Grouping strategies for assessing and managing persistent and mobile substances

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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 identifying, assessing and managing PMT/vPvM substances. The aim is to facilitate early identification of lesser-known or new substances that potentially meet PMT/vPvM criteria, prompt additional testing, avoid regrettable use or substitution, and integrate into existing risk management strategies. Thus, this article 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]. Some of these 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]. Recently, the EU Chemicals, Labelling and Packaging (CLP) regulation (1272/2008) introduced the new hazard classes PMT and vPvM, as well as defined criteria for PMT/vPvM substances based on chemical properties [11], as presented below in Figure 1. 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 [12–14]. 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 [15]. They can cause long-term harm to humans and the environment and are also costly and difficult to remove from drinking water [16–19]. 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 classified as PMT/vPvM substances by the German Environmental Agency (UBA) [20] (but not yet officially classified under the CLP Regulation), 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) [12]. The commonality between PMT/vPvM and PBT/vPvB

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86 substances is their elevated potential for long-lasting and long-range exposure when released to
87 the environment in substantial quantities. Their difference is related to the exposure pathway, with
88 PMT/vPvM substances likely to be first monitored in water resources where they are most likely
89 to accumulate and PBT/vPvB substances being first monitored in the food supply, humans and
90 living organisms. Though this was not stated within the CLP regulation [11], it may be assumed
91 this was introduced due to concerns from enhanced exposure potential leading to unforeseen
92 effects, be they odour, aesthetic, geophysical, economical or other than established toxicological
93 criteria. As an example, REACH Annex 1, Section 0.10 refers to "particular effects, such as ozone
94 depletion, photochemical ozone creation potential, strong odour and tainting, for which […] the
95 risks associated with such effects shall be assessed on a case-by-case basis". Considering these
96 concerns, a key consideration for vP substances is to further check if they exhibit enhanced
97 exposure-related properties (vB or vM), toxicological or other hazards, following the current
98 regulatory approaches.

99 Furthermore, due to the high mobility of PMT/vPvM substances, many of them can break through
100 artificial barriers in wastewater treatment plants, including granular activated carbon filtration and
101 ultrafiltration systems, posing challenges for removal and remediation [12, 21]. These substances
102 can be further transported through natural media such as soils, riverbanks, aquifers and
103 groundwater, making them hard to contain and remove from the environment. As such, these
104 substances are problematic in drinking water, and many are detected frequently in European
105 surface waters [12]. For example, 1,4-dioxin was found in Bavarian surface waters [22] and
106 melamine in the Netherlands, France and Belgium [23].

107 Approximately 2% of identifiable unique chemicals registered under REACH are considered to
108 meet the PMT/vPvM criteria (259 out of 13405 unique, identifiable chemicals registered under
109 REACH); however, the true number is likely higher due to data gaps related to persistent, mobility
110 or toxicity, with a potential maximum of 28% of REACH registered substances (3677 out of 13405
111 substances) [24]. Developing and applying substance grouping strategies is one way to potentially
112 identify and manage PMT/vPvM substances more effectively. There are two main motivations for
113 a substance grouping approach. The first is to expedite hazard assessments related to the large
114 number of substances being introduced to the global chemical market. The second is to avoid
115 regrettable substitution caused by drop-in substitution [25], where one substance is replaced by
116 another with similar hazardous properties and effects [26]. Thus, this paper aims to explore how
117 grouping strategies can be generally developed and used to identify, assess and manage new,
118 emerging and well-known PMT/vPvM substances. To provide context, the paper first provides an

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119 overview of PMT/vPvM substances, including scoping the numbers of substances covered by
120 existing definitions, reviewing previous successful grouping strategies, and determining the
121 relevance of grouping strategies in the context of PMT/vPvM substances while exploring the
122 future efforts required to achieve this effectively. The principle aim of this article is not specifically
123 targeting the ECHA technical guidance for PMT/vPvM substance assessment, but rather it is on
124 how grouping strategies can be used to screen, assess, regulate and manage groups of
125 PMT/vPvM substances more efficiently.

Methods

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Definition of key terms

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128 The International Union of Pure and Applied Chemistry (IUPAC) defines a chemical substance as
129 "*matter of constant composition best characterized by the entities (molecules, formula, units,*
130 *atoms) it is composed of. Physical properties such as density, refractive index, electric*
131 *conductivity, melting point etc. characterize the chemical substance*" [27]. The term "substance"
132 in this article is used in this context. Databases also refer to chemical entities as compounds and
133 substances, but the context may be different. PubChem, for instance, define these as "*a*
134 *substance is a chemical sample description provided by a single source and a compound is a*
135 *normalized chemical structure representation found in one or more contributed substances*" [28].
136 Since this article later refers to calculations performed on PubChem queries, "compound" in this
137 article refers to a chemical that fulfils the definition of a compound according to PubChem with a
138 unique PubChem Compound Identifier (CID). A mixture, according to IUPAC, is a "*portion of*
139 *matter consisting of two or more chemical substances called constituents*" [29]. Mixtures can be
140 simple (*e.g.*, xylene is a mixture of three isomers, *o*-xylene, *m*-xylene and *p*-xylene) or complex
141 (*e.g.*, C_9-C_{14} alcohols, or mineral oils). The latter are often referred to as "substances of Unknown
142 or Variable composition, Complex reaction products or Biological origin" (UVCBs) [30].

143 A group of substances is defined by REACH as substances that have "(1) a common functional
144 group; (2) the common precursors and/or the likelihood of common breakdown products via
145 physical and biological processes, which result in structurally similar chemicals; or (3) a constant
146 pattern in the changing of the potency of the properties across the category." (REACH Regulation
147 EC No 1907/2006, Annex XI, Section 1.5) [31]. In other words, the term "group" and "category"

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148 are used interchangeably in this article. As an example, two widely regulated groups of
149 substances that fulfil all three aspects of grouping substances in the REACH regulation are
150 dioxins (polychlorinated dibenzo-p-dioxins and polychlorinated dibenzo-furans) [32] and
151 polychlorinated biphenyls (PCBs) [33], which are composed of about 210 [34] and 209 individual
152 congeners, respectively [35].

Literature analysis

154 To obtain relevant literature to underpin the arguments in this paper, a comprehensive literature
155 search spanning both policy-related documents (e.g., regulations, guidelines, analysis, dossiers)
156 and scientific literature was conducted using keywords like "persistent, mobile and toxic", "very
157 persistent very mobile", "substance grouping" and "chemical regulation" in electronic databases
158 such as PubMed and Google Scholar, while filtering for relevance. As the study focus area was
159 mainly the European Union, recent policy documents in the EU and United Nations were
160 considered most relevant due to the greater activity on PMT/vPvM substances, while detailed
161 policy analysis of areas outside the European Union was considered out of scope. Scientific
162 studies focused on grouping strategies for the assessment and management of substances,
163 including chemicals, pollutants, and contaminants that exhibit persistence and mobility in the
164 environment were also considered relevant. Backward citation searching was also conducted
165 from the list of relevant articles to identify additional studies that may have been overlooked during
166 the electronic search. By systematically executing the search strategy across multiple databases
167 and supplementing it with hand-searching reference lists, a comprehensive selection of relevant
168 literature with findings focused on the topic was compiled and considered in this article.

Cheminformatics analysis

170 For cheminformatics analysis, the search functions available in the PubChem database [4] were
171 used to obtain the structural and substructural data of compounds of interest. The OPERA
172 ReadyBiodegradable model version 2.9 [36] was used to predict the persistence of compounds,
173 along with the KOCWIN model version 2.00 [37] to predict the mobility (log K_{oc} values) of the
174 compounds from the PubChemLite for Exposomics dataset, Version 1.27.0 [38] and other subsets
175 of compounds extracted from PubChem. Further details of other datasets used can be found in
176 the "availability of data and material" section below. The toxicity predictions were performed with
177 MS2Tox version 0.3.2 [39]. Data processing was performed in R version 4.3.1 [40] using the

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178 packages Tidyverse version 2.0.0 [41, 42] and ggplot2 version 3.4.3 [43, 44] for data
179 transformation and plotting, and RChemMass 0.1.28 [45] for obtaining the exact mass before
180 MS2Tox calculations. Additional information is given in the "Cheminformatics challenges in
181 grouping PMT/vPvM substances" section below.

Overview of PMT/vPvM Substances

183 Assessment of the number of substances being introduced to the global chemical market that
184 may be PMT/vPvM substances requires a clear set of criteria and the ability to scale the
185 application of these criteria to large numbers. The EU Chemicals, Labelling and Packaging (CLP)
186 regulation (EC 1272/2008) criteria for PMT/vPvM substances [11] are displayed in Figure 1. The
187 **mobility** (M) aspect (see Figure 1A) is defined based on the organic-carbon-water partition
188 coefficient (K_{OC}, with units of L/kg) of a chemical which is then log transformed to log K_{OC} values,
189 this is used as a proxy to describe the sorption potential of a chemical to organic carbon. Since
190 experimental log K_{OC} data are rare, it was suggested that the logarithmic octanol-water partition
191 coefficient (log K_{OW} or log P) or the pH-adjusted log D_{OW} (or log D) could be used as a screening
192 parameter for hydrophobicity where high-quality log K_{OC} data are not available [24, 46]. Though
193 the two parameters have some variance, particularly for ionogenic substances, substances with
194 very low log D_{OW} values tend to have very low log K_{OC} values, hence log D_{OW} values were seen
195 as a good alternative screening parameter for mobility. As such they are often used in a
196 complementary fashion (see [24, 47] for more details), where log K_{OW} and log D_{OW} data are used
197 when log K_{OC} data are unavailable. **Persistence** (P) is defined based on the half-lives of a
198 chemical in different environmental water, sediment and soil systems (see Figure 1B), and
199 **toxicity** (T) is defined based on one or a combination of the following: carcinogenicity,
200 mutagenicity, reproductive toxicity, endocrine disruption and specific target organ toxicity after
201 repeated exposure as well as long-term no-observed effect concentration (NOEC) and effect
202 concentration at a given percentage of the population (EC_x) shown in Figure 1C.

203 A compound is a considered a PMT substances when it fulfils the persistence, mobility and toxicity
204 criteria (i.e. a combination of at least one persistency criterion, one mobility criterion and one
205 toxicity criterion are met) or in the case of vPvM at least one of the criteria for very persistent and
206 the very mobile criterion must be met (see Figure 1). Some examples of PMT/vPvM substances
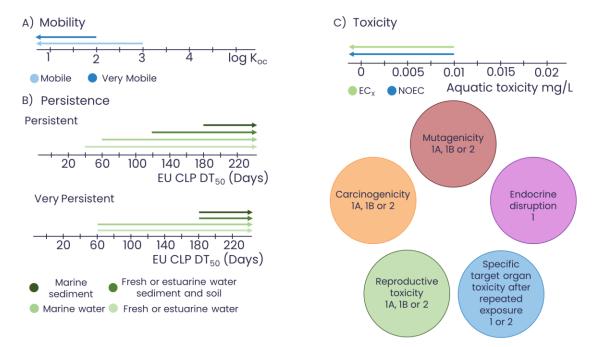207 are shown in Figure 2.

