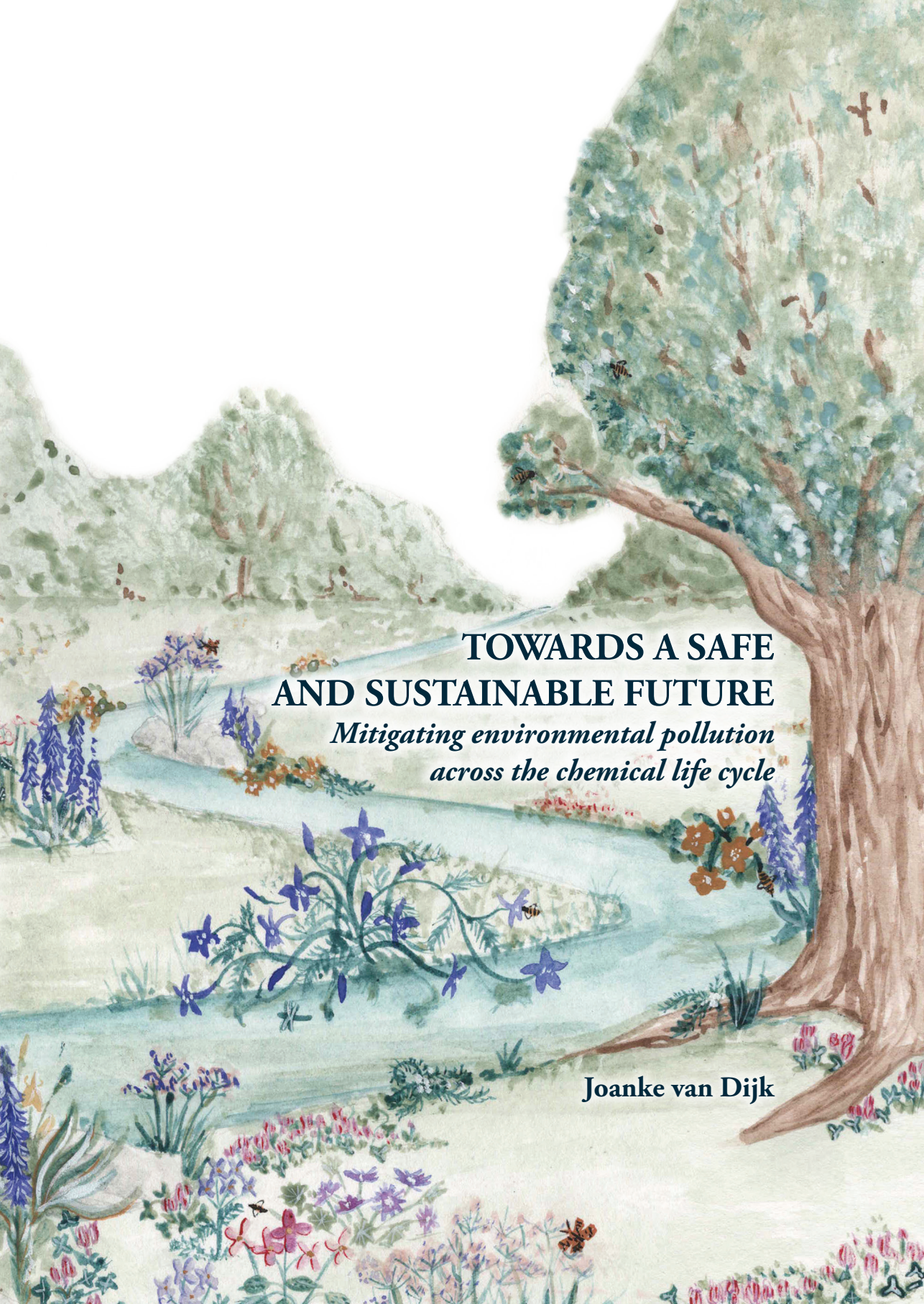

TOWARDS A SAFE AND SUSTAINABLE FUTURE

Mitigating environmental pollution across the chemical life cycle

Joanke van Dijk

Towards a Safe and Sustainable Future

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Mitigating environmental pollution across the chemical life cycle

Naar een Veilige en Duurzame Toekomst

Het verminderen van milieuvervuiling gedurende de chemische levenscyclus

(met een samenvatting in het Nederlands)

Proefschrift

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CHAPTER ONE

GENERAL INTRODUCTION

Chapter 1 - General Introduction

1.1 Entering the Chemocene

Humanity has become the dominant force altering the global environment. As a result, the resilience of Earth's systems on which all societies rely is threatened, defining the current geological epoch known as the "Anthropocene" (Crutzen, 2006). This epoch marked by human-induced changes, resulting in a triple planetary threat of climate change, biodiversity loss and pollution. According to Steffen et al. (2011), the Anthropocene started around 1800 during advent of the Industrial Revolution, eventually leading to a range of human activities, such as population growth, urbanization, industrialization, and the increasing use of fossil fuels. Another key signature of the Anthropocene is the omnipresence of human-made, synthetic chemicals in the environment (Waters et al., 2016). These chemicals play an important role in daily life and can help contribute to economic growth, food production, welfare, and health. With over 350,000 chemicals and mixtures currently available world-wide (Wang et al., 2020), the production and consumption of chemicals will continue to grow driven by societal and technological developments (Bunke et al., 2019; Nagesh et al., 2022; UNEP, 2019a). Chemical diversification (i.e. increasing chemodiversity) surpasses other factors of global change, such as nutrient pollution, atmospheric CO_2 concentrations and habitat destruction (Bernhardt et al., 2017). In addition, the chemical industry is a major consumer of resources and emitter of greenhouse gases, contributing to the acceleration of global change-related phenomena (IEA, 2022; Levi and Cullen, 2018).

Consumption behaviour is influenced by different factors, including physical and social structures and provisioning systems (Poças Ribeiro et al., 2019). As economies grow and people's income increases, consumption typically increases. In Figure 1.1 we can observe that the export value of European goods and services increased more than 4 fold in the year 2021 compared to 1990. Moreover, the amount of people over the age of 65 is growing 9 times faster than the total population in Europe. An aging population is considered one of the main drivers for increased pharmaceutical use (Bunke et al., 2019). Owing to growing consumer demands, more raw materials are currently extracted globally than ever before (Schandl et al., 2018). In addition, technological advancements lead to the development of products that are increasingly complex and chemical-intensive (Graedel et al., 2015; Schandl et al., 2018). So far, new chemicals are reported with a stable 4.4% annual growth rate. This growth rate is even not being affected on the long-term by major events such as world wars (Llanos et al., 2019). However, not all types of chemicals are increasing (Figure 1.1). For example, the diversity of pesticidal and biocidal active ingredients did not increase since 1990 in the Netherlands, amongst others due to more strict regulation (Sparks, 2013). In these sectors, a shift in the type of substances marketed towards biologically based alternatives is expected due to improved legislation and innovation (European Commission, 2020a). Furthermore, the introduction of chemical intensive

products outpaces the growth of introduction of new chemicals (UNEP, 2019a). We can observe this in Figure 1.1 for pesticidal and biocidal products introduced on the European market.

During their life cycle, chemicals are emitted into the environment through various processes (Wang and Hellweg, 2021). During production, chemicals may be spilled or leaked. Next, some chemicals are used in so-called 'open applications' (such as field use of pesticides, fire-fighting foams and uses of polypropylene in soil) meaning they directly enter the environment as a result of their use. Other emission pathways happen via consumer products that can leach chemicals into the environment over time, either through the degradation of products or through the release of chemicals into water, atmosphere or soil during the use of these products. Furthermore, the disposal of waste that contains a wide variety of chemicals, such as electronic waste or household hazardous waste, can result in long-term releases and accumulation of these chemicals and their transformation products in the environment. Increasing chemodiversity and increased use and diversity of chemical intensive products since turn of the millennium is said to herald the start of a new era called the Chemocene. The Chemocene can be seen as an integral part of the Anthropocene in which humanity's impact on the environment through the use of chemicals is a primary concern (de Baat, 2020).

1.2 Environmental and Human Health Risks of Chemicals

Many chemicals that are emitted into the environment end up in aquatic systems. Properties such as persistency, mobility and bioaccumulation that determine the fate and behaviour of chemicals can make certain substances of higher concern than others, next to toxicological properties. Bioaccumulative chemicals can accumulate in organisms and soils, whilst mobile chemicals pose a high risk to (drinking) water sources (Hale et al., 2020). An important factor controlling the overall threat of a chemical is the scale of emission and whether the chemical is persistent. Persistent chemicals can accumulate to greater concentrations than short-lived chemicals emitted at the same rate, and thus pose a long-term threat to human health and the environment (Cousins et al., 2019).

