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Review

Towards 'one substance – one assessment': An analysis of EU chemical registration and aquatic risk assessment frameworks

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ABSTRACT

With the Green Deal the EU aims to achieve a circular economy, restore biodiversity and reduce environmental pollution. As a part of the Green Deal a 'one-substance one-assessment' (OS-OA) approach for chemicals has been proposed. The registration and risk assessment of chemicals on the European market is currently fragmented across different legal frameworks, dependent on the chemical's use. In this review, we analysed the five main European chemical registration frameworks and their risk assessment procedures for the freshwater environment, covering 1) medicines for human use, 2) veterinary medicines, 3) pesticides, 4) biocides and 5) industrial chemicals. Overall, the function of the current frameworks is similar, but important differences exist between the frameworks' environmental protection goals and risk assessment strategies. These differences result in inconsistent assessment outcomes for similar chemicals. Chemicals are also registered under multiple frameworks due to their multiple uses, and chemicals which are not approved under one framework are in some instances allowed on the market under other frameworks. In contrast, an OS-OA will require a uniform hazard assessment between all different frameworks. In addition, we show that across frameworks the industrial chemicals are the least hazardous for the freshwater environment (median PNEC of 2.60E-2 mg/L), whilst biocides are the most toxic following current regulatory assessment schemes (median PNEC of 1.82E-4 mg/L). Finally, in order to facilitate a successful move towards a OS-OA approach we recommend a) harmonisation of environmental protection goals and risk assessment strategies, b) that emission, use and production data should be made publicly available and that data sharing becomes a priority, and c) an alignment of the criteria used to classify problematic substances.

1. Introduction

Chemical substances form a core part of our everyday lives as they provide vital services for our health, food security and industrial production. Over 350,000 chemicals for production and use have been registered world-wide and over 174,000 of those are registered at the European Chemicals Agency (ECHA) (ECHA, n.d.; Wang et al., 2020). Over the last decades, the worldwide consumption of chemicals has increased both in volume and in diversity and these trends are expected to continue, both due to increasing living standards and due to technological developments resulting in new chemicals entering the market (Bernhardt et al., 2017; United Nations Environment Programme, 2019). In Europe, the total consumption of chemicals has been around 300 million tonnes since 2005 (EUROSTAT, 2018), but for some specific groups of chemicals, for instance, medicines increasing consumption can be observed (OECD, 2014).

Before placement on the European market, chemicals need to be registered. The first EU chemicals policy was developed in the 1960s with the directive on classification, packaging and labelling of dangerous substances (Council Directive 67/548/EEC). Since then, EU chemicals legislation evolved with the development of new directives and regulations separated by market type. For instance, biocides, industrial chemicals, pesticides, medicines for human use and veterinary medicines are regulated independently by Reg (EC) No 528/2012, Reg (EC) No 1907/2006a, Reg (EC) No 1107/2009, Directive 2001a/83/EC and Directive 2001b/82/EC, respectively. European chemical regulations aim to safeguard human and environmental health, to ensure free movement of substances and products in the EU, to maintain the functioning of the internal market as well as to promote competitiveness and innovation. When compared to chemical legislations from countries

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such as the USA, Japan and Canada EU legislation is considered the most conservative (Botos et al., 2019; ECSIP Consortium, 2016; Handford et al., 2015). An important principle underlying all EU chemical legislation is the precautionary principle (Article 191, 2016/C 202/01). This principle relates to an approach where decision-makers should adopt precautionary measures when there is a risk of harm to human or environmental health, but scientific evidence on the risk is uncertain.

Despite this, several studies indicate that chemical pollution affects biodiversity in EU water bodies (Johnson et al., 2020; Malaj et al., 2014). Currently, more than 50% of EU water bodies are in poor ecological condition (European Environment Agency, 2018; Posthuma et al., 2019) and chemicals are increasingly being detected in EU surface and drinking waters (Baken et al., 2018; Escher et al., 2020). Future societal developments are also expected to result in higher concentrations of (new) chemicals in the environment (Bunke et al., 2019). From these observations it is clear that the current chemical legislation is not sufficiently protective of the environment. Also on a global scale further increase in the amount and diversity of chemicals being used is of high concern for both human and environmental health and chemical pollution is currently listed as one of the five main drivers for loss of global biodiversity (IPBES, 2019). Public awareness on harmful effects that chemicals can have is increasing and was, for example, highlighted by debates on the carcinogenicity of glyphosate (Van Straalen and Legler, 2018) and acrylamide (Rudén, 2004) or the endocrine disrupting properties of chemicals such as bisphenol A (Vandenberg et al., 2009). At present 90% of EU citizens worry about the impact of chemicals on the environment (European Union, 2020) increasing the pressure on policy makers to make EU chemicals regulation more stringent.