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209 **Figure 1:** EU CLP criteria [11] for PMT/vPvM substances. *A) Mobility criteria based on log K_{OC}*
210 *(blue). B) Persistence criteria, with persistent in green and C) Toxicity criteria, including*
211 *carcinogenicity, mutagenicity, endocrine disruption, specific target toxicity and reproductive*
212 *toxicity (1A, 1B, 1 and 2 refer to the categories for that criterion) as well as concentrations, where*
213 *long-term no observable effect concentration (NOEC), and effect concentration (EC_x) for marine*
214 *and freshwater organisms refers to the concentration where a toxic effect was observed in a given*
215 *percentage of the population e.g. 10% for EC_{10} at less than 0.01 mg/L.*
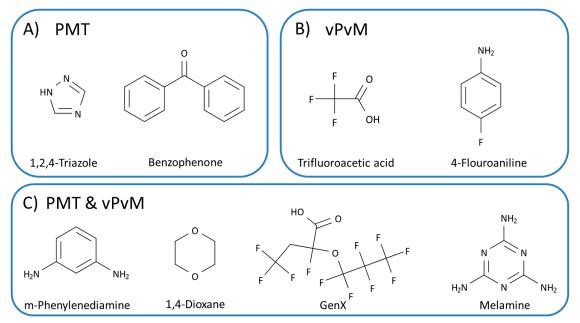
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218 **Figure 2:** Selected examples of potential PMT/vPvM substances from the UBAPMT list assessed
219 by Arp and Hale (2022) as meeting the criteria [20, 24]. *A) PMT substances; B) vPvM substances;*
220 *C) both PMT and vPvM substances.*

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There are several published lists containing PMT/vPvM substances (e.g. the PMT list by Holmberg et al., UBAPMT, EAWAGPMT, UFZHSFPMT, ZEROPM and PMTPFAS) [20, 48–52]. The later five have been digitized and are hosted on the NORMAN Suspect List Exchange (NORMAN-SLE) [53, 54] and thus openly available with a CC-BY license. The UBAPMT suspect list contains substances currently registered under REACH that meet the proposed PMT/vPvM criteria set by UBA in 2019 [47]. The original list has 254 substances [55, 56], while the 2022 revised version has 340 substances [57, 58] due to an increase in chemicals registered in REACH and updated chemical information [20]. The EAWAGPMT list contains 1,156 compounds identified in groundwater by Kiefer *et al.* [49, 59]. This list contains a mix of compounds on other PMT lists as well as compounds on the Swedish Chemical Agency (KEMI) market list [60] that have a low log *D*ow and high water exposure index, while the UFZHSFPMT list includes 1,063 potential persistent mobile compounds detected in surface water as described by Neuwald *et al.* [50, 61, 62]. The ZEROPMBOX1 contains 38 compounds, including representative per- and poly-fluoroalkyl substances (PFAS), triazines and triazoles used to start the H2020 ZeroPM project [51]. Finally, the PMTPFAS list contains 180 fluorinated compounds extracted from the UBAPMT, EAWAGPMT and UFZHSFPMT lists [52]. 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 [25]. Assessing chemicals individually also ignores cumulative exposures and risks of groups of substances [63]. 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 [64, 65] and specific groups of persistent organic pollutants (POPs) under the Stockholm Convention [66] are discussed below. Moreover, successfully grouping substances for regulation not only accelerates but also prevents and

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252 reduces inconsistencies in the regulatory process [67]. Grouping substances can enhance
253 chemical safety management, facilitating the identification of regulated substances and potential
254 substitutes for harmful ones [67].

255 While there may be several legislations about grouping substances globally, this section focuses
256 on the use of grouping in EU legislation. In the EU, the European Chemical Agency (ECHA)
257 coordinates the REACH regulation for the restriction, evaluation and authorization of substances
258 based on hazard classifications and the CLP regulation for labelling based on hazard
259 classifications. REACH Annex XI section 1.5 specifies how groups or categories of substances
260 can be defined and which regulatory actions can be applied [31]. It states that "*substances whose*
261 *physicochemical, toxicological and ecotoxicological properties are likely to be similar or follow a*
262 *regular pattern as a result of structural similarity may be considered as a group, or 'category' of*
263 *substances*" [31]. The toxicological or hazard properties referred to are described in the CLP
264 regulation shown in Figure 1.

265 According to Article 36 of the CLP regulation, certain substances, including those with respiratory
266 sensitizing properties (category 1), germ cell mutagenicity, carcinogenicity, and reproductive
267 toxicity (category 1A, 1B and 2), are considered hazardous and are subject to harmonized
268 classification. This also applies to active substances listed in Regulation (EC) No 1107/2009 and
269 Regulation (EU) No 528/2012 [68, 69]. Moreover, Article 57 of REACH includes substances that
270 are hazardous to the environment and are also subject to harmonized classification. A list of these
271 hazardous substances for which harmonized classification and labelling has been established at
272 the EU level can be found in Part 3 of Annex VI of the CLP regulation.

273 Under REACH, UVCBs are regulated based on the structural similarity of the constituents
274 identified and can also be regulated as part of a different group. This means that certain
275 components of these substances may be identified and registered as part of a different group.
276 Annex XI section 1.5 of REACH provides more information on the regulation of UVCBs [31, 70].

277 Existing grouping legislation and impacts

278 The Montreal Protocol on Ozone-Depleting Substances

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279　The Montreal Protocol regulates the manufacturing and consumption of ODS [64, 71]. This is a
280　group of over 100 substances including chlorofluorocarbons (CFCs), methyl chloroform,
281　hydrochlorofluorocarbons (HCFCs) and hydrobromofluorocarbons (HBFCs) that release chlorine
282　and bromine into the stratosphere, damaging the ozone layer [64, 72]. This can lead to increased
283　global warming, skin cancer and damage to marine ecosystems [73]. The Montreal Protocol is
284　considered to have drastically decreased relative consumption (total of production and imports -
285　total of exports and destroyed) of ODS in the EU (100% to 0.36%) and globally (100% to 1.35%)
286　between 1986 and 2021 [71, 74], as shown in Figure 3. This is an example of a property-based
287　regulatory effort that has been successful [71, 75]. However, the Montreal Protocol has also been
288　criticized for shifting the burden by transitioning from ODS to greenhouse gases and PMT/vPvM
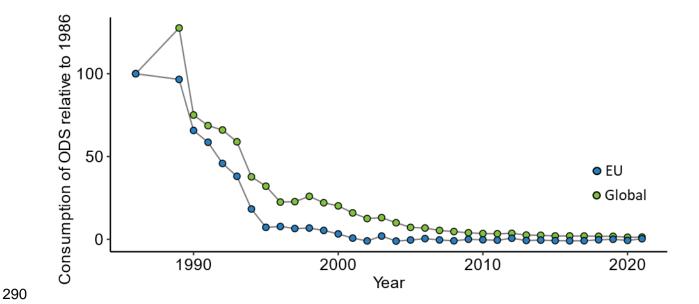289　precursors, as discussed further below.

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291　**Figure 3**: *EU and global relative consumption of ODS since 1986* [74] *showing the reduction of*
292　*the consumption of ODS due to the Montreal Protocol.*

The Stockholm Convention on Persistent Organic Pollutants

295　The Stockholm Convention was signed in 2001 to protect humans and the environment from
296　POPs [66]. An EU Legislation regulation (EC No 850/2004) was adopted later to implement the
297　Convention in the EU [76, 77]. Initially, the Convention regulated 12 POPs or groups of POPs

298 such as aldrin, chlordane and dichlorodiphenyltrichloroethane (DDT). Over time, the list expanded
299 to include 39 substances and substance groups as of January 2024, with the regulation covering
300 the manufacturing, sales, use, and waste management of these chemicals, as well as
301 unintentional releases in some cases [66, 78]. Structural similarity and the resulting similar
302 compound properties played a major role in managing the grouping of substances under the
303 Convention, for instance, polychlorinated biphenyls (PCBs), dioxins and DDT derivatives [79].
304 The Stockholm Convention has been successful in reducing the emission of regulated POPs
305 since its enforcement. The emission levels of PCBs, for example, decreased by over 60% from
306 2001 to 2020, while dioxin levels also dropped by 50% from 2001 to 2020 (top of Figure 4). This
307 reduction is also noticeable as the number of registered patents for 17 dioxins, 12 PCBs and
308 hexachlorobenzene (HCB) dropped since the Convention (bottom of Figure 4).
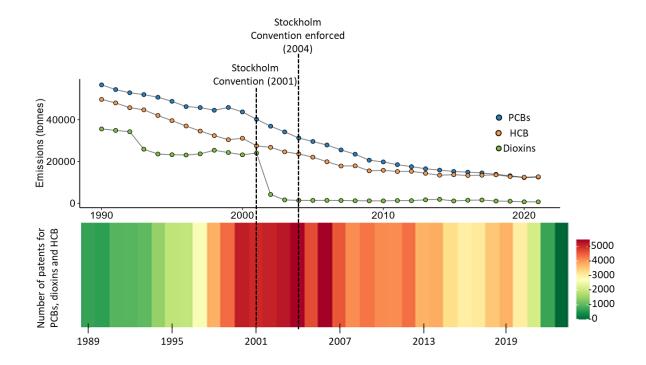

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*Figure 4: Top: Emission tonnage of PCB, dioxins and HCB from regulation (EU) No 277/2012,
between 1990 to 2020 [80]. Bottom: The chemical stripes drawn using the chemical stripes
package in R [81] show a decrease in the number of registered patents of PCB, dioxins and HCB
in PubChem; the date range was chosen to match the emission data.*

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Substitution of regulated substances with PMT/vPvM substances

The concept of regrettable substitution first appeared in the literature in 2011 [82]. 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 [83]. One well-known example is Bisphenol A, an endocrine-disrupting chemical (EDC) that was first discovered in 1891 [84]. 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 [85].