Increased chemical use has also increased the number of global deaths caused by so-called modern pollution. It is estimated that in the year 2019 pollution resulted in 9 million deaths, primarily in low-income and middle-income countries (Fuller et al., 2022). Given the large variety of synthetic chemicals and their pervasiveness in the environment, the disease burden caused by chemical pollution is possibly substantially greater than current estimates (UNEP, 2019a). The properties that make chemicals useful for society can simultaneously make them damaging for the wider environment (Johnson et al., 2020). A well-known example is ethinylestradiol, a synthetic derivate of estradiol and used as oral contraceptive. Its potency and persistence have made it an endocrine disrupter in wild fish resulting in feminization responses (Lange et al., 2009). For a number of substances, safe levels for the environment are already exceeded at various locations world-wide (aus der Beek et al., 2016; Wilkinson et al., 2022). Moreover, other stressors such as climate events can

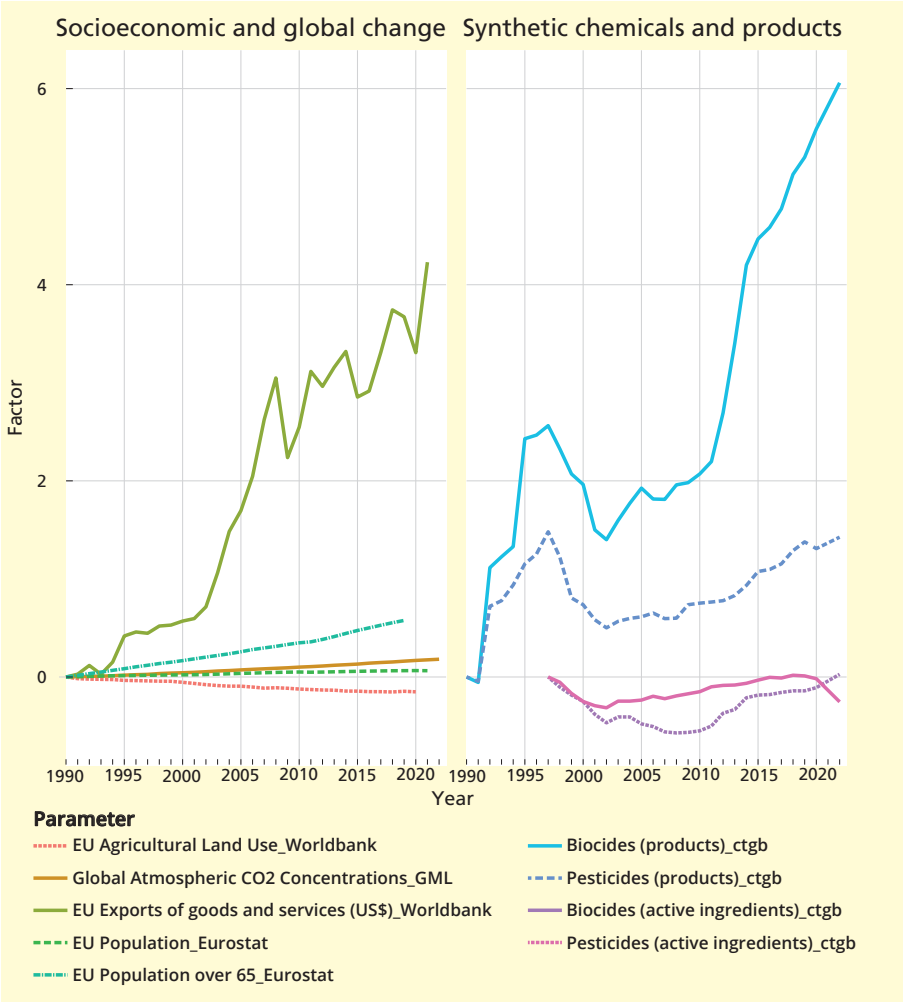

Figure 1.1. The annual increase of several forms of global change, socioeconomic and chemical parameters and their source, inspired by Bernhardt et al. (2017). The left pane shows the factor increase of the total population size in Europe, the European population of 65 years and older, European agricultural land use, European export value of goods and services and annual atmospheric CO_2 concentrations, normalized for the year 1990. The right pane shows the factor increase of biocidal and pesticidal active ingredients and products available on the Dutch market as a proxy for the European market, normalized for the year 1990, or as early as data was available (1997 for active ingredients).

drive compositional changes of ecosystems and could make them more susceptible to (simultaneous) chemical exposure, potentially affecting biodiversity and ecosystem functioning (Hermann et al., 2023; Polazzo et al., 2022a, 2022b). Adverse chemical effects on wildlife and ecosystems are thus becoming increasingly clear, identifying chemical pollution as one of the main drivers behind the global decline of biodiversity (IPBES, 2019; Jaureguiberry et al., 2022; Sigmund et al., 2023) and

making chemical pollution ('novel entities') one of the planetary boundaries humanity must not cross in order to avoid unacceptable global change (Rockström et al., 2009).

1.3 The History of Global and European Chemical Management Strategies

The discovery of hazardous and persistent organic pollutants in the environment in the 1960's (Carson, 1962) started the development of management strategies and legislation in many countries to reduce the risk of chemicals to human and environmental health caused by chemicals. In 1972 the United Nations Environment Programme (UNEP) was founded to monitor the state of the environment, inform policy making with science and coordinate responses to the world's environmental challenges. Since then, various conventions and protocols were adopted in order to manage chemical pollution, as shown in Box 1.1.

In Europe, legislation to limit the dangers associated with the use of chemicals also started to develop in the 1960's. Harmonisation of national legislation at the European level appeared necessary to prevent chaos in trade and administration as well as trade barriers as a result of differing legislation in the member states, making it possible for the predecessor of the European Union (EU) - the European Economic Community (EEC) - to exert influence in the chemicals sector (Bolt, 2008). The first directive was adopted by the EEC in 1967 focussed on the classification, labelling and packaging of dangerous substances. Arguments of removing trade barriers initially applied to the European internal market only, however, as economic globalisation progressed, many of the underlying arguments and principles also apply beyond the European sphere. Particularly important are the areas of safe use, safe transport and safe disposal of chemicals. This has led to efforts to regulate the classification and labelling of chemicals worldwide. As a result of such considerations, in 2002 the UN adopted a new system known as the Globally Harmonised System (GHS) of Classification and Labelling of Chemicals (UNECE, 2021). In turn, regulations were amended in Europe and the CLP regulation was entered into force in 2009 in order to harmonise systems classification of chemicals, labels, and safety data sheets.

Chemical accidents have played an additional triggering role for the adoption of legislation on the prevention and control of such accidents. Especially the catastrophe at Seveso in 1976, which resulted in the 'Seveso Directives' (European Commission, n.d.). At the same time, there was an urgent need to define the tests to be carried out to assess hazards of chemicals on the market. Initially, this led to the political compromise that only new substances were subjected to toxicological and ecotoxicological testing. This compromise was resolved under the REACH legislation, adopted in 2007, which aimed to obtain better information on the risks of all chemicals and an obligation by industry to file data as a prerequisite for market access (no data, no market). Furthermore, efforts were made to regulate specific substances groups at a European level, such as biocides, pesticides and pharmaceuticals and to set environmental quality standards (Box 1.2). As laid down In the Treaty

on the Functioning of the European Union, all European policies on the environment should be based on four core principles: 1) the precautionary principle, which prescribes regulatory action to be taken even if a risk has not been established with full certainty, 2) the prevention principle, which aims to prevent environmental damage; such as to protected species or to natural habitats, water and soil; rather than to react to it, 3) the rectification at source principle, which seeks to prevent pollution at its source rather than remedy its effects, and 4) the polluter pays principle, which requires polluters to bear the financial cost of their actions. These principles seem in practice however not always considered (Bleeker, 2009; Cousins et al., 2016). EU law is furthermore built around the free circulation of goods, for which the proportionality principle is important. Based on this principle, measures should be appropriate to its objective, necessary in the sense that there are no other measures which are equally effective and less restrictive for international trade and there should be a reasonable link between the objective sought and the constraints imposed on the circulation of goods (Godard, 2012). In other words, this principle is sometimes concerned with balancing conflicting interests (Kosta, 2019) and can restrict authorities in the exercise of their powers by requiring them to strike a balance between the means used and the intended aim.

Until today, most European and Global initiatives have been rather reactive than proactive, failing to manage the broad problem of chemicals and waste (Ågerstrand et al., 2023). The main focus has been placed on collecting basic information about physico-chemical properties, hazard identification and managing or prohibiting certain substance classes. Relatively little attention has been given to potential solutions as well as the interrelations between the global crises of biodiversity loss, climate change and pollution. This changes in 2002, with the World Summit on Sustainable Development (WSSD), that was held in response to the challenges posed by globalization and the intersection of environmental and development issues. At the summit, a resolution was adopted with the goal of ensuring safe management of chemicals throughout their lifecycle by the year 2020 (UN, 2002). This was translated to EU policy under the 7th Environment Action Programme (7 EAP), which explicitly stated that to meet the WSSD 2020 chemicals goal, and to achieve a non-toxic environment in 2020, 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 (EU, 2013). With the 7EAP, the European Commission wanted to achieve a non-toxic environment by the year 2020, mainly focussing on improving legislation and to improve the assessment of chemicals. The WSSD as well as goals under the 7 EAP for the year 2020 were not achieved (Figure 1.2) (UNEP, 2020a). And even though no quantitative boundary has been defined, it is assumed humanity has exceeded the safe operating space of the planetary boundary of novel entities as it is impossible to adequately assess and monitor the ever-increasing diversity, production volumes and emission of chemicals with currently available resources (Persson et al., 2022).