The current regulation of chemicals is fragmented and there are many signs that current regulation of chemicals in the EU can be further improved in order to safeguard both human and environmental health (Topping et al., 2020). The EU already committed to multiple (global) policy initiatives for safe management of chemicals. As agreed during the 2002 World Summit on Sustainable Development (WSSD), a safe management of chemicals throughout their lifecycle should be achieved by the year 2020. In addition, the 7th Environment Action Programme (7 EAP) explicitly stated that to meet the WSSD 2020 chemicals goal, adverse effects on human health and the environment need to be minimised and the ability to deal with emerging issues and challenges in an effective, efficient, coherent and coordinated manner needs to be improved. In the 7 EAP it was noted that to protect the health of citizens, a strategy for a non-toxic environment needs to be developed (European Parliament, 2013). Subsequently the EC evaluated its legislations for pesticides and industrial chemicals (European Commission, 2018a, 2018b; SAPEA, 2018) and conducted a study to identify shortcomings in current chemicals policies and legislative frameworks to reach a non-toxic environment (European Commission, 2017). Furthermore, a number of EU funded research projects provided input on how to protect the environment from chemical contamination (Bopp et al., 2018; Brack et al., 2019; Comero et al., 2020). An EU strategy for reaching a non-toxic environment was never published, but in December 2019 the European Commission (EC) presented the EU Green Deal: a package of measures intended to make Europe the first climate neutral continent by 2050 and to protect, conserve and enhance the environment. The Green Deal builds on the ambitions of the 7 EAP and includes a zero-pollution ambition for a toxic-free environment in order to protect citizens and the environment. For the aquatic environment the EU Green Deal states that natural functions of ground and surface water must be restored and chemical pollution of water will be addressed (European Commission, 2019).

The EC outlined several actions needed to reach the zero-pollution ambition, among them the development of a chemicals strategy for sustainability by summer 2020. The strategy will include changes to legislation and includes a shift towards a 'one substance – one assessment' (OS-OA) approach (European Commission, 2019). The EC has yet to specify the criteria for OS-OA, but the approach seems based on the 'one substance-one registration' principle currently in place under REACH. This was implemented within REACH to increase the efficiency of the registration system, to reduce costs and to reduce unnecessary testing on vertebrate animals (EU, 2006a). Implementation of OS-OA should result in better protection, more harmonisation and increased consistency across the different EU registration frameworks (Hansen, 2020), implying that chemical risk assessment approaches will be more aligned.

The aim of this review is to provide an understanding of the differences between the various EU chemical legislations and analyse how a shift towards an OS-OA approach can be realised. Five frameworks which are currently in place and together cover a large part of chemicals on the EU market are analysed in this paper: (i) Biocides (Reg (EC) No 528/2012); (ii) Industrial chemicals (REACH, (Reg (EC) No 1907/2006); (iii) Pesticides (Reg (EC) No 1107/2009); (iv) Medicines for human use (Directive, 2001/83/EC); (v) Veterinary medicines (Directive, 2001/82/EC). Under all of these frameworks, risks of chemicals to the freshwater environment can be assessed. We first compare the different EU chemical legislations by analysing registration requirements and processes. Secondly, we analyse the risk assessment frameworks for hazard and exposure assessments for the freshwater environment and analyse the different classification schemes of chemical substances. Finally, we propose possible solutions and consequences to implement an OS-OA in practise. The data collection from the present review can be found online at Mendeley Data (van Dijk et al., 2020).

2. Registration of chemicals in relation to an OS-OA

Current European chemicals legislation covering chemicals for specific uses include regulations on pesticides, biocides and medicines for human or veterinary use (Table 1). At EU level, the registration of so-called active substances -i.e. the functional chemicals that are biologically active-is coordinated. In contrast to active substances, individual member states (MS) are responsible for the assessment and approval of pesticidal and biocidal products on a national or regional level while for medicines an assessment of the whole product can be accomplished at EU level.

The registration of chemicals at EU level is coordinated by various agencies. The registrant -a manufacturer, importer or user-of a chemical submits a dossier which among other things contains information on physicochemical and (eco)toxicological properties, environmental fate as well as estimates of emissions during a chemical's intended use. This information forms the basis for the hazard, exposure and risk assessment (RA) which is carried out by either an EU committee or a MS. For chemicals regulated under REACH the compound is simply registered with ECHA and the chemical will only be evaluated, and potentially be restricted, by the MSs if risks are shown not to be manageable. In contrast, for pesticides, biocides and medicines, the dossier and RA are reviewed by both MSs and EU agencies, after which the EU agencies write an opinion on the chemical's safety. This opinion is used by the EC and forms the basis for the approval, restriction or ban of a chemical.

Despite the fact that the general principles of the registration of chemicals is the same, relevant differences between the frameworks and thereby shortcomings to realise the OS-OA approach can be identified.

2.1. Exemptions from EU registration

All active substances of biocides and pesticides are registered at EU level, but under other frameworks some exemptions for EU-wide registration exist (Table 1). Medicines can for example be placed on the market via a national or central authorised procedure. Only the centralised procedure results in the marketing on the basis of an EU-wide registration (European Medicines Agency, 2016). Under REACH, many chemicals are exempted from registration as well, including polymers and chemicals manufactured or imported below 1 tonne per year. As a consequence, the safety of many substances is not assessed. Polymer

Table 1
Overview of registration criteria and ERAs within different frameworks.