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 [63]. Unfortunately, similar toxicological effects are likely to occur as well [26], 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 [86, 87]. Later, hydrobromofluorocarbons (HBFCs) were introduced as replacements but were only briefly commercialized [88]. They were then replaced with hydrochlorofluorocarbons (HCFCs), which exhibited substantially less ozone-depleting potential, and exhibited the same commercial properties as CFCs [89]. HCFCs were eventually also included under the Montreal Protocol and were again replaced by chemicals with similar chemistry, hydrofluorocarbons (HFCs) [64]. Due to the removal of chlorine atoms from the molecules, HFCs no longer pose a threat to the stratospheric ozone layer [90], 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 [90, 91]. 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 [92, 93]. 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 [94, 95], other studies have shown

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mild liver hypertrophy in rats, and eye and skin irritation [94, 96]. 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 [97]. 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 [98]. To date, many monitoring programs have seen an increase in these replacements in water resources and fish due to increasing use and emissions [99]. 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 [12]. 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 [100].

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

Grouping based on structural similarity

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 [101]. This method relies on justified similarities in structure, toxicokinetic, physicochemical and molecular properties, transformation process/endpoints and other similar data for interpolation and extrapolation of relevant information [102] and is recommended in Section 1.5 of Annex XI of the REACH regulation for groups of substances [70]. 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) [101, 103]. 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 [101, 102]. The Read-Across Assessment Framework (RAAF) by ECHA and the OECD guidance on the grouping of chemicals have been developed to guide systematic and consistent applications of read-across [104, 105].

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) [106]. 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 [107]. However, read-across requires an adequate justification for use, and appropriate documentation covering all assumptions and conclusions [36, 107]. This can be complex and may require a certain level of expertise for interpretation [108]. Despite its limitations, read-across can be applied to the grouping of PMT/vPvM substances.

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 [109].

15

407   Compounds with molecules containing high bond dissociation energies can be flagged for
408   persistence assessment and subsequent inclusion as PMT/vPvM if each of the M and/or T criteria
409   are met. Biodegradability models can be used to quickly provide relevant information about the
410   persistence of many substances or the presence of many persistent substructures, pending
411   further investigation and confirmation by experimental studies [110]. However, the applicability
412   domain of available models is dependent on their training data, resulting in unreliable predictions
413   for compound classes that may not be covered yet [110].

414   For mobility, the chemical substructures that are associated with low K_{OC} values are those that
415   are highly polar or ionic, as this favours their water solubility over sorption to soil organic carbon
416   [24, 111]. A 2022 review found that most ionic compounds with measured log K_{OC} values have
417   log K_{OC} values <4.0 [24]. Thus, the presence of many hydrophilic substituents may be a predictor
418   of mobility, and conversely, chemicals with largely hydrophobic substructures are unlikely to be
419   mobile in the environment. However, an important limitation of mobility is size. Extremely large
420   molecules that are highly polar and ionic may not be mobile if they have sufficient hydrophobic
421   substructures to decrease their solubility, or (as in the case of water-soluble polymers) can
422   aggregate for charge neutrality and therefore lose/reduce their mobility as an aggregate [112].
423   Quantitative structure-activity relationship (QSAR) models are available to predict the mobility of
424   certain substances and can be applied effectively (within their respective applicability domains)
425   to classify the mobility of substances.

426   The toxicity of a substance is related to its chemical structure and determines the type of health
427   effects it induces in the biological systems [113]. The interaction of a chemical with a biological
428   system is determined by the functional groups, stereochemistry and other molecular features
429   [114]. A change in the structure can lead to changes in toxicity, depending on how this change
430   affects the toxicophore – the structural portion associated with the toxicity of the chemical [115].
431   The descriptors used for toxicity predictions vary between models, some models consider only
432   2D descriptors, while others use a mix of 2D and 3D descriptors. In recent years some models
433   have also attempted to predict toxicity through graph neural networks which take the position of
434   the different functional groups into consideration [116, 117]. Toxicity is also related to the
435   absorption, distribution, metabolism and excretion ability of the body, which depends on the
436   chemical structure of the substance. Increased hydrophobicity leads to increased absorption and
437   increased potential toxic effects (due to potential bioaccumulation). A concern with PMT/vPvM
438   substances is chronic exposure via water consumption, which can lead to elevated concentrations
439   in humans and diverse biota [12, 118].

16

440 Considering the chemical features that make these substances P, M and T, and the provided
441 criteria for classification, PMT/vPvM substances can be identified and grouped accordingly. Read-
442 across can be applied to identify PMT substances on the basis that they have similar
443 (sub)structures, similar properties and available toxicological data. This can be done through a
444 fragment-based approach, which relies on the identification of small similar fragments or
445 functional groups with similar properties [119]. Substance grouping approaches take the fragment
446 models one step further. Substances can have similar properties due to the similarity in structures
447 – this includes functional groups, common precursors or reaction products, and a constant pattern
448 in the changing of the potency of the properties across the group [31, 104]. The substance
449 grouping approach is used in read-across techniques and alternative assessments [104]. This
450 has been supported by the use of various models that predict physical-chemical property
451 information such as the KOCWIN model [120]. This is a fragment-based model that relates
452 substructures and mobility (K_{OC}) based on appropriate training data [120].. The mobility (K_{OC}) of
453 new chemicals can be predicted using the established relationship (when they are within the
454 applicability domain). Similarly, the ReadyBiodegradable model in OPERA [36] and CERAPP and
455 CoMPARA models [116, 121]can be used to predict the biodegradability and toxicity, respectively,
456 of many new PMT/vPvM substances.

Grouping based on retained moieties from transformation reactions

459 Both biotic and abiotic transformations generally result in transformation products (TPs) with
460 significantly higher mobility (lower log K_{OW}) than their parent compounds or precursors, making
461 them more mobile in the environment. This seems intuitive as one of the "goals" of metabolism
462 and wastewater treatment processes is to increase the polarity of the compounds. For metabolic
463 processes, this allows the compounds to be expelled from the body with the urine. However, some
464 persistent substructures may be retained during the transformation resulting in similar toxic
465 properties between the parent compound and TPs. For example, decabromodiphenyl ethane
466 forms 6 metabolites that were found to be carcinogenic like the parent compound [122]. In other
467 cases, even small structural changes can result in large differences in toxicity such as for
468 bis(pentabromophenyl) ether, which has low thyroid binding affinity itself but can form the TP
469 2,3,5,6-tetrabromo-4-(2,3,4,5,6-pentabromophenoxy)phenol with a strong thyroid binding affinity
470 [122]. Therefore, it is of interest not only to identify parent compounds that may be PMT/vPvM,

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471   but also compounds that can form PMT/vPvM TPs, along with identifying the common persistent

472   and mobile moieties that were retained and not readily metabolized. Such an approach would be

473   consistent with the approach to substance grouping in REACH of identifying "common breakdown

474   products via physical and biological processes, which result in structurally similar chemicals"

475   (REACH Annex XI, Section 1.5).

476   One way to do this identification is by using known reactions, such as those contained within the

477   "transformations" section in PubChem, which links parent compounds to TPs with basic reaction

478   information [123]. Of all the substances on the five suspect lists mentioned above,

479   perfluorooctanoic acid (PFOA) has the highest number of recorded parent compounds (22) in the

480   PubChem transformations section (from version 0.1.6 of the dataset archived on Zenodo) [124].

481   This is also one of several PMT/vPvM TPs where parent compounds are included in the legislation

482   as part of the substance group. Specifically, the Stockholm Convention restricts the use of PFOA-

483   related compounds, which include compounds that form PFOA after degradation [78]. TFA is also

484   a known TP of several different compounds containing a CF_3- moiety. Since there are over 5

485   million compounds containing a CF_3- moiety included in PubChem [125], many of which are also

486   industrially relevant, there are myriad potential sources of TFA.

487   Triazoles are another example of moieties preserved from parent compounds to TPs. Out of the

488   triazole compounds in PubChem, 62 have recorded TPs (12 Jan 2024) [124]. This corresponds

489   to 233 unique reactions, out of which the triazole moiety is retained in 88% of the cases, showing

490   its high stability. While usually not acutely toxic in low doses, triazoles may cause several severe

491   chronic toxic effects such as endocrine disruption and neurotoxicity [126]. Triazole substances

492   such as benzotriazoles are present in the environment at high levels [126]. Thus, the retention of

493   this functional group and other PMT/vPvM moieties may be concerning from an exposure point

494   of view, supporting the idea that grouping based on retained moieties or TPs is relevant to obtain

495   comprehensive and inclusive groups for PMT/vPvM substances.

496   Another example of how substances can be regulated based on their precursors are the aromatic

497   amines registered under REACH some of which can also be found on PMT/vPvM suspect lists,

498   such as 4,4'-methylenedianiline, 4,4'-oxydianiline, 4-chloroaniline, 3,3'-dichlorobenzidine, 4,4'-

499   methylenebis(2-chloroaniline), 4,4'-methylenedianiline, and 2-methoxy-5-methylaniline [20, 31,

500   50]. However, there are several other aromatic amines that have multiple known precursors listed

501   in the PubChem transformations library (e.g. 4-aminophenol and aniline) that are also listed as

18

502   PMT by the UBAPMT suspect list. As such, regulating aromatic amines and precursor substances

503   as a group based on PMT/vPvM substances warrants further investigation and consideration.

504

Cheminformatics challenges in grouping PMT/vPvM substances

507   The strategies mentioned above regarding grouping can be matched to substance regulation in

508   various ways. Firstly, substances falling within a PMT/vPvM group with little known data could be

509   flagged for follow-up to see if persistence and mobility measurements have been conducted in

510   literature, and if read-across methods (based on patterns with other substances) could be used

511   to fill data gaps. This could help prioritise filling data gaps and would help develop read-across

512   approaches for further substances within the group. Secondly, if any other substance with a

513   similar structure exists in the group and is hazardous (source substance), this could be seen as

514   a reason to investigate for similar toxicological hazards for this substance (target substance). If

515   several members within a group are shown to be PMT/vPvM substances, then a precautionary

516   approach would be to assume all group members with no assessments are similarly hazardous,

517   until there is sufficient scientific data to show otherwise. An overview of an assessment procedure

518   to identify PMT/vPvM substances has also been presented by Neumann and Schliebner (2019),

519   suggesting to first assess compounds for persistence followed by mobility and toxicity for both

520   precursors and transformation products [47].