Box 1.1. Global timeline of some of the most important events regarding the management of chemicals and preventing adverse effects to the environment.

- ***1962**: Silent Spring*
- ***1972**: UNEP was founded*
- ***1973**: Leaders sign Convention for the Prevention of Pollution from Ships (MARPOL treaty, imposes strict rules on the shipping industry, helping to prevent spills and pollution from routine operations)*
- ***1976**: adoption of Barcelona Convention for the Protection of the Mediterranean Sea Against Pollution, which was amended in 1995 and became into force in 2004*
- ***1979**: Convention on Long-range Transboundary Air Pollution as a result of acid rain, to working together to limit, to gradually prevent and to reduce their discharges of air pollutants in order to combat the resulting transboundary pollution.*
- ***1981**: Water for Life Decade, aimed to conserve drinking water sources*
- ***1985**: States sign Vienna Convention for the Protection of the Ozone Layer*
- ***1987**: Adoption of The Montreal Protocol on Substances that Deplete the Ozone Layer to protect the Earth's ozone layer by phasing out the chemicals that deplete it. This phase-out plan includes both the production and consumption of ozone-depleting substances. The agreement was signed in 1987 and entered into force in 1989.*
- ***1989**: Adoption of the Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal. The treaty places strict rules on the movement and disposal of hazardous waste. It would help prevent the jettisoning of dangerous chemicals in the developing world, including in Africa which had seen an epidemic of toxic dumping. It enters into force in 1992.*
- ***1992**: the Rio Declaration on Environment and Development, which consisted of 27 principles intended to guide countries in future sustainable development.*
- ***1998**: Aarhus Convention on Access to Information, Public Participation in Decision-Making and Access to Justice in Environmental Matters.*
- ***1998**: Rotterdam Convention is adopted to help developing countries make informed decisions about whether to import a range of pesticides and industrial chemicals, preventing them from unwittingly accepting potentially dangerous pollutants (enters into force in 2004)*
- ***2000**: Millennium declaration to combat., among others, environmental degradation*
- ***2001**: Stockholm Convention on Persistent Organic Pollutants is adopted to help protect human health and the environment from dangerous, long-lasting chemicals by restricting and ultimately eliminating their production, trade and use (enters into force in 2004)*
- ***2002**: WSSD summit, a resolution was adopted with the goal of ensuring safe management of chemicals throughout their lifecycle by the year 2020*
- ***2003**: United Nations adopted the GHS criteria*
- ***2006**: Adoption of the Strategic Approach to International Chemicals Management (SAICM) policy framework by the First International Conference on Chemicals Management in Dubai.*
- ***2013**: Minamata Convention on Mercury is adopted to protect human health and the environment from the adverse effects of mercury. Major highlights include a ban on new mercury mines, the phase-out of existing ones, the phase-out and phase-down of mercury use in products and processes, control measures on emissions and the regulation of artisanal and small-scale gold mining.*
- ***2015**: Sustainable Development Goals (SDGs) are adopted, providing a shared blueprint for peace and prosperity for people and the planet*
- ***2021**: UN Human Rights Council adopts resolution recognizing the right to a clean, healthy and sustainable environment as a human right*

Box 1.2. Overview of some of the most important European directives and regulations related to chemicals management and the environment.

- ***1967**: Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances*
- ***1978**: Council Directive 79/117/EEC, prohibiting the placing on the market and use of plant protection products containing certain active substances, later replaced by Regulation (EC) 1107/2009*
- ***1982**: Seveso-Directive 82/501/EEC on the major-accident hazards of certain industrial activities*
- ***1991**: Council Directive 91/414/EEC, concerning the placing of plant protection products on the market, later repealed by Regulation (EC) No 1107/2009*
- ***1993**: Council Regulation (EEC) No 793/93, evaluation and control of the risks of existing substances*
- ***1994**: Commission Regulation (EC) No 1488/94, laying down the principles for the assessment of risks to man and the environment of existing substances in accordance with Council Regulation (EEC) No 793/93*
- ***1996**: Seveso-II Directive 96/82/EC on the control of major-accident hazards involving dangerous substances. Later amended and repealed by Seveso-III Directive 2012/18/EU on the control of major-accident hazards involving dangerous substances*
- ***1998**: Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market, in 2013 repealed by Regulation (EU) No 528/2012*
- ***1999**: Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations*
- ***2000**: Adoption of the precautionary principle, stating that if it is possible that a given policy or action might cause harm to the public or the environment and if there is still no scientific agreement on the issue, the policy or action in question should not be carried out. The policy or action may however be reviewed when more scientific information becomes available (Treaty on the Functioning of the European Union Article 191)*
- ***2000**: Directive 2000/60/EC (Water Framework Directive) establishing a framework for Community action in the field of water policy, to ensure that the quality of European surface water and groundwater in Europe meets standards of the Environmental Quality Standards directive*
- ***2006**: Publication of the Guideline On The Environmental Risk Assessment Of Medicinal Products For Human Use, which needs to be applied to all newly marketed active pharmaceutical ingredients*
- ***2009**: CLP entered into force, replacing directives related to the classification, packaging and labelling of dangerous substances (Directive 67/548/EEC) and preparations (Directive 1999/45/EC)*
- ***2012**: Regulation (EU) No 528/2012 of the European Parliament and of the Council concerning the making available on the market and use of biocidal products*
- ***2019**: Publication EU Green Deal to make Europe carbon neutral, decouple economic growth from resource use and to ensure equality for all citizens*
- ***2020**: United Nations adopted the GHS criteria*

1.4 Current Chemicals Management and Future Ambitions

Chemical management has improved in recent decades, but many issues related to chemicals that are needed to advance sustainable development and meet policy objectives (shown in Figure 1.2) remain unresolved. The issue of chemical pollution and waste management is complex, spans multiple time and spatial scales and sectors, with each their own interests and goals. Hence, a comprehensive solution and collaboration between sectors is required. This complexity is taken into account in recently set ambitions in EU and global targets that aim to safeguard biodiversity, and promote a shift towards a more sustainable and circular economy that prioritizes the use of safer chemicals and reduces the use of hazardous substances.

The European Commission adopted eight political priorities in the European Green Deal, of which some are particularly relevant to the management of chemicals and waste, such as the 'zero pollution ambition for a toxic-free environment', 'farm to fork' and 'mobilising industry for a clean and circular economy' (European Commission, 2019). Building upon the 7EAP, which aimed to achieve a non-toxic environment, actions are defined under the zero pollution ambition for a toxic-free environment. As part of the zero pollution ambition, the chemicals strategy for sustainability (CSS) was published (European Commission, 2020b). Here, more attention is given to different approaches over the chemical life cycle in order to minimise, prevent and remediate pollution and to a transition towards safe and sustainable chemicals. It is furthermore acknowledged that chemical manufacturing and supply chains are complex and globalised, and that collaboration with all relevant stakeholders is needed.

The interconnectedness of the three planetary crises is furthermore recognized on a global level with, among others, the SDGs and the recently formulated targets under the Montreal COP15 on biodiversity (Convention on Biological Diversity, 2022). In order to protect biodiversity and ecosystem functions and services, COP15 aims to reduce the overall risk from pesticides and highly hazardous chemicals by at least half by 2030. Critique however remains, as not all relevant pollutants are taken into account, pushing for a more comprehensive approach (Mueller et al., 2023). Furthermore, it is essential to define specific goals and to develop a better understanding of what specific measures can be implemented. Actions to manage chemical pollution consisted so far mainly of regulatory and technological (end-of-life) measures, but a more effective approach would identify and combine various options throughout the chemical life cycle (van Wezel et al., 2017).