	Pharmaceuticals	Veterinary pharmaceuticals	Pesticides	Biocides	Industrial chemicals
Legislation	Directive 2001/83/EC	Directive 2001/82/EC	Reg no 1107/2009	Reg no 528/2012	Reg no 1907/2006
Number of registered and/or approved substances in October 2019	1149[a]	212[a]	477	148	22286
Agency responsible for the substance coordination	EMA	EMA	EFSA	ECHA	ECHA
Exemption from EU registration	National authorised medicines	National authorised medicines	Products	Products	Polymers; Articles; Products; Substances used and/or produced in <1 tonne/year
Amount of registration dossiers checked	100%	100%	100%	100%	20 %[b]
Environmental protection goal	No	No	Ensure a high level of protection of the environment; Prevent any unacceptable effects on the environment.	Ensure a high level of protection of the environment; Prevent harmful effects on animal health or unacceptable effects on the environment.	Ensure a high level of protection of the environment; Prevent adverse effects on the environment; Minimise significant adverse effects (by 2020, WSSD goal)
Exemption from an ERA possible	Yes[c]	Yes[d]	No	No	Yes[e]
Classification of hazardous substances	Directive 2001/83/EC	Directive 2001/82/EC	Reg (EC) No 1272/2008 (CLP)	Reg (EC) No 1272/2008 (CLP)	Reg (EC) No 1272/2008 (CLP)
Renewal of registration dossier	5 years Once renewed, authorisation is valid unlimited unless decided otherwise	5 years Once renewed, authorisation is valid unlimited period unless decided otherwise	Every 10 years Every 7 years for 'Candidates for Substitution'	Every 10 years Every 5 years for 'Candidates for Substitution'	No renewal

[a] Amount of products registered on the EU market.
[b] The target of 20% should be achieved by December 31, 2023 for registrations in tonnage bands of 100 tonnes or more per year and by December 31, 2027 for registrations in tonnage bands of less than 100 tonnes per year.
[c] Products containing: vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates, lipids as active pharmaceutical ingredient; Vaccines and herbal medicines; All substances for which the initial PEC is < 0,1 μg/L; Chemicals that were on the market before 2006.
[d] Electrolytes, peptides, proteins, vitamins and other compounds that occur naturally in the environment; When the substance is extensively metabolised in the animal, is only used in non-food animals, is used to treat a small number of animals in a flock or herd; When entry into the environment is prevented by disposal of the waste matrix; For aquatic species when they are reared in a confined facility; When the environmental introduction concentration is < 1 μg/L water or <100 μg/kg soil; Chemicals that were on the market before 2006.
[e] Substances that do not fulfil the criteria of Article 14(4) of 1907/2006/EC; Substances for which no hazards are identified in the hazard assessment.

assessment is for example only based on the individual monomers they are produced from. However, polymers exhibit different properties and are generally more persistent than individual monomers (Cousins et al., 2019; Steensgaard et al., 2017). Meanwhile, synthetic polymers have increasingly been detected in the aquatic environment and they are currently seen as major environmental pollutants (Arp and Knutsen, 2019; Klein et al., 2018; Mintenig et al., 2020).

Chemical products (mixtures such as paints and detergents) or articles (such as clothing, furniture and electrical appliances) are not considered as substances and are also not registered under REACH. Chemical products and articles are assessed based on their individual ingredients in accordance with Regulation (EC) No 1272/2008, but the safety of the whole mixture often remains unknown. Whole pesticidal and biocidal products are assessed and authorised on MS basis only. Under the biocide regulation there are mechanisms in place to settle possible disagreements on a product's safety, while for the pesticide regulation such a mechanism is lacking (European Commission, 2018a). Outcomes of product authorisation may therefore vary across MSs as details of their assessments differ.

2.2. Review of dossiers

Reviewing chemical dossiers and the included RAs, as performed by both MSs and EU agencies, is an inherent part of the registration process. However, not all substance dossiers are reviewed at EU level (Table 1). Although improvements have been made and the minimum percentage of dossiers to be checked under REACH was recently increased from 5 to 20% (Commission Regulation (EU) 2020/57), few chemicals are re-evaluated once they are registered or authorised. Renewed assessments are only required for biocides and pesticides. As a result, the vast majority of EU registration dossiers do not reflect the latest scientific evidence on a chemical's risk (ECHA, 2016; European Commission, 2018a). Furthermore, the review of chemical dossiers is influenced by expert judgement. Expert judgement plays an integral part during the chemical safety assessment, but can also be a driver for diverging RA outcomes due to experts' different expertise and experience (Maxim, 2019; Rudén et al., 2017).

We analysed the overlap of registered chemicals under each framework based on their CAS-number. At the time of the analysis (i.e. winter 2019/2020) 73 biocides were also registered within another framework, with the largest overlap between the REACH and pesticide frameworks (Table 2). In addition, 53 of the pesticides, 42 medicines for human use, 29 veterinary medicines and 97 of the registered industrial chemicals are listed within another framework as well. Table 2 shows that chemicals can be registered under multiple frameworks, meaning they were subjected to multiple assessments. At time of the analysis 49% (17 out of 35) and 15% (114 out of 743) of the banned biocides and pesticides, respectively, were still on the market under a different framework, most often under REACH. 1 of the banned biocide and 7 of the banned pesticides were approved under more than one additional framework.