521   Estimating the number of individuals and groups of chemicals that fit the PMT/vPvM classification

522   is a challenging task. Most substances lack readily available persistence, mobility and toxicity

523   data. Due to the limited data availability, the prediction models of these properties are also limited

524   in their accuracy and applicability domains. However, some data and models are available as a

525   starting point, especially for log K_{OW}. For example, both XlogP and the newer XlogP3 [127, 128]

526   and the KOWWIN [129] module in EPI Suite [130] use a multivariate regression approach to K_{OW}

527   prediction. While K_{OC} data is more limited than K_{OW} data, there are also several models which

528   attempt to predict K_{OC}, including KOCWIN from EPI Suite [37] and the K_{OC} module of OPERA

529   [36], which both utilise the training data from the PHYSPROP database [36, 37]. For persistence,

530   OPERA also contains three modules for predicting biodegradability (BiodegHL,

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531 ReadyBiodegradable and Km) as well as one module predicting rate constants for gas-phase
532 reactions with hydroxyl-radicals, though with more limited applicability domains compared to the
533 K_{OC} module [36]. The prediction of toxicity is even more challenging due to the limited availability
534 of training data. However, models already exist for several toxicological endpoint predictions such
535 as endocrine disruption, mutagenicity and developmental toxicity for many possible structures
536 [131, 132]. For example, the CERAPP and CoMPARA models in OPERA can be used to predict
537 estrogen and androgen receptor interactions [116, 121].

538 An example of how a combination of experimental and predicted property data has been used to
539 classify compounds as PMT/vPvM is the study by Arp and Hale (2022), which focused on the
540 compounds in the REACH inventory [24]. Their study concluded that about 1.9% of substances
541 registered in REACH and 24% of REACH-registered substances that were detected in drinking
542 water sources would be classified as PMT. However, over 40% of the inventory could not be
543 assessed due to data gaps. This illustrates the importance of acquiring experimental data for a
544 wider range of compounds.

545 To further illustrate how predicted properties can be used for assessing PMT compounds, the
546 PubChemLite for Exposomics [133] dataset was used to give a preliminary estimate of the number
547 of potential environmental contaminants that are predicted to meet the CLP definition of mobility.
548 PubChemLite is a subset of ~350,000 compounds from PubChem with environmentally relevant
549 annotation content [133]. In total, K_{OC} values were predicted for 346,133 compounds (96.0% of
550 PubChemLite) using the molecular connectivity index (MCI) model from KOCWIN [37, 120]. The
551 results of the log K_{OC} distribution are shown in Figure 5. Based on these predicted values log K_{OC},
552 147,930 compounds (41%) would be considered mobile and 78,107 compounds (21%) would be
553 considered very mobile. The MCI model assigns values of 1 and 0 for chemicals when K_{OC}
554 predictions have been overcorrected. The large peak at log K_{OC} 10 is an upper bound for these
555 predictions within the MCI model output. Note that the results of this analysis will differ if the K_{OW}-
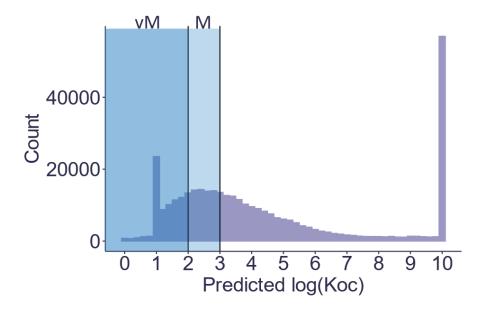556 based model in KOWWIN is used.

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Figure 5: Predicted log K_{OC} via KOCWIN values for PubChemLite (346,133 compounds total) [38, 133]. *Some K_{OC} predictions fall outside the applicability domain of the model.* The "count" *is the number of compounds inside each bin. Bin widths are 0.2.*

To investigate this concept 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) [20, 49–52]. 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) [125]. 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

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577   based on the predicted log K_{OW} from XlogP3. As such the substructures used when discussing

578   PMT/vPvM compound grouping for regulation purposes should be more specific.

579   More specific substructure queries were used to interrogate these results further according to the

580   PMT/vPvM criteria, shown in the remaining rows of Table 1 and Figure 6, using the structures of

581   melamine, benzotriazole and benzidine as well as the "larger PFAS parts" definition (contains –

582   CF_2CF_{2-}) from the PubChem PFAS tree [125]. The search was then progressively restricted to

583   exclude the searched substructures from being part of larger ring systems and substances with

584   molecular weights greater than 300 g/mol. The results of this search were also used to perform

585   persistence and toxicity prediction as discussed above. The top two rows of Figure 6 show these

586   substructure query results. Like their less specific triazine counterpart, they seem too broad to

587   capture only PMT/vPvM substances. However, when restricting the search to only compounds

588   below 300 g/mol, between 87 and 99% of the compounds would meet the CLP definition of

589   mobility. The most restricted PubChem search results were also used for biodegradability and

590   LC_{50} predictions using the ReadyBiodegradable model from OPERA and MS2Tox (compounds

591   which fell outside the applicability domain of the ReadyBiodegradable model were excluded in

592   the biodegradability results; this information is not given by MS2Tox). As can be seen in Figure

593   6, almost all compounds inside the applicability domain were classified as non-biodegradable.

594   This indicates that in addition to their mobility, most compounds within these classes are

595   potentially persistent. Based on the EU CLP definition of toxicity, an EC_{10} less than 0.01 mg/L is

596   toxic for marine or freshwater organisms. Some of the predicted LC_{50} toxicity values (the lethal

597   concentration at 50% of the population) shown in Figure 6 go below 0.1 mg/L. As toxicity is usually

598   observed before lethality, this indicates that some of the compounds may be toxic below 0.01

599   mg/L. In addition, it is important to note that this is not the only toxicity criterion used in the CLP,

600   for example, triazole compounds have been shown to have endocrine-disrupting properties by

601   e.g., Wang et al. (2022) [134] and thus it is likely that at least a fraction of these compounds would

602   be classified as PMT.

603

22

604 *Table 1: Overview of the PubChem substructure searches (queries performed on 19/12/2023).*
605 *Default settings for all queries were (1) single or double bonds match aromatic bonds (2) chain*
606 *bonds in the query may match rings in hits and (3) remove any explicit hydrogens before*
607 *searching. Extra settings "Ring" (rings may not be embedded in a larger system) and the filter*
608 *"MW<300" (Molecular weight < 300 g/mol) are indicated in the respective column. Query URLs*
609 *are embedded into the substructure column. The first three rows in italics are generic queries, the*
610 *latter rows are the queries used to generate Figure 6 and are coloured accordingly. The OECD*
611 *PFAS results were obtained via the PubChem classification browser. DB = database, values in*
612 *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

23
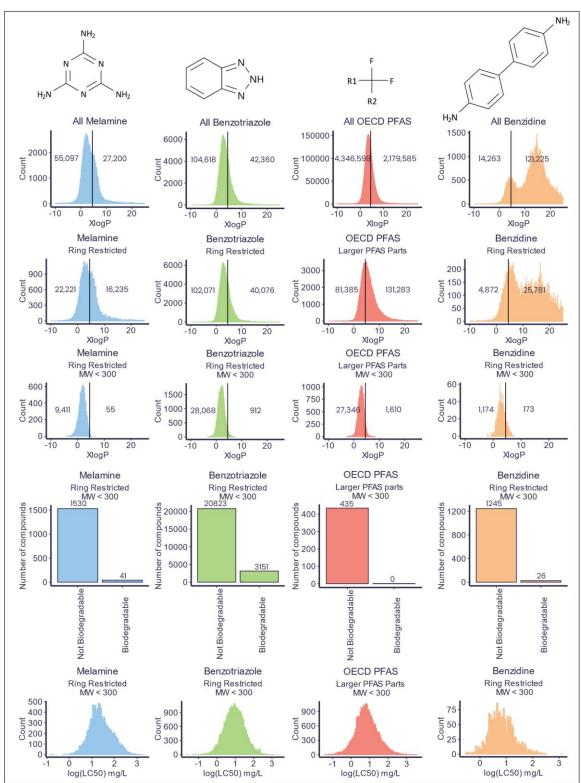
Figure 6: *Distribution of PubChem XlogP3 values for four searches with varying restrictions (top three rows), plus predicted biodegradability from the OPERA ReadyBiodegradable model and LC$_{50}$ values (in mg/L) predicted from MS2Tox for the most restricted search queries (last two rows). Search settings and total numbers are given in Table 1. It should be noted that MS2Tox is used for illustration purposes only, and does not reflect the CLP toxicity criteria in Figure 1.*

Perspectives for grouping strategies

Challenges for assessing and managing PMT/vPvM substances

Based on the criteria for persistence, mobility and toxicity, many chemicals (as shown from the prediction results above) 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 [135]. 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 [136].

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. Non-target analysis can be a first step in identifying unknown and emerging PMT/vPvM substances and their TPs in environmental and biological matrices. It can also be used for the monitoring of known PMT/vPvM substances, yet regulatory acceptance of non-targeted monitoring is still lacking [137]. 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 [22].

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

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646 grouping strategies above to prioritize chemicals for assessing their PMT/vPvM properties.
647 Exposure and emission information could serve in the prioritization of chemicals for testing.
648 Utilising exposure information such as mode of exposure (chemicals in food or drinking water)
649 [138, 139] or Occupational Exposure Banding strategy for categorization of airborne substances
650 lacking defined limits [140], could help identify chemicals with high exposure potential.
651 Additionally, the hazard level of the toxicity can be used as a criterion, where specific persistent
652 and mobile substances with high toxicity can be targeted for prioritization.

653 The use of *in vitro*, *in vivo*, and *in silico* approaches can aid the grouping and prioritization of
654 chemicals for testing or assessments by regulatory bodies. This can be done by generating
655 grouping hypotheses and justification for inclusion or exclusion criteria for substances in groups
656 [140]. In particular, novel approaches may generate huge amounts of toxicological and high-
657 throughput "omics" data including metabolomics, transcriptomics, and exposomics to support the
658 validation and establishment of grouping hypotheses needed by regulatory authorities [141]. An
659 example of a grouping hypothesis is the mode of action (MOA) hypothesis, which states that all
660 chemicals that share a common mode of action are candidates for grouping [142]. Additionally,
661 concepts such as adverse outcome pathways and toxicity pathways can be translated into
662 prioritization hypotheses that can target specific substances, hence advancing prioritization for
663 hazard assessment [143, 144]. These can facilitate regulator efforts to restrict hazardous
664 substances.