1.5 Aims and outline of this thesis

The current thesis is part of the European funded project ECORISK2050 (Welch et al., 2022), which aimed to analyse and address risks of chemicals of emerging concern in the aquatic environment. In order to inform policy-makers about potential effects of chemicals, a better understand-

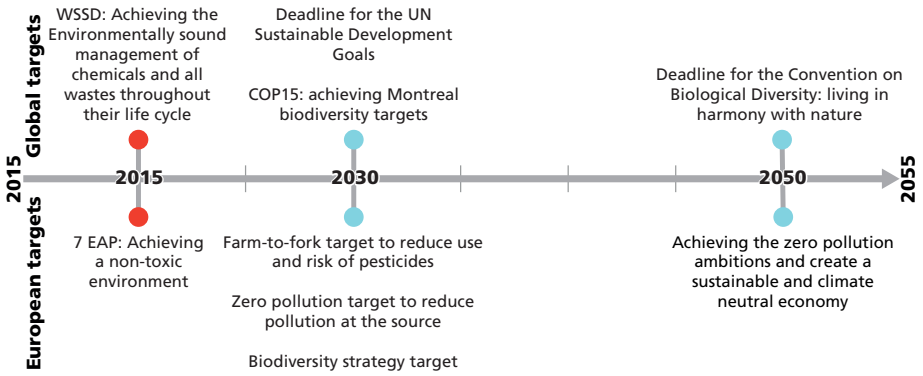

Figure 1.2. Timeline most European and Global targets relating to chemicals management from the year 2020 till 2050. Past goals not met are shown in red, whilst future targets are shown in blue.

ing is required about current and possible future use, emissions, persistence and transformation, and fate and transport of chemicals, as well as potential management options (Desrousseaux et al., 2022; Hader et al., 2022). This thesis aims to identify and assess multiple mitigation options over the chemical life cycle in order to reduce the emission of chemicals into the environment and thereby contributing to environmental policy ambitions. The main aim of the thesis was translated into the following research questions:

1. **Policy goals:** Is there agreement within the scientific community on the interpretation of (European) environmental policy goals in order to help its implementation? (Chapter 2)
2. **Chemical design and production:** Can chemicals be (re-)designed by taking both safety and sustainability parameters into account?
3. **Registration and market entry:** What regulatory gaps need to be addressed in order to improve environmental risk assessment and management of chemicals?
4. **Use stage:** What uses and which functions do hazardous chemicals in consumer products have? And do safer alternatives exist?
5. **Waste stage:** What is the added benefit to nature by introducing more advanced treatment of urban wastewater to reduce chemical emissions?

Figure 1.3 provides an overview of the current thesis.

Chapter 2 proposes a definition for a "toxic-free environment" in order to facilitate the implementation of the Chemicals Strategy for Sustainability (CSS). The chapter identifies key issues that are critical to achieving a toxic-free environment but are not included in the CSS. It provides recommendations on how the goals of the European Green Deal can be realized and highlights the role of scientists in achieving these goals. The chapter is based on a survey and discussion held at the 2020 SETAC Europe Annual Meeting.

Chapter 3 focusses on the chemical design and production stage. Here, a systematic and computer-aided workflow is proposed that can facilitate the chemical redesign for reduced environmental hazards whilst also taking sustainability parameters into account in order to mitigate chemical pollution and help enable a safe circular economy. The approach implements several concepts mentioned in the CSS, such as Essential Use and Alternatives Assessments, and is based on openly available software to generate potential alternative structures and predict chemical properties. The most desirable alternative structures are identified via a multi-criteria decision analysis based on the predicted properties and synthesizability.

The registration and market entry stage is assessed in **Chapter 4**. This chapter focuses on the EU registration and risk assessment procedures for freshwater environments and the need for a "one substance-one assessment" (OS-OA) approach. The chapter is based on openly available information in EU registration documents, such as predicted no effect concentrations (PNECs). Regulatory risk assessments for the aquatic environment are analysed, and it is assessed whether chemicals can be registered under multiple frameworks due to their diverse uses and if inconsistent assessments of similar chemicals exist.

Chapter 5 investigates the use phase of chemicals. In this chapter, the market share of PMT/vPvM substances in cosmetic products is identified via cosmetic ingredient information contained in governmental and industry databases. The three most prevalent PMT/vPvM substances found in cosmetic products are selected as case studies to assesses their functionality in cosmetic products, availability of safer alternatives, and essentiality in order to reveal whether the use of these case-study chemicals can be phased-out or substituted.

In **Chapter 6**, the waste stage is discussed and a European-wide analysis of sewage treatment plants (STPs) is presented. Here, a spatial analysis is made of the added benefits to nature of advanced treatment (such as ozonation and activated carbon) to reduce pharmaceutical emissions. This chapter is based on STP characteristics reported under the Urban WasteWater Treatment Directive (UWWTD) and STP removal rates which were based on a literature review.

Finally, in **Chapter 7**, the overall findings of this thesis are synthesised and put into perspective. To successfully implement the management options discussed in this thesis and achieve global and regional policy goals, it is crucial to optimize and when possible reduce the wide variety of uses of the vast amount of chemicals.

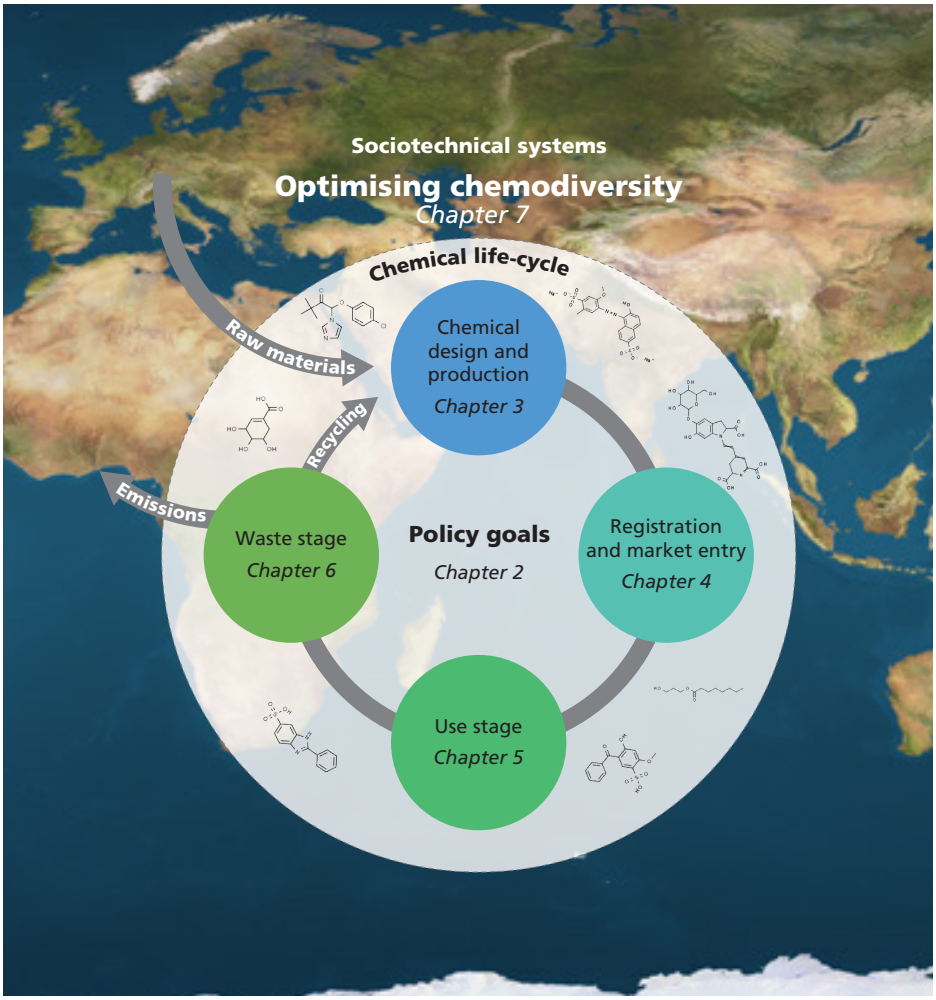

Figure 1.3. A schematic overview of the research presented in this thesis.

CHAPTER TWO

POLICY GOALS | THE EU GREEN DEAL'S AMBITION FOR A TOXIC-FREE ENVIRONMENT: FILLING THE GAP FOR SCIENCE-BASED POLICYMAKING

Chapter 2 - Policy goals | The EU Green Deal's ambition for a toxic-free environment: filling the gap for science-based policymaking

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Abstract

Around the world, many ambitious conventions and regulations have been implemented over recent decades. Despite this, the environment is still deteriorating. An increase in the volume and diversity of chemicals is one of the main drivers of this deterioration, of which biodiversity loss is a telling indicator. In response to this situation, in October 2020, a Chemicals Strategy for Sustainability (CSS) was published in the EU. The CSS is the first regional framework aiming to address chemical pollution in a holistic manner. The CSS covers the complete lifecycle of a chemical, including the design of better substances and remediation options, to remove chemicals from the environment. The strategy contains terms, such as a 'toxic-free environment', for which no clear definition exists, potentially hampering the implementation of the CSS. In this paper, a definition for a 'toxic-free environment' is proposed based on a survey and a discussion held at the 2020 SETAC Europe Annual Meeting. Additionally, key issues that are absent from the CSS but are considered to be key for the realisation of a toxic-free environment are identified. To achieve the policy goals, it is recommended to align the definition of risk across the different chemical legislations, to establish a platform for open data and data sharing, and to increase the utility and use of novel scientific findings in policymaking, through the development of a strong science to regulation feedback mechanism and *vice versa*. The paper concludes that environmental scientists have the tools to address the key challenges presented in the CSS, but an extra step is needed by both policymakers and scientists to make these applicable.