Table 2
The total number of chemicals under each framework that were registered at time of the analysis (i.e. autumn/winter 2019) and for which CAS-numbers were identified. The total amount of substances that were also registered under one or more other registration frameworks are shown.

	Total number of Registered Chemicals with CAS	Total number of chemicals also registered under other frameworks	Overlapping chemicals per framework				
			Biocides	Industrial Chemicals	Pesticides	Medicines for Human Use	Veterinary Medicines
Biocides	148	73	–	49 (33%)	28 (19%)	1 (0.7%)	5 (3.4%)
Industrial Chemicals	9518	97	49 (0.5%)	–	28 (0.3%)	23 (0.2%)	5 (0.1%)
Pesticides	393	53	28 (7%)	28 (7%)	–	6 (2%)	2 (0.5%)
Medicines for Human Use	752	42	1 (0.1%)	23 (3%)	6 (0.8%)	–	16 (2%)
Veterinary Medicines	130	29	5 (4%)	5 (4%)	2 (2%)	16 (12%)	–
Non-approved Biocides	35	17	–	15 (43%)	3 (9%)	0	0
Non-approved Pesticides	743	114	19 (3%)	94 (13%)	–	5 (0.7%)	3 (0.4%)

3. Risk assessment for the freshwater environment

RA for the freshwater environment forms an essential part of the registration process and helps to identify and address risks. However, not every chemical is assessed for its environmental risks (Table 1). The principles for conducting the RAs are laid down in independent guidance documents for each legislative framework. Environmental risk assessments (ERAs) are based on the ratio between the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC). If the PEC/PNEC ratio is higher than 1, a risk is identified. For pesticides some effects to the environment can be accepted as long as recovery of populations takes place. For these types of assessments 'regulatory acceptable concentrations' are used instead of PNECs.

Environmental risks are assessed according to a tiered system, starting with a low tier which requires little data but is assumed to be conservative. If a risk is identified in these low-tier ERA, higher tier assessments are performed that are more data-intensive, more ecologically relevant and less conservative. In this analysis we focus on schemes for lower-tier testing only.

3.1. Environmental protection goals

The different registration frameworks seek to anticipate effects of chemicals in order to protect the environment. Their environmental protection goals are however only vaguely defined, aiming to prevent 'unacceptable effects' and ensure that the 'environment is not adversely affected' (Table 1). Alternatively, ERAs for pesticides may be based on the "ecological recovery option", in which some population-level effects are accepted if ecological recovery takes place within an acceptable time period (EFSA, 2013). Under both medicine directives environmental impacts only have to be assessed, and no explicit protection goal is defined.

For some locations where no sensitive species are present, current ERAs for individual chemicals may be overprotective, which could result in unnecessary restrictions on chemical use. Defining safe concentrations for chemicals for different locations or ecological scenarios could overcome this (Brown et al., 2017). Scientific committees have also recognised that specific protection goals will take better account of environmental complexity and improve ERAs (SCHER, SCENIHR, SCCS, 2013).

3.2. Hazard assessment

Within the registration processes a PNEC is derived by applying an assessment factor (AF) on the most sensitive endpoint from a battery of ecotoxicity tests. The minimal number of studies that are required and the applied AFs differ between the frameworks and there is little empirical evidence to support the regulatory AFs (Syberg and Foss Hansen, 2016; Topping et al., 2020). Together this results in additional uncertainties in setting the environmentally safe concentration. It is for example still under debate whether AFs are sufficiently covering extrapolations from acute to chronic exposures and from controlled laboratory conditions to the environment (Ahlers et al., 2006; Barmentlo et al., 2018; Malkiewicz et al., 2009). Moreover, current AFs do not account for mixture effects and some have therefore proposed to increase the AF for single substance risk assessments (Rudén, 2019; Schäfer et al., 2019).

By comparing all PNECs for industrial chemicals, biocides and pesticides, and PNECs derived for human medicines (for method see S.I.) it can be seen that biocides on average are the most hazardous group of chemicals, followed by pesticides, medicines for human use and industrial chemicals (Fig. 1, Table 3). Veterinary medicines were excluded from the analysis as no freshwater PNECs could be obtained from the open literature. Furthermore, out of the close to 23000 chemicals registered under REACH only 5850 had derived a PNEC for freshwater. For biocides a PNEC could obtained for 76 out of 148 substances and for pesticides for 298 out of 393 substances (Gustavsson et al., 2017). In addition, it was only possible to derive PNECs for 130 of the medicines registered for human use (see S.I. for method, data collected from Gunnarsson et al., 2019). It should also be noted that regulatory requirements typically exclude the assessment of effects which are non-lethal and involve effects on specific organs, behaviour or early development. This has shown to particularly be of concern for higher organisms such as fish when exposed to medicines (Brodin et al., 2013).