665 Measurable biological and physiological effects of chemical exposure, known as effect
666 biomarkers, can be used to group PMT/vPvM substances according to their toxicological profiles.
667 If two substances induce similar biomarker responses indicative of for instance genotoxicity, or
668 endocrine disruption, they can be grouped. This approach can also help to identify common
669 pathways of toxicity, adverse outcome pathways (AOPs), or mechanisms of toxicity. By grouping
670 substances with similar toxic profiles as PMT/vPvM substances, effect biomarkers can aid in
671 characterizing cumulative risks posed by mixtures and complex chemical substances. This
672 proactive approach focuses on biological effects rather than relying solely on the structural and
673 chemical properties of PMT/vPvM substances [145, 146]

674 It is crucial to recognize that the effectiveness of strategies used for prioritizing substances largely
675 depends on the availability of relevant data, including hazard and exposure data. To improve the
676 availability and quality of such data, it is necessary to foster collective efforts such as high-quality
677 data generation, community-level data collection, Open Science, FAIR data, and enhanced data

678 sharing policies. When potential vPvM substances are identified by read-across and experimental
679 evidence as substances that meet the PMT/vPvM criteria, then a hazard classification would be
680 required. The data collected through these efforts can then be used to enhance the prioritization,
681 identification, and regulation of PMT/vPvM substances. To manage PMT/vPvM substances
682 effectively, manufacturers can be encouraged to submit a plan to remove these substances from
683 wastewater. This approach can help improve the overall management of PMT/vPvM substances.
684 As a precaution, the principle of "as low as reasonably achievable" (ALARA) can be applied to
685 minimize exposure levels and reduce the risk of harm to PMT/vPvM substances [147].

686

Conclusion

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

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

702 Read-across based on structural or substructural similarity is one of the strategies that could be
703 used to group PMT/vPvM substances, which relies on the idea that substances with similar
704 structures have similar properties. Commonly retained moieties from transformation reactions
705 could also be a grouping strategy for PMT/vPvM substances. Substances that are structurally

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706   similar to PMT/vPvM according to read-across, or form persistent, mobile TPs could be flagged
707   for subsequent assessment and/or regulatory actions.

708   Cheminformatics may be used for substance grouping based on predictive models for properties
709   such as biodegradability, mobility, and toxicity. PubChemLite predictions suggest that 41% of
710   potentially environmentally relevant compounds would be considered mobile (147,930
711   compounds) and 21% would be considered very mobile (78,107 compounds). Certain compound
712   classes, such as triazines, aromatic amines, triazoles and PFAS, are likely to be persistent, non-
713   biodegradable, and toxic. As shown in Table 1, the numbers are high and restricting these
714   compounds as a group would be challenging; however, prioritizing members of these large groups
715   for property testing is warranted as they contain a substructure associated with a PMT/vPvM
716   substance group. Additional strategies are needed to prioritize some substances for regulation,
717   such as mapping the uses of these chemicals and exposure which requires more data availability
718   following FAIR principles.

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

726   **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_x	Effect concentration at X percentage
ECHA	European Chemical Agency
EDC	Endocrine-disrupting chemical
EU	European Union
HBFCs	Hydrobromofluorocarbons

28

Abbreviations	Full Meaning
HCB	Hexachlorobenzene
HCFCs	Hydrochlorofluorocarbons
HFCs	Hydrofluorocarbons
HFOs	Hydrofluoroolefins
HTS	High-Throughput Screening
IUPAC	International Union of Pure and Applied Chemistry
KEMI	Swedish Chemical Agency
K_{OC}	Organic-carbon-water partition coefficient
K_{OW}	Octanol-water partition coefficient at pH = 7
log P	Logarithm of K_{OW}
M	Mobility
MCI	Molecular Connectivity Index
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
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
SVHCs	Substances of Very High Concern
T	Toxicity
TFA	Trifluoroacetic acid
TPs	Transformation products
UBA	Umweltbundesamt (German Environmental Agency)
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

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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).

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Competing interests

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References

1. Fuller R, Landrigan PJ, Balakrishnan K, et al (2022) Pollution and health: a progress
    update. The Lancet Planetary Health 6:e535–e547. https://doi.org/10.1016/S2542-
    5196(22)00090-0

2. United Nations (2015) Resolution adopted by the General Assembly on 25 September
    2015. Transforming our world: the 2030 Agenda for Sustainable Development.
    https://undocs.org/Home/Mobile?FinalSymbol=A%2FRES%2F70%2F1&Language=E&De
    viceType=Desktop&LangRequested=False

3. Wang Z, Walker GW, Muir DCG, Nagatani-Yoshida K (2020) Toward a Global
    Understanding of Chemical Pollution: A First Comprehensive Analysis of National and

781   Regional Chemical Inventories. Environ Sci Technol 54:2575–2584.
782   https://doi.org/10.1021/acs.est.9b06379

783 4.   Kim S, Chen J, Cheng T, et al (2023) PubChem 2023 update. Nucleic Acids Research
784   51:D1373–D1380. https://doi.org/10.1093/nar/gkac956

785 5.   PubChem (2023) PubChem-Explore Chemistry. https://pubchem.ncbi.nlm.nih.gov/.
786   Accessed 4 Dec 2023

787 6.   CAS CAS REGISTRY | CAS. https://www.cas.org/cas-data/cas-registry. Accessed 30 Jan
788   2024

789 7.   Resnik DB, Portier CJ (2022) Environment, Ethics, and Human Health - The Hastings
790   Center. https://www.thehastingscenter.org/briefingbook/environmental-health/. Accessed
791   6 Nov 2023

792 8.   Persson L, Carney Almroth BM, Collins CD, et al (2022) Outside the Safe Operating Space
793   of the Planetary Boundary for Novel Entities. Environ Sci Technol 56:1510–1521.
794   https://doi.org/10.1021/acs.est.1c04158

795 9.   Eurostat (2023) Chemicals production and consumption statistics - Statistics Explained.
796   https://ec.europa.eu/eurostat/databrowser/view/sdg_12_10/default/bar?lang=en.
797   Accessed 4 Oct 2023

798 10.   SCHEER (Scientific Committee on Health, Environmental and Emerging Risks) (2018)
799   Statement on emerging health and environmental issues.
800   https://health.ec.europa.eu/system/files/2019-02/scheer_s_002_0.pdf

801 11.   European Commission (2022) Commission Delegated Regulation (EU) 2023/707 of 19
802   December 2022 amending Regulation (EC) No 1272/2008 as regards hazard classes and
803   criteria for the classification, labelling and packaging of substances and mixtures.
804   https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32023R0707

805 12.   Hale SE, Arp HPH, Schliebner I, Neumann M (2020) Persistent, mobile and toxic (PMT)
806   and very persistent and very mobile (vPvM) substances pose an equivalent level of concern
807   to persistent, bioaccumulative and toxic (PBT) and very persistent and very
808   bioaccumulative (vPvB) substances under REACH. Environ Sci Eur 32:155.
809   https://doi.org/10.1186/s12302-020-00440-4

810 13.   Matthies M, Solomon K, Vighi M, et al (2016) The origin and evolution of assessment
811   criteria for persistent, bioaccumulative and toxic (PBT) chemicals and persistent organic
812   pollutants (POPs). Environ Sci: Processes Impacts 18:1114–1128.
813   https://doi.org/10.1039/C6EM00311G

814 14.   Shrestha P, Junker T, Fenner K, et al (2016) Simulation Studies to Explore Biodegradation
815   in Water–Sediment Systems: From OECD 308 to OECD 309. Environ Sci Technol
816   50:6856–6864. https://doi.org/10.1021/acs.est.6b01095

817 15.   Van Dijk J, Figuière R, Dekker SC, et al (2023) Managing PMT/vPvM substances in
818   consumer products through the concepts of essential-use and functional substitution: a

32

819   case-study for cosmetics. Environ Sci: Processes Impacts 25:1067–1081.
820   https://doi.org/10.1039/D3EM00025G

821   16.   Albergamo V, Escher BI, Schymanski EL, et al (2020) Evaluation of reverse osmosis
822   drinking water treatment of riverbank filtrate using bioanalytical tools and non-target
823   screening. Environ Sci: Water Res Technol 6:103–116.
824   https://doi.org/10.1039/C9EW00741E

825   17.   Camacho L, Kelly KP, Beland FA, Gamboa da Costa G (2011) Gene expression of
826   biomarkers of nephrotoxicity in F344 rats co-exposed to melamine and cyanuric acid for
827   seven days. Toxicol Lett 206:166–171. https://doi.org/10.1016/j.toxlet.2011.07.009

828   18.   Habotta OA, Abdeen A, Roomi AB, et al (2023) Nootkatone Mitigated Melamine-Evoked
829   Hepatotoxicity by Featuring Oxidative Stress and Inflammation Interconnected
830   Mechanisms: In Vivo and In Silico Approaches. Toxics 11:784.
831   https://doi.org/10.3390/toxics11090784

832   19.   Hau AK, Kwan TH, Li PK (2009) Melamine Toxicity and the Kidney. Journal of the American
833   Society of Nephrology 20:245–250. https://doi.org/10.1681/ASN.2008101065

834   20.   Arp HPH, Hale SE, Schliebner I, Neumann M (2022) S36 | UBAPMT | Prioritised PMT/vPvM
835   substances in the REACH registration database _all versions.
836   https://doi.org/10.5281/ZENODO.2653212

837   21.   Aumeier BM, Georgi A, Saeidi N, Sigmund G (2023) Is sorption technology fit for the
838   removal of persistent and mobile organic contaminants from water? Science of The Total
839   Environment 880:163343. https://doi.org/10.1016/j.scitotenv.2023.163343

840   22.   Rüdel H, Körner W, Letzel T, et al (2020) Persistent, mobile and toxic substances in the
841   environment: a spotlight on current research and regulatory activities. Environ Sci Eur 32:5.
842   https://doi.org/10.1186/s12302-019-0286-x

843   23.   Lütjens LH, Pawlowski S, Silvani M, et al (2023) Melamine in the environment: a critical
844   review of available information. Environmental Sciences Europe 35:2.
845   https://doi.org/10.1186/s12302-022-00707-y

846   24.   Arp HPH, Hale SE (2022) Assessing the Persistence and Mobility of Organic Substances
847   to Protect Freshwater Resources. ACS Environ Au 2:482–509.
848   https://doi.org/10.1021/acsenvironau.2c00024

849   25.   Tickner JA, Schifano JN, Blake A, et al (2015) Advancing safer alternatives through
850   functional substitution. Environmental science & technology 49:742–749.
851   https://doi.org/10.1021/es503328m

852   26.   Žalmanová T, Hošková K, Nevoral J, et al (2016) Bisphenol S instead of bisphenol A: a
853   story of reproductive disruption by regretable substitution - a review. Czech J Anim Sci
854   61:433–449. https://doi.org/10.17221/81/2015-CJAS

855   27.   IUPAC (2019) IUPAC Compendium of Chemical Terminology, "chemical substance." 3rd
856   ed. International Union of Pure and Applied Chemistry; 2006,
857   https://doi.org/10.1351/goldbook.C01039