Abbreviations

CSS	Chemicals Strategy for Sustainability
DALY	Disability-adjusted Life Year
EC	European Commission
EU	European Union
EUGD	European Green Deal
SDGs	Sustainable Development Goals
SETAC	Society of Environmental Chemistry and Toxicology

2.1 Introduction

Chemical substances provide vital services for our health, food security and daily life. The use of chemicals is intimately linked to our society's modern life-style and has steeply increased over recent decades (Bernhardt et al. 2017). Wang et al. (2020) provided a global overview of chemicals on the market, which showed that over 350,000 chemicals and mixtures of chemicals have been registered for production and use. Despite their increased use, relatively little is known about the possible adverse effects of the vast majority of chemicals on the environment and human health (EEA, 2019). Global chemical sales, excluding pharmaceuticals, are expected to double from 3.47 trillion Euro in 2017 to 6.6 trillion Euro by 2030 (UNEP, 2019a).

The World Health Organization (2018) estimated the burden of disease that can be prevented by sound management of chemicals as approximately 1.6 million lives and approximately 45 million Disability-Adjusted Life Years (DALYs) in 2016, corresponding to 2.7% and 1.7% of total global deaths and global DALYs, respectively. Landrigan et al. (2018) identify air pollution as the worldwide number one cause for premature deaths. Chemical pollution is identified as one of the main drivers behind biodiversity decline (IPBES 2019). There is increasing evidence of adverse chemical effects on wildlife and ecosystems (Johnson et al., 2020). Examples include the effects of neonicotinoids on bee health (Woodcock et al., 2017) and the effects of sunscreen UV filters on coral reefs (Wijgerde et al., 2020).

In numerous countries around the world, chemicals legislation has been established to manage the adverse effects of chemicals. In the US, the first pesticides law was established in 1972 and the Toxic Substances Control Act has been in place since 1976. Global agreements have been made to regulate chemicals, including the Basel Convention, the Rotterdam Convention, the Minamata Convention and the Stockholm Convention (UNEP, 2020b, 2020c, 2020d, 2019b). During the 2002 World Summit on Sustainable Development, it was agreed that the safe management of chemicals, throughout their lifecycle, should be achieved by the year 2020. Additionally, all UN Member States adopted the 2030 Agenda for Sustainable Development, including the 17 Sustainable Development Goals (SDGs). Several of these SDGs are linked to chemicals, including SDG2 (Safe food and sustainable agriculture), SDG3 (Good health), SDG6 (Clean water), SDG8 (Safe working environments), SDG11 (Sustainable cities), SDG12 (Sustainable consumption and production patterns), SDG14 (Protection of ecosystems) and SDG15 (Protecting biodiversity).

In Europe, the chemicals policy has evolved since the 1960s and has generated over 40 pieces of legislation. As stated in the consolidated version of the Treaty on European Union, (Article 191, EU 201 6/C 202/01) all European policy on the environment should be based on the precautionary principle, on the principles that preventive action should be taken, that environmental damage should as a priority be rectified at the source and that the polluter should pay. The precautionary principle means that decision-makers should adopt precautionary measures when a scientific

evaluation does not allow the risk to be determined with sufficient certainty (EC 2000). Risk assessments of chemicals allow safe exposure levels to be determined, according to the context of the authorised use under REACH, pesticide, biocide and pharmaceutical legislations. Although, there are synergies between the risk assessments, analyses also show that cooperation, harmonisation and information exchange between different legislations need to be further improved, and opportunities for this have been identified (Munthe et al., 2019; van Dijk et al., 2020b).

The European Commission (EC) recently adopted eight political priorities in the EU Green Deal (EUGD), of which some are particularly relevant to the challenge of chemical sustainability (EC 2019). This includes the zero-pollution ambition for a 'toxic-free environment', but also relates to the ambition around biodiversity (EC 2020c) and that of a 'fair, healthy and environmentally-friendly food system' as expressed in the Farm-to-Fork Strategy (European Commission, 2020a). This builds upon the 7th European Action Programme, which aimed to achieve a non-toxic environment. The EUGD does not focus only on the state of the European environment, it also has a global dimension, by supporting the EU's commitment to the UN SDGs and the World Summit on Sustainable Development. The EUGD defines the actions related to a toxic-free environment: pollution prevention as well as measures to clean and remedy it, restoration of natural functions of ground and surface water, addressing pollution from industrial installations, and creating a Chemicals Strategy for Sustainability (CSS). The CSS aims to protect human health and the environment, and encourages innovation in the chemical sector by outlining multiple goals and actions. The strategy is an opportunity to rethink the EU's approach to chemicals management and would stop the most hazardous substances from entering the European market. Figure 2.1 shows the main topics and actions that are addressed in this paper and in the CSS, to achieve a toxic-free environment.

Independent scientific advice has an eminent role in European policymaking and can contribute directly to improving the quality of legislations (EC 2016a). There is however a need for a strong science-policy interface to effectively manage chemicals, in which scientists are involved in the decision-making processes, while policymakers have direct access to experts in the scientific community (Wang et al., 2021, 2019). Setting aside political and business considerations, and focusing strictly on the scientific foundation, this paper builds on a Discussion Forum held in a multi-partite setting at the 2020 Society of Environmental Toxicology and Chemistry (SETAC) Europe Annual Meeting, which was a virtual event. The Discussion Forum was informed by a survey of the SETAC scientific community (Supplementary Information). Building on these outcomes, this paper has three aims. Firstly, the meaning and implications of the term 'toxic free' used in the EUGD is explored. Secondly, knowledge and communication gaps raised in the survey and Discussion Forum are discussed. The final aim is to identify actions that are required to address the described gaps. An outlook is also presented and recommendations are given on how to provide a strong scientific basis for the measures required to execute on the EUGD.

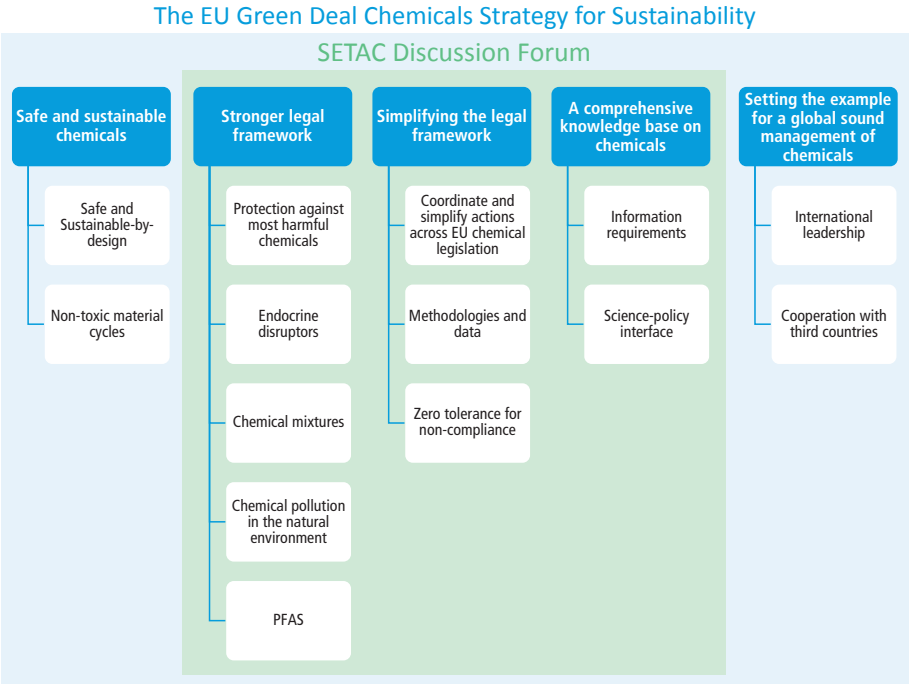

Figure 2.1. Topics covered in the new long-term vision for the EU chemicals policy, the Chemicals Strategy for Sustainability, to achieve a toxic-free environment (EC, 2020b). The green box highlights the topics discussed at the SETAC Discussion Forum and that are addressed in this paper.

2.2 Gaps to achieve a toxic-free environment

2.2.1 Establishing common ground - definition of 'toxic-free'

First of all, it is essential to determine what the concepts, such as 'toxic-free' mean, in order to understand what is required to achieve this target, and to involve stakeholders. The importance of this has been demonstrated by the 'circular economy' concept, which has over 100 different interpretations. It is argued that these different interpretations hamper the implementation of the circular economy and could eventually result in the collapse of the concept (Kirchherr et al. 2017). The EUGD's toxic-free environment and zero pollution ambition build upon previous EU ambitions for a non-toxic environment (European Commission, 2017). The new term 'toxic-free environment' is considered, by some, to be political. Whilst For others, the phrase might appear non-scientific as, in the end, everything can be toxic depending on the dose or concentration. However, this ambition appears to reflect the opinion of society, as many Europeans are concerned about the environmental impact of chemicals present in everyday products (EC 2016b). In the CSS, a toxic-free environment is described as an environment "*... where chemicals are produced and used in a way that maximises their*

contribution to society including achieving the green and digital transition, while avoiding harm to the planet and to current and future generations". However, to determine how the risk of chemicals should be assessed and what risk management decisions need to be taken on a regulatory level, we argue that a more specific definition is needed for the successful implementation of the concept.