For registration of medicines and industrial chemicals relatively few

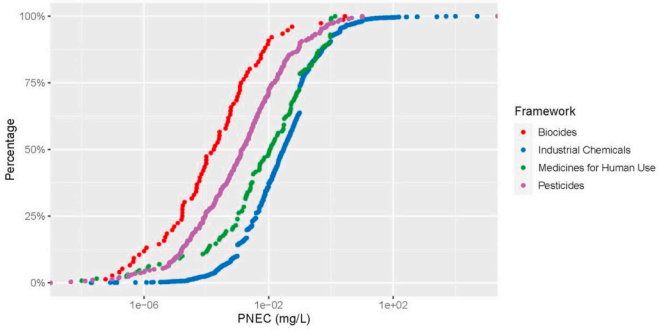

Fig. 1. Cumulative distribution of PNECs for biocides, industrial chemicals and pesticides as reported in registration dossiers. PNECs from biocides and pesticides dossiers were obtained from Gustavsson et al. (2017), PNECs for medicines for human use were derived from data collected by Gunnarsson et al. (2019). PNECs for industrial chemicals are available online (van Dijk et al., 2020).

Table 3
Summary statistics for the four different regulatory frameworks for which freshwater PNECs were obtained. Further details are provided in the S.I.2.

	Number of Chemicals	Maximum PNEC (mg/L)	Minimum PNEC (mg/L)	Median PNEC (mg/L)
Biocides	76	2.82	5.8E-8	1.82E-4
Industrial Chemicals	5850	50000.00	0.00	2.60E-2
Pesticides	298	10.20	4.46E-9	1.5E-3
Medicines for Human Use	130	1.37	1.0E-8	1.15E-2

studies are required to derive a PNEC, whilst the PNECs for biocides and pesticides are based on a more extensive ecotoxicity dataset. Despite this, on average higher AFs are applied to biocides than to pesticides (Fig. 2). For industrial chemicals, generally higher AFs are applied to substances in low tonnage-bands that require less data. More data is required in higher tonnage-bands, and consequently, lower AFs can be used. Industrial chemicals are on average the least hazardous group, but several of these substances do have a PNEC in the same order of magnitude as biocides. Furthermore, different RA strategies under the registration frameworks are one of the reasons for incoherent assessments of similar chemicals. PNEC values for 65 substances registered under multiple frameworks can differ with a factor of 1–5625, with a median difference of 3.6 (Fig. 3). The highest difference of 5625 was found for aluminium sulphate, which has a PNEC of 0.0008 mg/L when assessed as a pesticide and 4.5 mg/L as an industrial chemical.

3.3. Emission and exposure estimation

In exposure assessments used in regulatory assessments, it is assumed that chemicals are only emitted by one user into a pristine environment. Therefore, actual environmental concentrations from multiple sources might exceed predicted concentrations from individual ERAs (Topping et al., 2020). Due to their multiple uses chemicals can also be registered under multiple frameworks. But all registration frameworks fall short in providing this information. The overlap of registered chemicals under each framework based on their CAS-number are shown in Table 2.

In 1998 it was agreed in the Aarhus Convention that chemical emission data is essential to protect the environment and that it should therefore be made publicly available (Aarhus Convention, 1998). The Aarhus convention was adopted by the EU in 2001, and resulted in the European Pollutant Release and Transfer Register (E-PRTR, Reg (EC) No 166/2006b). However, large data gaps remain as the E-PRTR only documents emission of 91 chemicals from point sources -such as discharges from industry and wastewater treatment plants-which exceed predefined thresholds. In addition to the point source emission of

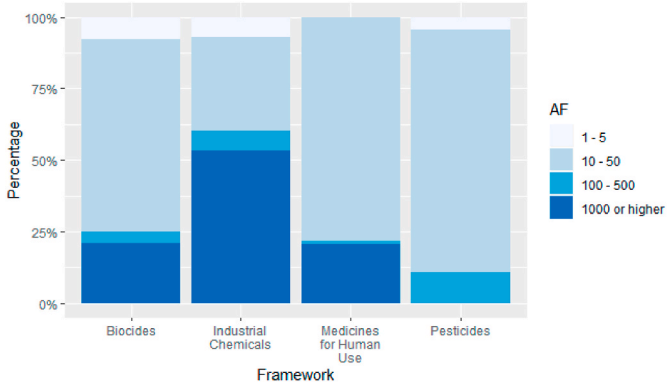

Fig. 2. AFs used for freshwater PNEC derivations in current regulatory risk assessments.

chemicals not registered in the E-PRTR many chemicals are also emitted from diffuse sources (van Wezel et al., 2018). Diffuse emissions can for example be the result of agriculture or the use of everyday products that contain chemicals. To estimate diffuse emissions, it is necessary to quantify the release of chemicals from products, for which both the composition of the product and the specific type of use need to be known. The composition of products is relatively well known for biocidal, pesticidal and medicinal products. This is however not the case for products such as clothing, electrical appliances and plastic. The complex supply chain of these products that involve many actors (such as suppliers and producers) makes such information even more challenging to obtain. In addition, for chemicals registered under REACH only limited information is provided regarding specific uses of a chemical. More specifically, no information is publicly available on the amounts of chemicals used when more than one use is reported. This clearly hampers realistic emission and exposure assessments and more extensive registration of use types and product contents have therefore been suggested (Bolinius et al., 2018; van Gils et al., 2020).