33

858   28.   PubChem (2024) Explore PubChem Documentation.
859   https://pubchem.ncbi.nlm.nih.gov/docs/. Accessed 23 Jan 2024

860   29.   IUPAC (2019) IUPAC Compendium of Chemical Terminology, "mixture." 3rd ed.
861   International Union of Pure and Applied Chemistry; 2006,
862   https://doi.org/10.1351/goldbook.M03949

863   30.   Dimitrov SD, Georgieva DG, Pavlov TS, et al (2015) UVCB substances: Methodology for
864   structural description and application to fate and hazard assessment. Environmental
865   Toxicology and Chemistry 34:2450–2462. https://doi.org/10.1002/etc.3100

866   31.   European Commission (2006) EUR-Lex - 02006R1907-20140410 - EN - EUR-Lex
867   Consolidated text: Regulation (EC) No 1907/2006 of the European Parliament and of the
868   Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and
869   Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending
870   Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission
871   Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission
872   Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. https://eur-
873   lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02006R1907-20140410, Accessed
874   2023-12-20

875   32.   Åberg A, MacLeod M, Wiberg K (2008) Physical-Chemical Property Data for Dibenzo-p-
876   dioxin (DD), Dibenzofuran (DF), and Chlorinated DD/Fs: A Critical Review and
877   Recommended Values. Journal of Physical and Chemical Reference Data 37:1997–2008.
878   https://doi.org/10.1063/1.3005673

879   33.   European Commission (2017) Commission Regulation (EU) 2017/644 of 5 April 2017
880   laying down methods of sampling and analysis for the control of levels of dioxins, dioxin-
881   like PCBs and non-dioxin-like PCBs in certain foodstuffs and repealing Regulation (EU) No.
882   589/2014. Official Journal of the European Union L 92/9, https://eur-
883   lex.europa.eu/eli/reg/2017/644/oj

884   34.   Mukherjee A, Debnath B, Ghosh SK (2016) A Review on Technologies of Removal of
885   Dioxins and Furans from Incinerator Flue Gas. Procedia Environmental Sciences 35:528–
886   540. https://doi.org/10.1016/j.proenv.2016.07.037

887   35.   Garmash O, Hermanson MH, Isaksson E, et al (2013) Deposition History of Polychlorinated
888   Biphenyls to the Lomonosovfonna Glacier, Svalbard: A 209 Congener Analysis. Environ
889   Sci Technol 47:12064–12072. https://doi.org/10.1021/es402430t

890   36.   Mansouri K, Grulke CM, Judson RS, Williams AJ (2018) OPERA models for predicting
891   physicochemical properties and environmental fate endpoints. J Cheminform 10:10.
892   https://doi.org/10.1186/s13321-018-0263-1

893   37.   Meylan W, Howard PH, Boethling RS (1992) Molecular topology/fragment contribution
894   method for predicting soil sorption coefficients. Environ Sci Technol 26:1560–1567.
895   https://doi.org/10.1021/es00032a011

896   38.   Bolton E, Schymanski E, Kondic T, et al (2023) PubChemLite for Exposomics (V. 1.27.0).
897   https://doi.org/10.5281/zenodo.10126889

898   39.   Peets P, Wang W-C, MacLeod M, et al (2022) MS2Tox Machine Learning Tool for
899   Predicting the Ecotoxicity of Unidentified Chemicals in Water by Nontarget LC-HRMS.
900   Environ Sci Technol 56:15508–15517. https://doi.org/10.1021/acs.est.2c02536

901   40.   R Core Team (2023) A Language and Environment for Statistical Computing. R Foundation
902   for Statistical Computing. https://cran.r-project.org/bin/windows/base/old/4.3.1/

903   41.   Wickham H, Averick M, Bryan J, et al (2019) Welcome to the Tidyverse. JOSS 4:1686.
904   https://doi.org/10.21105/joss.01686

905   42.   Hadley Wickham (2023) tidyverse 2.0.0. https://www.tidyverse.org/blog/2023/03/tidyverse-
906   2-0-0/

907   43.   Wickham H, Chang W, Wickham MH (2016) Package 'ggplot2.' Create elegant data
908   visualisations using the grammar of graphics Version 2:1–189.
909   https://ggplot2.tidyverse.org/reference/ggplot2-package.html

910   44.   Thomas Lin Pedersen (2024) ggplot2 3.5.0.
911   https://github.com/tidyverse/ggplot2/releases/tag/v3.5.0

912   45.   Emma L. Schymanski (2020) RChemMass: Various Cheminformatic, Curation and Mass
913   Spectrometry Functions. https://github.com/schymane/RChemMass

914   46.   Arp HPH, Hale SE, Schliebner I, Neumann M (2023) Prioritised PMT/vPvM substances in
915   the REACH registration database | Umweltbundesamt.
916   https://www.umweltbundesamt.de/publikationen/prioritised-pmtvpvm-substances-in-the-
917   reach. Accessed 9 Oct 2023

918   47.   Neumann M, Schliebner I (2019) Protecting the sources of our drinking water: The criteria
919   for identifying persistent, mobile and toxic (PMT) substances and very persistent and very
920   mobile (vPvM) substances under EU Regulation REACH (EC) No 1907/2006.
921   https://www.umweltbundesamt.de/sites/default/files/medien/1410/publikationen/2019-11-
922   29_texte_127-2019_protecting-sources-drinking-water-pmt.pdf

923   48.   Holmberg R, Wedebye EB, Nikolov NG, Tyle H (2021) How many potential vPvM/PMT
924   substances have been registered under REACH?-vPvM/PMT-screening by using the
925   Danish (Q) SAR database.
926   https://backend.orbit.dtu.dk/ws/portalfiles/portal/240040384/111514_909384_DTU_Rapp
927   ort_vPvM_PMT_CB_7kor_links.pdf

928   49.   Kiefer K, Du L, Singer H, Hollender J (2021) S82 | EAWAGPMT | PMT Suspect List from
929   Eawag. https://doi.org/10.5281/ZENODO.5500131

930   50.   Neuwald I, Muschket M, Zahn D, et al (2021) S84 | UFZHSFPMT | PMT Suspect List from
931   UFZ and HSF. https://doi.org/10.5281/ZENODO.5535287

932   51.   Schymanski E, Wang Z, Wolf R, Arp HP (2022) S90 | ZEROPMBOX1 | ZeroPM Box 1
933   Substances. https://doi.org/10.5281/ZENODO.5854251

934   52.   Schymanski E (2023) S111 | PMTPFAS | Fluorine-containing Compounds in PMT Suspect
935   Lists. https://doi.org/10.5281/ZENODO.8417075

936 53. Mohammed Taha H, Aalizadeh R, Alygizakis N, et al (2022) The NORMAN Suspect List
937   Exchange (NORMAN-SLE): facilitating European and worldwide collaboration on suspect
938   screening in high resolution mass spectrometry. Environ Sci Eur 34:104.
939   https://doi.org/10.1186/s12302-022-00680-6

940 54. NORMAN Network (2024) NORMAN Suspect List Exchange. https://www.norman-
941   network.com/nds/SLE/. Accessed 30 Jan 2024

942 55. Arp HPH, Hale SE (2020) S36 | UBAPMT | Potential Persistent, Mobile and Toxic (PMT)
943   substances_V.0.2. https://doi.org/10.5281/ZENODO.3637611

944 56. UBA (2019) REACH: Improvement of guidance and methods for the identification and
945   assessment of PMT/vPvM substances | Umweltbundesamt.
946   https://www.umweltbundesamt.de/en/publikationen/reach-improvement-of-guidance-
947   methods-for-the. Accessed 4 Oct 2023

948 57. Arp HPH, Hale SE (2020) S36 | UBAPMT | Potential Persistent, Mobile and Toxic (PMT)
949   substances V.0.3. https://doi.org/10.5281/ZENODO.3637611

950 58. UBA (2023) Prioritised PMT/vPvM substances in the REACH registration database.
951   https://www.umweltbundesamt.de/sites/default/files/medien/11850/publikationen/21_2023
952   _texte_pmt_vpvm_substances_reach_v23032023.pdf

953 59. Kiefer K, Du L, Singer H, Hollender J (2021) Identification of LC-HRMS nontarget signals
954   in groundwater after source related prioritization. Water Research 196:116994.
955   https://doi.org/10.1016/j.watres.2021.116994

956 60. Fischer S (2023) S17 | KEMIMARKET | KEMI Market List.
957   https://doi.org/10.5281/ZENODO.2628786

958 61. Neuwald I, Muschket M, Zahn D, et al (2021) Filling the knowledge gap: A suspect
959   screening study for 1310 potentially persistent and mobile chemicals with SFC- and HILIC-
960   HRMS in two German river systems. Water Research 204:117645.
961   https://doi.org/10.1016/j.watres.2021.117645

962 62. Neuwald I, Muschket M, Zahn D, et al (2021) A suspect screening list of 1310 persistent
963   and mobile (PM) candidates. https://doi.org/10.5281/zenodo.5503380

964 63. Blum A, Behl M, Birnbaum LS, et al (2019) Organophosphate Ester Flame Retardants: Are
965   They a Regrettable Substitution for Polybrominated Diphenyl Ethers? Environ Sci Technol
966   Lett 6:638–649. https://doi.org/10.1021/acs.estlett.9b00582

967 64. UNEP (2023) About Montreal Protocol. https://www.unep.org/ozonaction/who-we-
968   are/about-montreal-protocol. Accessed 7 Oct 2023

969 65. United Nations (1989) Montreal Protocol on Substances that Deplete the Ozone Layer (with
970   annex). Concluded at Montreal on 16 September 1987.
971   https://treaties.un.org/doc/publication/unts/volume%201522/volume-1522-i-26369-
972   english.pdf Vol. 1522, 1-26369:

973 66. Stockholm Convention (2023) Overview.
974 https://www.pops.int/TheConvention/Overview/tabid/3351/Default.aspx. Accessed 7 Oct
975 2023

976 67. ECHA (2020) Grouping speeds up regulatory action Integrated Regulatory Strategy Annual
977 Report.
978 https://echa.europa.eu/documents/10162/5641810/irs_annual_report_2019_en.pdf

979 68. European Commission (2022) Consolidated text: Regulation (EC) No 1107/2009 of the
980 European Parliament and of the Council of 21 October 2009 concerning the placing of plant
981 protection products on the market and repealing Council Directives 79/117/EEC and
982 91/414/EEC. https://eur-lex.europa.eu/legal-
983 content/EN/TXT/?uri=CELEX%3A02009R1107-20221121

984 69. European Commission (2022) Consolidated text: Regulation (EU) No 528/2012 of the
985 European Parliament and of the Council of 22 May 2012 concerning the making available
986 on the market and use of biocidal products (Text with EEA relevance)Text with EEA
987 relevance. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02012R0528-
988 20220415