In the survey of the SETAC scientific community (full datasheet available via the online publication (van Dijk et al., 2021)), four definitions of the term 'toxic-free' were presented (Figure 2.2). 25.2% of the respondents interpret a toxic-free environment as '*an environment in which only low risk compounds can be emitted*'. 32.2% of the respondents consider this term to mean zero chemical emissions: of which 16.1% see this as zero emission of synthetic chemicals to the environment, and 16.1% as zero-emission of any chemicals as result from human activity. However, most respondents (42.6%) interpreted the term toxic-free environment as '*an environment in which all chemicals can be emitted as a result of human activities, but in low concentrations, so that no adverse effects to organisms occur*'. For the remainder of this paper, the latter interpretation of the term 'toxic free' will be used. However, this definition of 'toxic free' raises other important points, including what is meant by 'no adverse effects'. Hence, as a next step, it will be crucial to define what organisms, functions and environmental effects are to be protected, to achieve the toxic-free ambition. This step has also been identified as one of the priority research questions in the field of environmental sciences (Van den Brink et al., 2018).

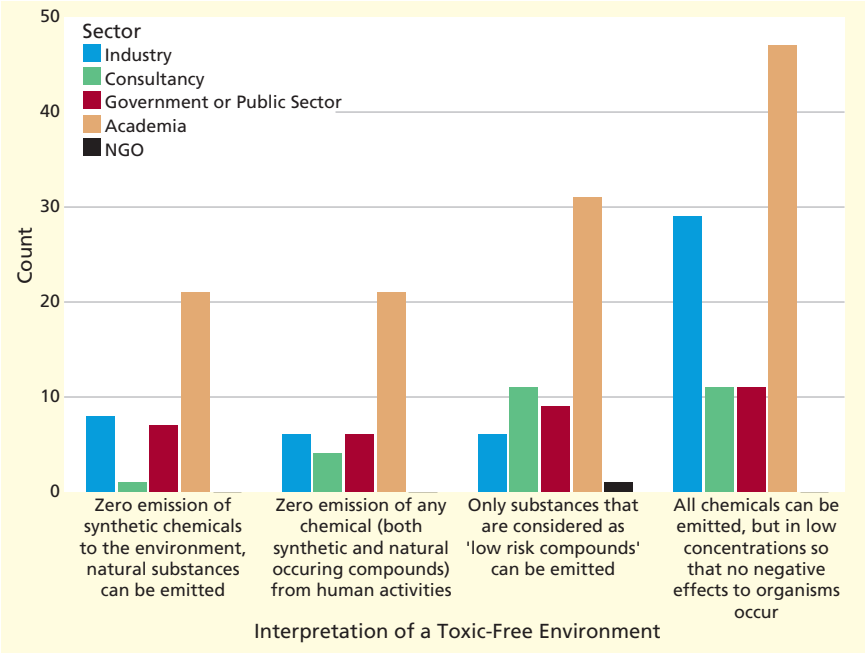

Figure 2.2. Interpretation of the term "toxic-free environment" by the survey respondents (n = 230) from the four different sectors represented within SETAC. SETAC = Society of Environmental Toxicology and Chemistry

2.2.2 Addressing environmental concerns through an improved risk assessment framework

On a global scale, the EUGD is the first regional policy instrument that aims to address all chemical pollution and focuses on the whole chemical lifecycle. The EUGD starts with the design of better chemicals, moving through to the support of research and the development of decontamination methods. In the EU, it is acknowledged that chemical pollution can have long-term and large-scale environmental impacts, and the multiple aims and corresponding actions in the CSS cover a wide range of topics that need to be addressed, according to the EC (Figure 2.1). Mainly, the EC places emphasis on reducing the risks of endocrine-disrupting chemicals, chemicals that are mobile in the environment, PFAS and other persistent chemicals, and mixtures. However, by only focussing on these chemicals a toxic-free environment will not be achieved as many more issues concerning chemical pollution of the environment exist.

The SETAC Global Horizon Scanning Project identified the specific research requirements to deliver the SDGs and move towards sustainable environmental quality (Fairbrother et al., 2019; Gaw et al., 2019; Leung et al., 2020; Van den Brink et al., 2018). These research requirements mainly focus on developing a better understanding of the adverse impacts of stressors on environmental sustainability, but some are also directly related to policy and regulation. With regards to the ambition of a toxic-free environment, it will be key to update regulatory risk assessments with new knowledge about exposure and effects.

Currently, risk assessments used within the regulatory context do not reflect realistic conditions and consequently, might underestimate the true risks of chemicals (Johnson et al., 2020; Schäfer et al., 2019; Topping et al., 2020). In the CSS, it is acknowledged that current regulatory and policy frameworks fail to take into account the long-term and large-scale environmental impacts of chemicals (and their mixtures) and their interaction with other (environmental) stressors. However, many of these interactions are not fully understood. At the SETAC Discussion Forum, it was highlighted that current risk assessments do not sufficiently consider where substances end up in the environment, nor do they accurately predict which non-target species will be affected.

The zero pollution ambition for a toxic-free environment implies a continuous improvement of the environmental status, but currently risk assessments do not predict the impact of a chemical, especially a persistent one, in years from now by continued emission. The future risk of chemicals is not explicitly covered in the CSS. However, this is essential as the fate and behaviour might change and hence the risk of chemicals in the environment might be exacerbated, due to their accumulation and due to climate change (Bunke et al., 2019; Cousins et al., 2019b). Hence, to achieve policy goals and identify appropriate risk management actions, the variation of pollution and effects over space and time need to be considered in risk assessments. Identification of appropriate *ex-ante* management actions to protect the environment and human health is key, as it can be very challenging to *ex-post* remove chemicals once they are present in the environment (Cousins et al., 2016; Kümmerer et al., 2018).

2.2.3 Simplifying the legal framework: one substance - one assessment

In the EU, chemical risks are assessed per sector (e.g. pesticide, pharmaceutical, industrial chemical) and assessment schemes of these sectors differ. The result is inconsistent outcomes, such as a chemical being banned under one but approved under another framework (van Dijk et al., 2020b). Inconsistent risk assessments can create public mistrust, as with glyphosate and bisphenol-A (Van Straalen and Legler, 2018; Vandenberg et al., 2009), for example. As a solution, the risk assessment process should be harmonised. The EU tries to achieve this by enabling a 'one substance-one assessment' approach. With such an approach, one assessment can be used to define the environmental hazard potential of a chemical. It would be even better if the long-term and combined exposures were considered, so that a more holistic risk assessment would be achieved. There are plans at the EC level to combine efforts that are currently performed separately, including regulatory instruments, databases, regulatory timelines, expertise involved, and IT tools (ECHA 2020). However, experts agreed that there is currently not enough information available on chemical uses, emissions and environmental fate to perform risk assessments that are inclusive for all uses and enable a 'one substance-one assessment' approach. It will also be essential to have an understanding of the different types of uncertainty for each substance, as uncertainties have a role in framing what is considered as a risk.

The definition of risk is driven by regulations and hence, protection goals vary depending on the type of application. During the Discussion Forum, concerns were raised about taking these different protection goals into account and it was questioned whether it is desirable for one risk assessment to be protective for all chemical uses. This is especially relevant for human health impacts, where for example genotoxic substances are by default banned for use as a pesticide, but pharmaceuticals with this property can still be marketed as treatment of diseases or symptoms when benefits outweigh the associated risks. For the environment however, it is desirable to align and define specific protection goals, to protect the environment as a whole (Brown et al., 2017).

2.2.4 A comprehensive knowledge base on chemicals: communication and open information

2.2.4.1 Information requirements

In the CSS, it is acknowledged that a comprehensive information base of all the substances placed on the European market is missing, which prevents proper management of chemicals (EC 2020b). Currently, databases such as IUCLID and the IPCHEM database could provide a good starting point for such an information base. Risk management decisions will however be based on risk assessment outcomes, for which open and transparent information on all chemical use and emission is essential to allow for accurate exposure estimations. As emphasised in the Discussion Forum, there is a lack of information on different chemical uses, emission volumes and their spatial differences (van Gils

et al., 2019) and this aspect is not yet picked up in the CSS. This implies that key uncertainties considering the environmental concentrations of chemicals will remain in place, when framing what risk management actions are needed to reach a toxic-free environment. Therefore, the knowledge base should include information on the use and emission of chemicals. It is proposed to create a European Safety Data platform that spans all regulatory frameworks and that will connect with the EU Chemicals Legislation Finder and monitoring databases (Brack et al., 2019; ECHA, n.d.).