4. Classification of problematic substances

If concerns are identified regarding a chemical's safety, the chemical can be classified as a substance of very high concern (SVHC) under REACH or as a candidate for substitution (CfS) under the pesticide and biocide frameworks. SVHCs and CfSs can in some cases still be authorised if the socio-economic benefits from their use outweigh their risks and if no suitable (non-)chemical alternatives are available. For instance, this means that banned pesticides can be used under special circumstances. Thus, classification as a SVHC or CfS does not necessarily result in complete removal from the market.

4.1. Current classification criteria

Currently, SVHCs and CfSs are identified according to the CLP classification (Reg (EC) No 1272/2008) when they have endocrine disrupting properties or are carcinogenic, mutagenic or reprotoxic to humans. With exception from endocrine disrupting effects, environmental hazards do not merit a compound to be classified unless the chemical is also both persistent and bioaccumulative. Harmonized CLP classification is however only available for around 4600 substances in total (ECHA, n.d.). Furthermore, the CLP regulation does not apply to medicines which have their own classification system. That system does not include any systematic classification of environmental hazards, and medicines are often exempted from environmental risks assessments (Table 1). Hence appropriate mitigation efforts to prevent medicines from being release to the environment are often not considered.

4.2. Persistent chemicals and degradation products

Chemicals are screened and evaluated for their persistency, bioaccumulation and toxicity, which can result in classification of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB). Even though the PBT/vPvB classification is shared between all frameworks, the classification frameworks and their risk management follow up can differ (Moermond et al., 2012). Concerns have also been raised that current classification schemes do not cover all relevant chemicals, including substances that are persistent, mobile in the aquatic environment and toxic (PMT). PMTs are problematic substances as they are highly polar, and are therefore not readily removed by sorption processes during waste water treatment (Reemtsma et al., 2016). More than 3500 PMT suspects that are currently registered under REACH have been identified (Arp and Hale, 2019), and some of these substances have also been detected in drinking, surface and/or groundwater samples (Schulze et al., 2019). 15 compounds which were already classified as SVHC under REACH were also identified as PMT compounds, but many other substances are so far not

