegradable, and toxic. As shown in Table 1, the numbers are high and restricting these compounds as a group would be challenging; however, prioritizing members of these large groups for property testing is warranted as they contain a substructure associated with a PMT/vPvM substance group. Additional strategies are needed to prioritize some substances for regulation, which requires more data availability following FAIR principles.

Some strategies proposed for the prioritization of substances for testing or assessment of PMT/vPvM include (i) the use of exposure and emissions information such as Occupational Exposure Banding, and (ii) the use of *in vitro*, *in vivo* and *in silico* techniques to generate relevant toxicological data that will support prioritization, identification and regulation of PMT/vPvM substances. These strategies in combination with substance grouping could result in substituting PMT/vPvM substances with safer alternatives.

602 **List of abbreviations**

Abbreviations	Full Meaning
CAS	Chemical Abstracts Service
CFCs	Chlorofluorocarbons
CID	PubChem Compound Identifier
CLP	Chemicals, Labelling and Packaging
DDT	Dichlorodiphenyltrichloroethane
D_{OW}	pH-dependent octanol-water partition coefficient
EC	European Commission
EC_{10}	Effect concentration at 10%
ECHA	European Chemical Agency
EDC	Endocrine-disrupting chemical
EU	European Union
HBFCs	Hydrobromofluorocarbons
HCB	Hexachlorobenzene
HCFCs	Hydrochlorofluorocarbons
HFCs	Hydrofluorocarbons
HFOs	Hydrofluoroolefins
HTS	High-Throughput Screening
IUPAC	International Union of Pure and Applied Chemistry
K_{OC}	Organic-carbon-water partition coefficient
K_{OW}	Octanol-water partition coefficient at pH = 7
log *P*	Logarithm of K_{OW}
M	Mobility
MOA	Mode Of Action
NOEC	No Observable Effect Concentration
NORMAN-SLE	NORMAN Suspect List Exchange
ODS	Ozone-Depleting Substances
P	Persistence
PBT	Persistent, Bioaccumulative and Toxic
PCBs	Polychlorinated biphenyls
PFAS	Per- and poly-fluoroalkyl substances
PFBS	Perfluorobutane sulfonic acid
PFECAs	Per- and polyfluoroalkylether carboxylic acids
PFOA	Perfluorooctanoic acid
PMT	Persistent, Mobile and Toxic
PMT/vPvM	Persistent, Mobile and Toxic or very Persistent and very Mobile
POPs	Persistent Organic Pollutants
QSAR	Quantitative Structure-Activity Relationship
RAAF	Read-Across Assessment Framework
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals

Abbreviations	Full Meaning
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SVHCs	Substances of Very High Concern
T	Toxicity
TFA	Trifluoroacetic acid
TPs	Transformation products
UVCBs	Substances of Unknown or Variable composition, Complex reaction products or Biological origin
vM	very Mobile
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
vPvM	very Persistent and very Mobile

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets analysed during the current study are available in PubChem, the NORMAN Suspect List Exchange (NORMAN-SLE - https://www.norman-network.com/nds/SLE/) and on Zenodo under the following URLs: S36 UBAPMT (DOI: 10.5281/zenodo.6482414), S82 EAWAGPMT (DOI: 10.5281/zenodo.5500132), S84 UFZHSFPMT (DOI: 10.5281/zenodo.5535288), S90 ZeroPMBox1 (DOI: 10.5281/zenodo.5854252), S111 PMTPFAS (DOI: 10.5281/zenodo.8417075), PubChemLite for Exposomics (Version 1.27.0, Oct. 27th 2023, DOI: 10.5281/zenodo.10126889, PubChem Transformations Dataset (Version 0.1.6, Jul. 5th, 2023, DOI: 10.5281/zenodo.8117741) and the PubChem PFAS Tree (https://pubchem.ncbi.nlm.nih.gov/classification/#hid=120).

Competing interests

The authors declare that they have no competing interests.

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Author contributions:

PC: Investigation (lead), Visualization, Writing original draft (lead), Writing review and editing, EHP: Investigation, Formal analysis (lead), Visualization, Writing original draft (lead), Writing review and editing, SB: Writing the original draft, Writing review and editing, ELS: Investigation, Writing the original draft, Writing review and editing, Conceptualization, Supervision, Funding acquisition, ZW: Writing the original draft, Writing review and editing, Funding acquisition, RW: Writing review and editing, SH: Writing original draft, Writing review and editing, Funding acquisition, Conceptualization, HPA: Writing original draft, Writing review and editing, Funding acquisition, Conceptualization

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