Information on a manufacturing process and substance use can currently be claimed under REACH to be confidential, e.g. due to commercial interest or potential harm caused by publication. However, in 1998 it was agreed in the Aarhus convention - adopted by the EU in 2001 - that chemical emission data are essential to protect the environment and should be openly available (Aarhus Convention, 1998). Moreover, the EC wants to adopt the concept of 'essential use' as reported by Cousins et al. (2019) to promote safe and sustainable chemicals, and to protect human health and the environment. For the essential use concept to be fully embedded in chemical risk management decisions, there is a need for information on chemical use to be openly available.

2.2.4.2 Science-policy interface

Almost half of the survey respondents from academia (44.2%) thought that a toxic-free environment is achievable, while a similar number of respondents from the industry sector (44.9%) do not think that a toxic-free environment can be achieved (Figure 2.3). The EC aims to establish tools and practices to ensure that relevant academic data are easily and readily accessible for safety assessments, and are usable for regulatory purposes. Thus, strengthening the science-policy interface is important, and the CSS provides several actions for policymakers to achieve this. There is a need for scientists to be aware of how their science is received, to effectively inform policymaking (Spruijt et al., 2014), (SI3). When developing advice around chemical safety issues, there is a need for scientists to provide clarity and transparency (EU 2019). It was shown that transparency improves science communication for example, clearly communicating about the uncertainties and trade-offs is critical (Supplementary Information). Scientists can also play a key role by removing the hype around certain chemicals and highlighting the consequences of chemical use and non-use to the general public.

Capturing uncertainties and clearly communicating about them will improve stakeholder trust in scientists and their research (van der Bles et al. 2020; EC 2019). While there is an assumption that a consensus will be reached during discussions related to chemical safety, disagreements between experts can remain, as was the case for acrylamide and glyphosate (Rudén, 2004; Van Straalen and Legler, 2018). To ensure that regulatory outcomes are robust, actionable and democratic, it is of critical importance to provide procedural transparency (Beatty and Moore, 2010; McIlroy-Young et al., 2021; Van Der Sluijs et al., 2012). Finally, scientists need to engage in interdisciplinary interactions, when providing policy advice on issues that are embedded in a wider environmental, social, economic, legislative and political context.

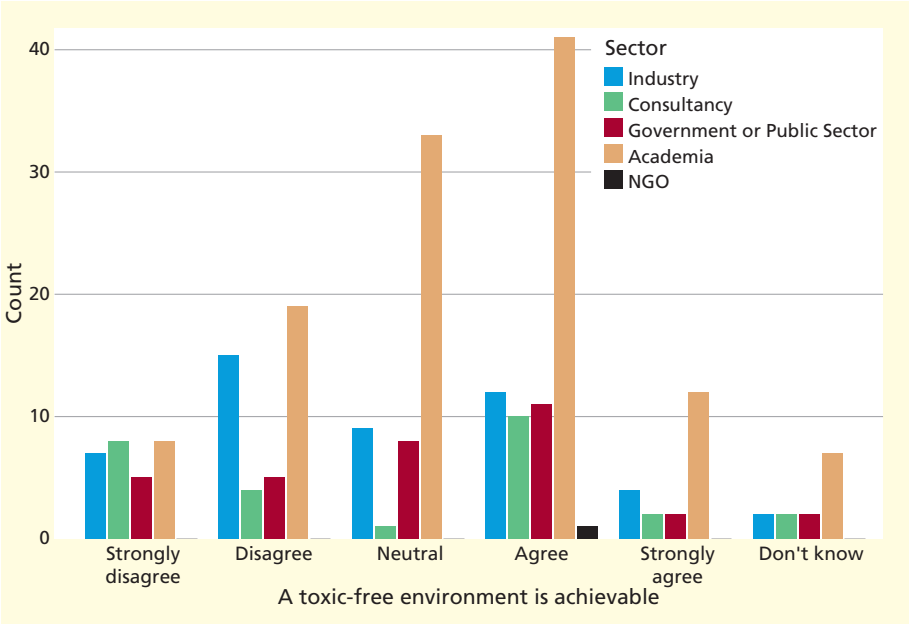

Figure 2.3. An indication of how achievable a toxic-free environment is according to the survey respondents (n = 230)

2.3 Conclusion and Outlook

In order for environmental scientists to contribute meaningfully to the CSS and the EUGD ambitions, the SETAC Discussion Forum recognised the need for debate among environmental scientists and other disciplines, such as but not exclusive to, civil engineers, environmental engineers, economists and social scientists. By having regular exchanges and debates in (to be) established platforms, by participating in public consultations of the European strategies and action plans, and by contributing to impact assessment reports, policymakers can gather independent advice from wide range of scientific sources. Where uncertainties exist, such an exchange provides the opportunity for additional consultation around complex areas. The Scientific Advice Mechanism, in cooperation with the Scientific Advice for Policy by European Academies, has recommended panel deliberation techniques, taking care that differing views are identified and recognised (EU 2019). Unintended consequences of regulatory decisions will be minimised, since alternative approaches might have been foreseen during the deliberation, and thus making the final decision more robust (Beatty and Moore, 2010; McIlroy-Young et al., 2021).

During the SETAC Discussion Forum and the preparatory survey responses, the most recognised research requirements were: 1) The inclusion of spatial and temporal variation (mobility) in risk assessments, to predict future scenarios of global change. This need is also recognised by the GHSP

in van den Brink et al. (2018). Closely connected, is the need for improved emission data (van Gils et al., 2019) and to avoid using similar hazard data differently in different regulatory frameworks. 2) Given that ecosystems and humans are exposed to chemical mixtures and not to individual chemicals, there is a need to recognise which compounds drive the toxicity of these mixtures (Van den Brink et al., 2018) and how these drivers vary in space and time (tying back to the first research requirement that was identified above). 3) It was identified by the SETAC Discussion Forum panel of experts that environmental researchers are inclined to describe a problem, while a future research need is to integrate solutions into the risk assessment and risk management process. An example of this approach is the EU-Project SOLUTIONS (Brack et al., 2019; Posthuma et al., 2019a; van Wezel et al., 2017), which aimed at producing sustainable solutions for legacy, present and future chemicals that pose risks to environmental and human health in European water courses.

The solutions aspect of this project includes a set of potential activities that are foreseen to protect or restore water quality, following hazardous impacts from chemicals. Abatement options are included, for example improved wastewater treatment systems, but also the development of the concept of sustainable chemicals, as a forward thinking solution.

There is an urgent need to strengthen the utility of science for policy and to improve the science-policy interface (Wang et al., 2021). Politicians require the simplification and standardisation of risk assessments, but at the same time it is essential that the use and utility of novel scientific findings are increased, through the development of a strong science to regulation feedback mechanism and *vice versa*. As scientists become more involved in the complex deliberations that are required to achieve policy targets, the need intensifies for methods, processes and tools to increase the robustness and transparency of the deliberation process. However, this can be addressed through interdisciplinary research efforts. Finally, an extra challenge will be to identify how concepts can be applied in a global setting, to address the impacts of chemical pollution in all regions of the world. The scientific community is already interconnected on a global level, so these communities have great potential to share experiences and, by doing so, accelerate the processes that lead to global environmental protection.

2.4 Acknowledgements

The authors declare no conflicts of interest. Thanks to SETAC staff (Rebecca Bundschuh and Barbara Koelman) for their help setting up the 2020 SETAC Europe Green Deal Discussion Forum, SETAC members for completing the preliminary survey and for participating in the discussion. Also, special thanks to the expert panel at the Discussion Forum: Professor Colin Moffat (Scottish Government) and Dr Sylvie Lemoine (CEFIC). This work is part of the Innovative Training Network ECORISK2050 and was supported by the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No [813124].

2.5 Supplementary information

The supplementary excel sheets to this chapter are available via the online publication (van Dijk et al., 2021).

2.5.1 Methods

A survey was developed in preparation for a 'Green Deal Discussion Forum' at the SETAC Europe 30th Annual Meeting #SETACSciCon in May 2020. The purpose of the survey was to 1) investigate consensus on the EUGD terminology interpretation, 2) identify scientific knowledge gaps to reach the EUGD ambitions, 3) define the role of SETAC in informing policy-making and 4) to link the Chemicals Strategy for Sustainability to the different fields of expertise within the SETAC community. The survey, with both closed and open-ended questions, consisted of 18 questions in total. The global SETAC membership was emailed a link to access the anonymous survey hosted by SurveyMonkey on the 10th April 2020 (SurveyMonkey Inc, 2020). The survey remained open until the start of the Green Deal Discussion Forum on the 5th May 2020 at 14:30 UTC. In total, 230 responses were obtained from across the sectors and continents represented within SETAC (Figure S2-1 and S2-2).

All data was exported to excel and data processing and visualisation were performed by using R(Rstudio Team, 2020) and the R packages tidyverse (R v1.3.0)(Wickham et al., 2019) and rwordmap(South and South, 2016). Statistical analyses were performed using SPSS Statistics 25 software (IBM Corp, 2017) to identify statistical differences between sectors (i.e. academia, industry, consultants, governments/public sector and NGOs) in their given answers to the survey questions.