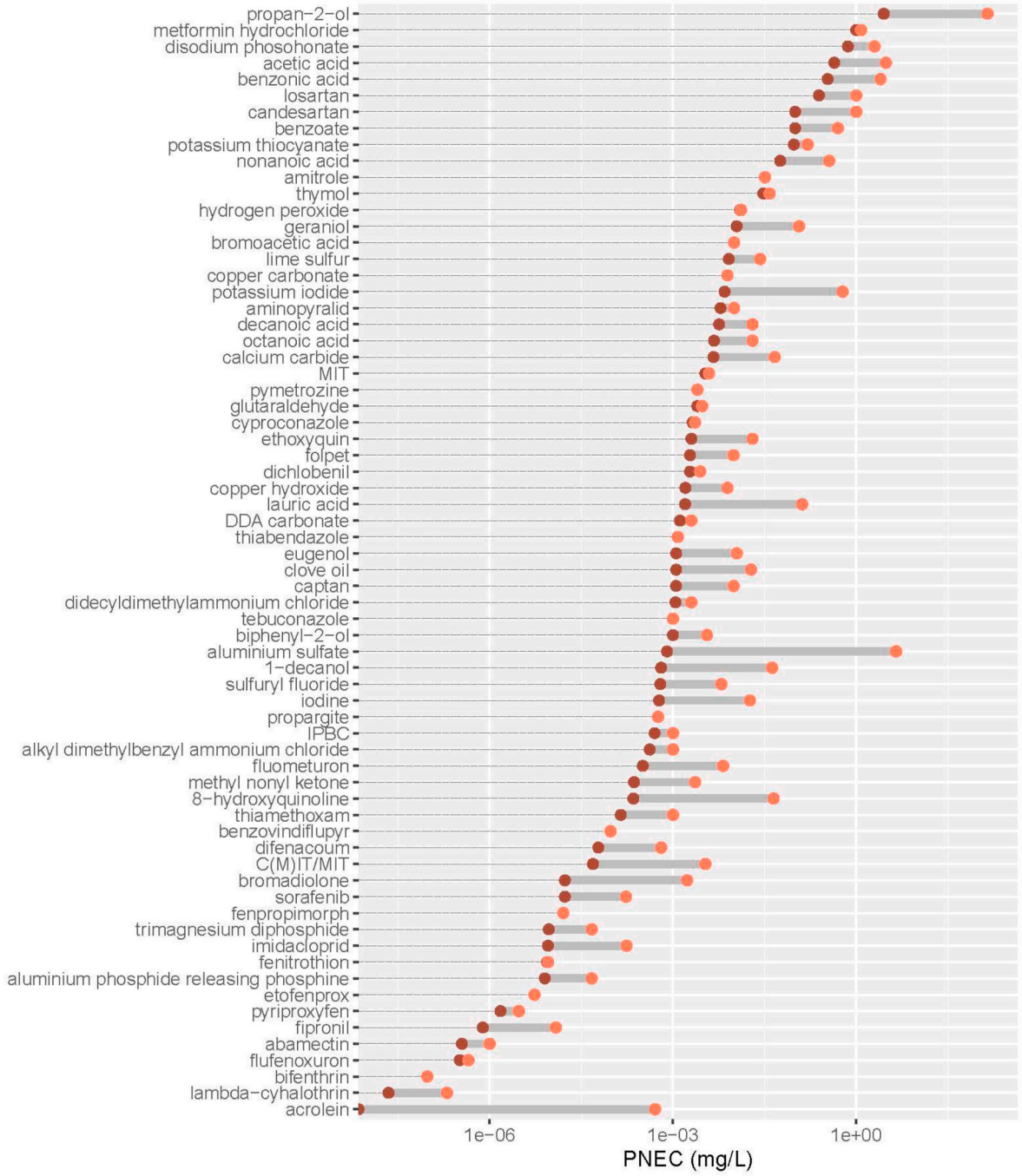

Fig. 3. Differences between PNEC values for chemicals registered under 2 or more frameworks. The dark red points show the minimum and the orange points the maximum reported PNEC value. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

assessed (Arp and Hale, 2019). Cousins et al. (2019) stated that persistency of chemicals alone is already a cause of concern. However, current OECD biodegradation test guidelines that are used for the ERA processes do not always reflect realistic environmental conditions and many knowledge gaps exists regarding test outcomes (Kowalczyk et al., 2015). In addition, there are many examples of degradation products detected in the environment that are persistent (Muir et al., 2019), emphasizing that an improved screening of degradation products should be performed during the registration process.

4.3. Alternative assessments

Chemicals placed on the classification lists for hazardous substances should ideally be phased-out and substituted by safer alternatives. REACH supports chemical substitution of SVHCs by making it mandatory to provide an analysis of alternative chemicals to be used (Article 62 (4), Reg (EC) No 1907/2006). A comparative assessment also needs to be performed for substances classified as CfS under the biocide and pesticide registration frameworks. This comparative assessment includes an analysis of alternative non-chemical methods as well (Article 23 Reg (EC) No 528/2012 and Article 50 Reg (EC) No 1107/2009). However, there is no universal protocol for identifying safer alternatives under the different frameworks and chemicals are often replaced by less-studied chemicals, with a similar structure and similar risks (Fantke et al., 2015; Sackmann et al., 2018). This results in so called regrettable substitutions: when a hazardous substance is replaced by a substance

that is equally or more hazardous. Examples of regrettable substitution include the substitution of the plasticizer bisphenol-A by bisphenol-S (Trasande, 2017), substitution of polybrominated diphenyl ethers as flame retardants by organophosphate esters (Blum et al., 2019) and substitution of PFOA (perfluorooctanoic acid) by GenX (a perfluorinated propanoic acid) in the production of fluoropolymers (Brandsma et al., 2019; Gomis et al., 2018).

5. Discussion

With the Green Deal the EU has an ambition to reduce chemical emissions and achieve a toxic-free environment. The strategy for achieving this will include recommendations for an OS-OA approach, which aims to increase efficiency and harmonisation across EU registration frameworks. Currently the registration of chemicals on the EU market is fragmented based on use and chemicals are sometimes registered under multiple frameworks.

In this review we found that the function of the different chemical frameworks is similar, but that their environmental protection goals and ERA strategies differ. Consequently, chemicals are currently assessed in an incoherent way. As predictability is a crucial factor in decisions regarding investments into (green) innovation (Bernauer et al., 2007) consistent assessment of chemicals could improve predictability of their RA outcomes, which in turn can be beneficial to achieve EU Green Deal ambitions. In addition, EU registration frameworks are based on the same general principles and should therefore provide the same level of protection and a high level of environmental protection is a fundamental right of EU citizens (Article 37, 2000/C 364/01). Further streamlining of RAs is not only key to achieve coherent and more transparent outcomes but is also essential for functioning of the EU single market. In this review we saw that the difference in the assumed safe concentrations differed between frameworks up to a factor 5625, with a median factor of 3.6. Of the 70 compounds registered under more than one framework, 33 had AFs which differed between the frameworks. This indicates that for some compounds the difference in perceived hazardousness is directly related to the used assessment factors, and for some compounds the difference is most likely in the underlying data. This furthermore illustrates that both data requirements and AFs could be aligned to allow for consistent assessment and subsequent risk management of chemicals. It is therefore recommended to harmonize protection goals along all chemical registration frameworks so that appropriate risk management decisions can be taken. Furthermore, current generic protection goals should be updated and better specify what species and endpoints need to be protected in order to reach the EU Green Deal ambitions, also in view of the ambitions with regard to preserving and restoring biodiversity (Brown et al., 2017).