989 70. European Commission (2021) Commission Regulation (EU) 2021/979 of 17 June 2021
990 amending Annexes VII to XI to Regulation (EC) No 1907/2006 of the European Parliament
991 and of the Council concerning the Registration, Evaluation, Authorisation and Restriction
992 of Chemicals (REACH). https://eur-lex.europa.eu/eli/reg/2021/979/oj. Accessed 16 Oct
993 2023

994 71. Gonzalez M, Taddonio KN, Sherman NJ (2015) The Montreal Protocol: how today's
995 successes offer a pathway to the future. J Environ Stud Sci 5:122–129.
996 https://doi.org/10.1007/s13412-014-0208-6

997 72. Ravishankara AR, Daniel JS, Portmann RW (2009) Nitrous oxide (N2O): the dominant
998 ozone-depleting substance emitted in the 21st century. Science 326:123–125.
999 https://doi.org/DOI: 10.1126/science.1176985

1000 73. Umar SA, Tasduq SA (2022) Ozone Layer Depletion and Emerging Public Health Concerns
1001 - An Update on Epidemiological Perspective of the Ambivalent Effects of Ultraviolet
1002 Radiation Exposure. Front Oncol 12:866733. https://doi.org/10.3389/fonc.2022.866733

1003 74. EEA (2023) EU and global consumption of controlled ozone-depleting substances —
1004 European Environment Agency. In: European Environmental Agency.
1005 https://www.eea.europa.eu/data-and-maps/figures/consumption-of-controlled-ozone-
1006 depleting-5/. Accessed 7 Oct 2023

1007 75. Nunez C (2023) Ozone layer facts and information.
1008 https://www.nationalgeographic.com/environment/article/ozone-depletion. Accessed 9 Jan
1009 2024

1010 76. ECOLEX (2004) Regulation (EC) No. 850/2004 of the European Parliament and of the
1011 Council on persistent organic pollutants and amending Directive 79/117/EEC.
1012 https://www.ecolex.org/details/legislation/regulation-ec-no-8502004-of-the-european-

1013 parliament-and-of-the-council-on-persistent-organic-pollutants-and-amending-directive-
1014 79117eec-lex-faoc087038/. Accessed 9 Oct 2023

1015 77. Wheeler AF (2017) Study on the cumulative health and environmental benefits of chemical
1016 legislation: final report. https://data.europa.eu/doi/102779/070159

1017 78. Stockholm Convention (2024) Listing of POPs in the Stockholm Convention.
1018 https://www.pops.int/TheConvention/ThePOPs/AllPOPs/tabid/2509/Default.aspx.
1019 Accessed 7 Oct 2023

1020 79. United Nations The 12 Initial POPs.
1021 https://www.pops.int/TheConvention/ThePOPs/The12InitialPOPs/tabid/296/Default.aspx,
1022 Accessed 2024-01-30

1023 80. EEA (2023) National emissions reported to the Convention on Long-range Transboundary
1024 Air Pollution (LRTAP Convention). In: European Environmental Agency.
1025 https://www.eea.europa.eu/en/datahub/datahubitem-view/5be6cebc-ed2b-4496-be59-
1026 93736fc4ad78?activeAccordion=1086857. Accessed 7 Oct 2023

1027 81. Aurich D (2024) Environmental Cheminformatics / chemicalstripes · GitLab.
1028 https://gitlab.lcsb.uni.lu/eci/chemicalstripes, Accessed 31 Jan 2024

1029 82. Maertens A, Golden E, Hartung T (2021) Avoiding Regrettable Substitutions: Green
1030 Toxicology for Sustainable Chemistry. ACS Sustainable Chem Eng 9:7749–7758.
1031 https://doi.org/10.1021/acssuschemeng.0c09435

1032 83. Young AS, Allen JG, Kim U-J, et al (2018) Phthalate and Organophosphate Plasticizers in
1033 Nail Polish: Evaluation of Labels and Ingredients. Environ Sci Technol 52:12841–12850.
1034 https://doi.org/10.1021/acs.est.8b04495

1035 84. Tyl RW (2014) Abbreviated assessment of bisphenol A toxicology literature. Seminars in
1036 Fetal and Neonatal Medicine 19:195–202. https://doi.org/10.1016/j.siny.2013.11.010

1037 85. ECHA (2021) Assessment of regulatory needs.
1038 https://echa.europa.eu/documents/10162/1bd5525c-432c-495d-9dab-d7806bf34312

1039 86. McKenzie R, Bernhard G, Liley B, et al (2019) Success of Montreal Protocol Demonstrated
1040 by Comparing High-Quality UV Measurements with "World Avoided" Calculations from Two
1041 Chemistry-Climate Models. Sci Rep 9:12332. https://doi.org/10.1038/s41598-019-48625-z

1042 87. UNEP-Ozone secretariat (2023) Consumption of controlled substances-Data in tables |
1043 Ozone Secretariat. https://ozone.unep.org/countries/data-
1044 table?report_type=0&output_type=odp-CO2e-
1045 tonnes&party_grouping=individual&eu_member%5Bis_eu_member%5D=is_eu_member
1046 &period_start=1986&period_end=2022&ignore_zero=1&baseline=1&group_by=group&op
1047 =GENERATE+REPORT&form_id=ozone_country_data_form__report_table_form.
1048 Accessed 15 Dec 2023

1049 88. Tapscott RE, Moore TA, Mather JD, Vitali JA (1998) Halon replacement research–a
1050 historical review of technical progress and regulatory decision points. Halons Options

38

1051   Technical Working Conference, Albuquerque, NM,
1052   https://www.nist.gov/system/files/documents/el/fire_research/R0000266.pdf

1053   89. Sukornick B (1989) Potentially acceptable substitutes for the chlorofluorocarbons:
1054   properties and performance features of HFC-134a, HCFC-123, and HCFC-141b. Int J
1055   Thermophys 10:553–561. https://doi.org/10.1007/BF00507978

1056   90. Benhadid-Dib S, Benzaoui A (2012) Refrigerants and their Environmental Impact
1057   Substitution of Hydro Chlorofluorocarbon HCFC and HFC Hydro Fluorocarbon. Search for
1058   an Adequate Refrigerant. Energy Procedia 18:807–816.
1059   https://doi.org/10.1016/j.egypro.2012.05.096

1060   91. Heath EA (2017) Amendment to the Montreal Protocol on Substances that Deplete the
1061   Ozone Layer (Kigali Amendment). Int leg mater 56:193–205.
1062   https://doi.org/10.1017/ilm.2016.2

1063   92. Luecken DJ, Waterland RL, Papasavva S, et al (2010) Ozone and TFA Impacts in North
1064   America from Degradation of 2,3,3,3-Tetrafluoropropene (HFO-1234yf), A Potential
1065   Greenhouse Gas Replacement. Environ Sci Technol 44:343–348.
1066   https://doi.org/10.1021/es902481f

1067   93. Rivela CB, Tovar CM, Teruel MA, et al (2019) CFCs replacements: Reactivity and
1068   atmospheric lifetimes of a series of Hydrofluoroolefins towards OH radicals and Cl atoms.
1069   Chemical Physics Letters 714:190–196. https://doi.org/10.1016/j.cplett.2018.10.078

1070   94. Boutonnet JC, Bingham P, Calamari D, et al (1999) Environmental Risk Assessment of
1071   Trifluoroacetic Acid. Human and Ecological Risk Assessment: An International Journal
1072   5:59–124. https://doi.org/10.1080/10807039991289644

1073   95. Solomon KR, Carr JA, Du Preez LH, et al (2008) Effects of atrazine on fish, amphibians,
1074   and aquatic reptiles: a critical review. Critical reviews in toxicology 38:721–772.
1075   https://doi.org/10.1080/10408440802116496

1076   96. Dekant W, Dekant R (2023) Mammalian toxicity of trifluoroacetate and assessment of
1077   human health risks due to environmental exposures. Arch Toxicol 97:1069–1077.
1078   https://doi.org/10.1007/s00204-023-03454-y

1079   97. Morgan K, Bonanno F (2022) Sustainability is no longer a "nice to have" goal for the data
1080   center industry | S&P Global Market Intelligence.
1081   https://www.spglobal.com/marketintelligence/en/news-insights/research/sustainability-is-
1082   no-longer-a-nice-to-have-goal-for-the-data-center-industry. Accessed 16 Oct 2023

1083   98. Wang Z, DeWitt JC, Higgins CP, Cousins IT (2017) A Never-Ending Story of Per- and
1084   Polyfluoroalkyl Substances (PFASs)? Environ Sci Technol 51:2508–2518.
1085   https://doi.org/10.1021/acs.est.6b04806

1086   99. Knutsen H, Mæhlum T, Haarstad K, et al (2019) Leachate emissions of short- and long-
1087   chain per- and polyfluoralkyl substances (PFASs) from various Norwegian landfills. Environ
1088   Sci: Processes Impacts 21:1970–1979. https://doi.org/10.1039/C9EM00170K

1089 100. Helmer RW, Reeves DM, Cassidy DP (2022) Per- and Polyfluorinated Alkyl Substances
1090   (PFAS) cycling within Michigan: Contaminated sites, landfills and wastewater treatment
1091   plants. Water Research 210:117983. https://doi.org/10.1016/j.watres.2021.117983

1092 101. ECHA (2013) Grouping of substances and read-across approach Part 1: Introductory note.
1093   https://www.echa.europa.eu/documents/10162/17221/read_across_introductory_note_en.
1094   pdf/1343b1b8-e5d1-4e72-b9b3-8a99e940ab29

1095 102. Lamon L, Asturiol D, Richarz A, et al (2018) Grouping of nanomaterials to read-across
1096   hazard endpoints: from data collection to assessment of the grouping hypothesis by
1097   application of chemoinformatic techniques. Part Fibre Toxicol 15:37.
1098   https://doi.org/10.1186/s12989-018-0273-1

1099 103. Schultz TW, Amcoff P, Berggren E, et al (2015) A strategy for structuring and reporting a
1100   read-across prediction of toxicity. Regulatory Toxicology and Pharmacology 72:586–601.
1101   https://doi.org/10.1016/j.yrtph.2015.05.016

1102 104. ECHA (2017) Read-across assessment framework (RAAF). ECHA-17-R-01-EN.
1103   https://doi.org/10.2823/619212

1104 105. OECD (2017) Guidance on Grouping of Chemicals, Second Edition.
1105   https://doi.org/10.1787/9789264274679-en