Concerns have been raised regarding the biological relevance of the required standard testing and on the ability of ERAs to address issues such as toxicity of low dose exposure and chemical mixtures (Bopp et al., 2018; Schäfer et al., 2019; Wilks et al., 2015). In addition, whole products are seldom tested and chemicals which are a part of solid consumer products such as textiles and plastics are also not assessed. For such products information on the chemical content is challenging to obtain and no central database collects such information. However, inspiration for such a database could be drawn, for example, from the automotive sector, where all suppliers are required to report on the chemical composition of products (Bolinius et al., 2018; Kogg and Thidell, 2010).

OS-OA requires aligned dossier renewals for all chemicals. Considering the vast number of chemicals on the EU market, use of 'in silico' screening strategies on chemical inventories will be key in order to screen and prioritise chemicals for RAs (Muir et al., 2019). One of the EU Green Deal goals is to rapidly reflect scientific evidence and studies reported in peer-review literature are essential in identifying (non-standard) effects of chemicals. However scientific evidence published in the peer-reviewed literature is often overlooked in the authorisation process. The reluctance towards using such studies for regulatory purposes can in part be overcome if the reporting of these studies is improved, and information such as the hypotheses and test conditions are better communicated (Ågerstrand et al., 2018; Moermond et al., 2016; Rudén et al., 2017). Moreover, a database could be set-up which enables sharing of data on chemical properties, hazards, uses, environmental fate and emissions between EU agencies as well as the research community. With better information on different chemical uses and emissions, more realistic ERAs can be performed and more relevant risk management decisions can thereby be made. The need for such a database is highlighted by the chemicals being registered within multiple frameworks. Such a database could also be linked to The European Union Chemical Legislation Finder (EUCLEF, accessible via https://echa.europa.eu/legislation-finder) which provides an overview of which EU legislations that apply to a specific substance. Assuming that only one assessment will be performed that considers all chemical uses, once the critical ratio of 1 between the PEC and PNEC is exceeded, the most essential uses or sectors might for example be prioritized, as is currently done for CO_2 emissions (https://ec.europa.eu/clima/policies/ets_en). In addition, the protection goals, ERA criteria and classification procedures of hazardous substances should be aligned across frameworks. Classification of substances is used to trigger risk management and substitution, and therefore key for the functioning of an OS-OA approach and achieving the EU Green Deal ambitions.

To achieve the Green Deal ambitions, there is a need for an alternative assessment protocol that takes a chemical's hazard, performance and economic viability into account (Jacobs et al., 2016). In-silico tools and group-based approach (i.e. read-across) can furthermore help to facilitate these alternative assessments (Benfenati et al., 2019). Tickner et al. (2015) proposed a framework for 'functional substitution', which aims to prevent replacement of one chemical with a structurally similar chemical and to find less hazardous alternatives to meet product performance instead. And hence would also provide information which can stimulate the use of new chemical and non-chemical alternatives (Tickner et al., 2015). Furthermore, the development of safer chemicals could be aligned with the concepts of green and sustainable chemistry in order to design chemicals that are not only less hazardous for human, but also for environmental health (Tickner et al., 2019) and could include comparative exposure estimates for informed considerations of the advantages and disadvantages of the substitute chemical (Greggs et al., 2019).

The ambition of a toxic-free environment cannot be reached by OS-OA alone. To sufficiently reduce environmental concentrations of chemicals and to achieve the EU Green Deal zero pollution ambition for a toxic-free environment it is essential that chemicals are managed during their whole life-cycle (Kümmerer et al., 2019; Van Wezel et al., 2017). The EU Green deal is a good opportunity to control chemical pollution and the source and drive innovation for the development of safer chemicals.

6. Conclusions

Despite the fact that the general principles of the registration of chemicals under the different frameworks is comparable, notable differences between the frameworks can be identified. We have identified the following key recommendations in order to improve and harmonize the RA process into an OS-OA approach.

- Exemptions for environmental risk assessments could be abolished. As an example, the environmental risk of many industrial chemicals and medicines are currently not assessed;
- Registration dossiers could be updated on a more regular basis in order to mitigate chemical risks. Currently only a subset of the registration dossiers for chemicals on the EU market require repeated re-evaluation, this results in dossiers which do not reflect the latest scientific findings;

- Environmental protection goals could be harmonized, with a common ambition of a toxic-free environment;
- Data requirements and AFs to derive PNECs should be harmonized between the registration frameworks. Currently AFs can differ up to a factor of 100 for the same organism and endpoint. We have shown that PNECs from the same chemical assessed under different frameworks have a median difference of a factor 3.6 with a range of 1–5625;
- Chemical use and emission data could be made publicly available, both to increase transparency and to allow for more realistic estimations of chemical concentrations in the environment;
- Once the critical ratio between the PEC and PNEC is exceeded when all uses are considered and no options exist to prevent pollution, the most essential uses or sectors could be prioritized;
- The classification of hazardous substances could both be harmonized and updated to better include environmentally hazardous chemicals and to trigger risk management.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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