1106 106. Patlewicz G, Helman G, Pradeep P, Shah I (2017) Navigating through the minefield of read-
1107   across tools: A review of in silico tools for grouping. Computational Toxicology 3:1–18.
1108   https://doi.org/10.1016/j.comtox.2017.05.003

1109 107. Tate T, Wambaugh J, Patlewicz G, Shah I (2021) Repeat-dose toxicity prediction with
1110   Generalized Read-Across (GenRA) using targeted transcriptomic data: A proof-of-concept
1111   case study. Computational Toxicology 19:100171.
1112   https://doi.org/10.1016/j.comtox.2021.100171

1113 108. ECHA (2023) Substance group and analogy concept - ECHA.
1114   https://echa.europa.eu/de/support/registration/how-to-avoid-unnecessary-testing-on-
1115   animals/grouping-of-substances-and-read-across. Accessed 20 Dec 2023

1116 109. Luo Y-R (2007) Comprehensive Handbook of Chemical Bond Energies.
1117   https://www.taylorfrancis.com/books/9781420007282 9780429128684:

1118 110. Hafner J, Fenner K, Scheidegger A (2023) Systematic Handling of Environmental Fate
1119   Data for Model Development—Illustrated for the Case of Biodegradation Half-Life Data.
1120   Environ Sci Technol Lett 10:859–864. https://doi.org/10.1021/acs.estlett.3c00526

1121 111. Sigmund G, Arp HPH, Aumeier BM, et al (2022) Sorption and Mobility of Charged Organic
1122   Compounds: How to Confront and Overcome Limitations in Their Assessment. Environ Sci
1123   Technol 56:4702–4710. https://doi.org/10.1021/acs.est.2c00570

1124 112. Zahn D, Neuwald IJ, Knepper TP (2020) Analysis of mobile chemicals in the aquatic
1125   environment—current capabilities, limitations and future perspectives. Anal Bioanal Chem
1126   412:4763–4784. https://doi.org/10.1007/s00216-020-02520-z

40

113. Barratt MD (2000) Prediction of toxicity from chemical structure. Cell Biology and Toxicology 16:1–13. https://doi.org/10.1023/A:1007676602908

114. Struyf J (2009) Relating Functional Groups to the Periodic Table. J Chem Educ 86:190. https://doi.org/10.1021/ed086p190

115. Singh PK, Negi A, Gupta PK, et al (2016) Toxicophore exploration as a screening technology for drug design and discovery: techniques, scope and limitations. Arch Toxicol 90:1785–1802. https://doi.org/10.1007/s00204-015-1587-5

116. Mansouri K, Abdelaziz A, Rybacka A, et al (2016) CERAPP: Collaborative Estrogen Receptor Activity Prediction Project. Environ Health Perspect 124:1023–1033. https://doi.org/10.1289/ehp.1510267

117. Liu J, Lei X, Zhang Y, Pan Y (2023) The prediction of molecular toxicity based on BiGRU and GraphSAGE. Computers in Biology and Medicine 153:106524. https://doi.org/10.1016/j.compbiomed.2022.106524

118. Freeling F, Scheurer M, Koschorreck J, et al (2022) Levels and Temporal Trends of Trifluoroacetate (TFA) in Archived Plants: Evidence for Increasing Emissions of Gaseous TFA Precursors over the Last Decades. Environ Sci Technol Lett 9:400–405. https://doi.org/10.1021/acs.estlett.2c00164

119. Li Q (2020) Application of Fragment-Based Drug Discovery to Versatile Targets. Front Mol Biosci 7:180. https://doi.org/10.3389/fmolb.2020.00180

120. US EPA (2012) Estimation programs interface suite^{TM} for Microsoft® windows, v 4.11. United States Environmental Protection Agency, Washington, DC, USA. https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface

121. Mansouri K, Kleinstreuer N, Abdelaziz AM, et al (2020) CoMPARA: Collaborative Modeling Project for Androgen Receptor Activity. Environ Health Perspect 128:027002. https://doi.org/10.1289/EHP5580

122. Zheng Z, Arp HPH, Peters G, Andersson PL (2021) Combining *In Silico* Tools with Multicriteria Analysis for Alternatives Assessment of Hazardous Chemicals: Accounting for the Transformation Products of decaBDE and Its Alternatives. Environ Sci Technol 55:1088–1098. https://doi.org/10.1021/acs.est.0c02593

123. Schymanski EL, Bolton EE (2022) FAIRifying the exposome journal: Templates for chemical structures and transformations. Exposome 2:osab006. https://doi.org/10.1093/exposome/osab006

124. Schymanski E, Bolton E, Cheng T, et al (2023) Transformations in PubChem - Full Dataset. https://doi.org/105281/zenodo8117741

125. Schymanski EL, Zhang J, Thiessen PA, et al (2023) Per- and Polyfluoroalkyl Substances (PFAS) in PubChem: 7 Million and Growing. Environ Sci Technol 57, 44, 16918–16928:acs.est.3c04855. https://doi.org/10.1021/acs.est.3c04855

1164   126.   Shi Z-Q, Liu Y-S, Xiong Q, et al (2019) Occurrence, toxicity and transformation of six typical
1165   benzotriazoles in the environment: A review. Science of The Total Environment 661:407–
1166   421. https://doi.org/10.1016/j.scitotenv.2019.01.138

1167   127.   Cheng T, Zhao Y, Li X, et al (2007) Computation of Octanol−Water Partition Coefficients
1168   by Guiding an Additive Model with Knowledge. J Chem Inf Model 47:2140–2148.
1169   https://doi.org/10.1021/ci700257y

1170   128.   Wang R, Fu Y, Lai L (1997) A New Atom-Additive Method for Calculating Partition
1171   Coefficients. J Chem Inf Comput Sci 37:615–621. https://doi.org/10.1021/ci960169p

1172   129.   Meylan WM, Howard PH (1995) Atom/Fragment Contribution Method for Estimating
1173   Octanol–Water Partition Coefficients. Journal of Pharmaceutical Sciences 84:83–92.
1174   https://doi.org/10.1002/jps.2600840120

1175   130.   Card ML, Gomez-Alvarez V, Lee W-H, et al (2017) History of EPI Suite^{TM} and future
1176   perspectives on chemical property estimation in US Toxic Substances Control Act new
1177   chemical risk assessments. Environmental Science: Processes & Impacts 19:203–212.
1178   https://doi.org/10.1039/C7EM00064B

1179   131.   Cassano A, Manganaro A, Martin T, et al (2010) CAESAR models for developmental
1180   toxicity. Chemistry Central Journal 4:S4. https://doi.org/10.1186/1752-153X-4-S1-S4

1181   132.   Honma M (2020) An assessment of mutagenicity of chemical substances by (quantitative)
1182   structure–activity relationship. Genes and Environ 42:23. https://doi.org/10.1186/s41021-
1183   020-00163-1

1184   133.   Schymanski EL, Kondić T, Neumann S, et al (2021) Empowering large chemical knowledge
1185   bases for exposomics: PubChemLite meets MetFrag. J Cheminform 13:19.
1186   https://doi.org/10.1186/s13321-021-00489-0

1187   134.   Wang Y, Ning X, Li G, Sang N (2022) New insights into potential estrogen agonistic activity
1188   of triazole fungicides and coupled metabolic disturbance. Journal of Hazardous Materials
1189   424:127479. https://doi.org/10.1016/j.jhazmat.2021.127479

1190   135.   Goss K-U, Arp HPH, Bronner G, Niederer C (2009) Nonadditive effects in the partitioning
1191   behavior of various aliphatic and aromatic molecules. Environmental Toxicology and
1192   Chemistry 28:52–60. https://doi.org/10.1897/08-189.1

1193   136.   Villeneuve DL, Coady K, Escher BI, et al (2019) High-throughput screening and
1194   environmental risk assessment: State of the science and emerging applications.
1195   Environmental Toxicology and Chemistry 38:12–26. https://doi.org/10.1002/etc.4315

1196   137.   Hollender J, Schymanski EL, Ahrens L, et al (2023) NORMAN guidance on suspect and
1197   non-target screening in environmental monitoring. Environmental Sciences Europe 35:75.
1198   https://doi.org/10.1186/s12302-023-00779-4

1199   138.   Cramer GM, Ford RA, Hall RL (1976) Estimation of toxic hazard—A decision tree approach.
1200   Food and Cosmetics Toxicology 16:255–276. https://doi.org/10.1016/S0015-
1201   6264(76)80522-6

1202 139. EFSA Scientific Committee, More SJ, Bampidis V, et al (2019) Guidance on the use of the
1203 Threshold of Toxicological Concern approach in food safety assessment. EFS2 17:.
1204 https://doi.org/10.2903/j.efsa.2019.5708

1205 140. Wohlleben W, Mehling A, Landsiedel R (2023) Lessons Learned from the Grouping of
1206 Chemicals to Assess Risks to Human Health. Angew Chem Int Ed 62:e202210651.
1207 https://doi.org/10.1002/anie.202210651

1208 141. Zhu H, Zhang J, Kim MT, et al (2014) Big Data in Chemical Toxicity Research: The Use of
1209 High-Throughput Screening Assays To Identify Potential Toxicants. Chem Res Toxicol
1210 27:1643–1651. https://doi.org/10.1021/tx500145h

1211 142. Enoch SJ, Roberts DW (2011) Approaches for Grouping Chemicals into Categories.
1212 https://doi.org/10.1039/9781849731744-00030

1213 143. Ankley GT, Bennett RS, Erickson RJ, et al (2010) Adverse outcome pathways: A
1214 conceptual framework to support ecotoxicology research and risk assessment. Enviro
1215 Toxic and Chemistry 29:730–741. https://doi.org/10.1002/etc.34

1216 144. Vinken M (2013) The adverse outcome pathway concept: A pragmatic tool in toxicology.
1217 Toxicology 312:158–165. https://doi.org/10.1016/j.tox.2013.08.011

1218 145. Rodríguez-Carrillo A, Rosenmai AK, Mustieles V, et al (2021) Assessment of chemical
1219 mixtures using biomarkers of combined biological activity: A screening study in human
1220 placentas. Reproductive Toxicology 100:143–154.
1221 https://doi.org/10.1016/j.reprotox.2021.01.002

1222 146. Zare Jeddi M, Hopf NB, Viegas S, et al (2021) Towards a systematic use of effect
1223 biomarkers in population and occupational biomonitoring. Environment International
1224 146:106257. https://doi.org/10.1016/j.envint.2020.106257

1225 147. Hansson SO (2013) Chapter 9 - ALARA: What is Reasonably Achievable? In: Oughton D,
1226 Hansson SO (eds) Radioactivity in the Environment. Elsevier, pp 143–155

1227

43