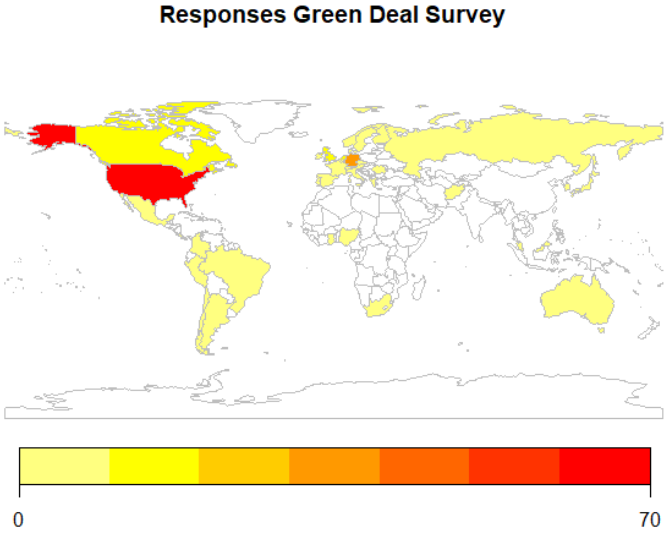

Figure S2-1. Geographical distribution of the number of survey respondents.

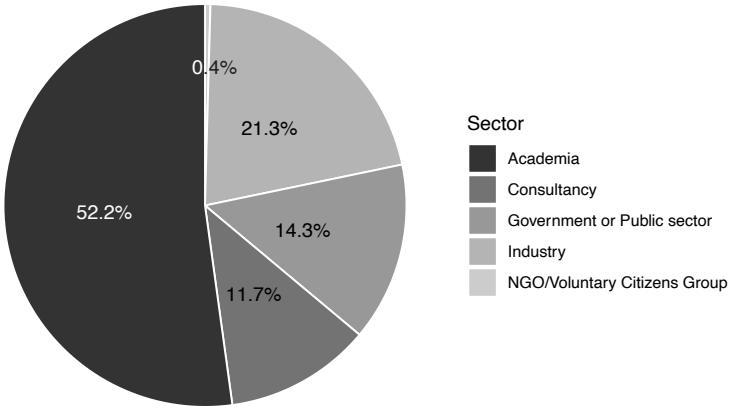

Figure S2-2. Percentage of survey respondents working for academia, consultancy, the government/public sector or NGOs.

2.5.2 Results

Results are shown for closed questions only. The answers to the open and closed questions can be found in the excel sheet available in the online publication via https://doi.org/10.1002/ieam.4429.

2.5.2.1 Statistical differences

Pearson Chi-Square tests were performed to identify differences between sectors and their given answers. For every question, p was always higher than 0.05. This tells us that there is no statistical significant between the Sector someone works in and 1) their interpretation of the EU Green Deal terminology, 2) how ambitious they think the EU Green deal is, and 3) how achievable they think a toxic-free environment is.

2.5.3 Perception on the European Green Deal Awareness

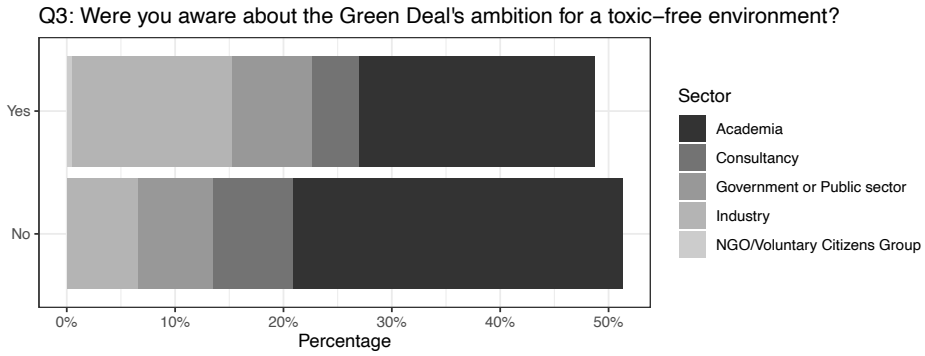

Figure S2-3. Awareness about the EU Green Deal by the survey respondents.

Table S2-1. Amount of respondents (per sectors and total) that were or were not aware of the Toxic-Free ambition of the European Green Deal.

Sector * Aware of the Toxic-Free ambition Crosstabulation					
			Aware of the Toxic-Free ambition		
			Yes	No	Total
Sector	Industry	Count	34	15	49
		% within Sector	69,4%	30,6%	100,0%
		% within Aware of the Toxic-Free ambition	30,4%	12,7%	21,3%
		% of Total	14,8%	6,5%	21,3%
	Consultancy	Count	10	17	27
		% within Sector	37,0%	63,0%	100,0%
		% within Aware of the Toxic-Free ambition	8,9%	14,4%	11,7%
		% of Total	4,3%	7,4%	11,7%
	Government or Public Sector	Count	17	16	33
		% within Sector	51,5%	48,5%	100,0%
		% within Aware of the Toxic-Free ambition	15,2%	13,6%	14,3%
		% of Total	7,4%	7,0%	14,3%
	Academia	Count	50	70	120
		% within Sector	41,7%	58,3%	100,0%
		% within Aware of the Toxic-Free ambition	44,6%	59,3%	52,2%
		% of Total	21,7%	30,4%	52,2%
	NGO	Count	1	0	1
		% within Sector	100,0%	0,0%	100,0%
		% within Aware of the Toxic-Free ambition	0,9%	0,0%	0,4%
		% of Total	0,4%	0,0%	0,4%
Total		Count	112	118	230
		% within Sector	48,7%	51,3%	100,0%
		% within Aware of the Toxic-Free ambition	100,0%	100,0%	100,0%
		% of Total	48,7%	51,3%	100,0%

2.5.3.1 The green deal is ambitious

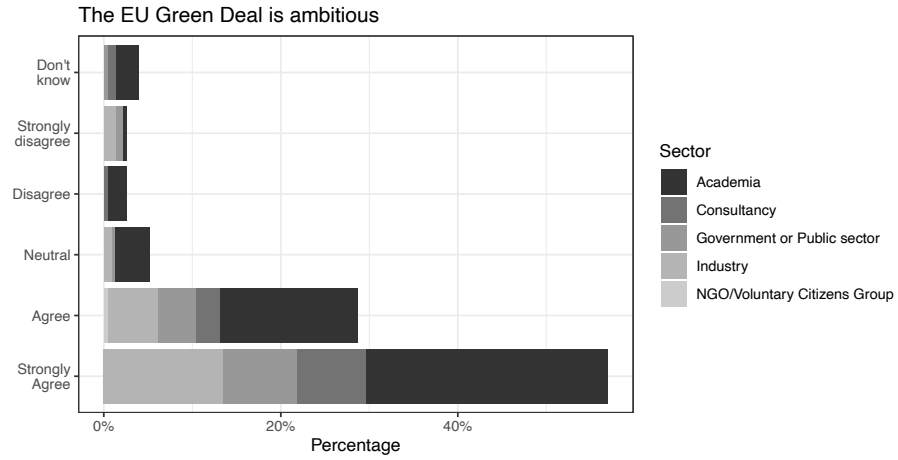

Figure S2-4. Results of how much SETAC members agree with the statement that the EU Green is ambitious.

Table S2-2. Amount of respondents (per sector and total) that agree or disagree with the statement that the European Green Deal is ambitious.

Sector * The European Green Deal is Ambitious Crosstabulation								
			The European Green Deal is Ambitious					
			Strongly disagree	Disagree	Neutral	Agree	Strongly agree	Don't know	Total
Sector	Industry	Count	3	0	2	13	31	0	49
		% within Sector	6,1%	0,0%	4,1%	26,5%	63,3%	0,0%	100,0%
		% within The European Green Deal is Ambitious	50,0%	0,0%	16,7%	19,7%	23,7%	0,0%	21,3%
		% of Total	1,3%	0,0%	0,9%	5,7%	13,5%	0,0%	21,3%
	Consultancy	Count	0	1	0	6	18	2	27
		% within Sector	0,0%	3,7%	0,0%	22,2%	66,7%	7,4%	100,0%
		% within The European Green Deal is Ambitious	0,0%	16,7%	0,0%	9,1%	13,7%	22,2%	11,7%
		% of Total	0,0%	0,4%	0,0%	2,6%	7,8%	0,9%	11,7%
	Government or Public Sector	Count	2	0	1	10	19	1	33
		% within Sector	6,1%	0,0%	3,0%	30,3%	57,6%	3,0%	100,0%
		% within The European Green Deal is Ambitious	33,3%	0,0%	8,3%	15,2%	14,5%	11,1%	14,3%

Sector * The European Green Deal is Ambitious Crosstabulation

			The European Green Deal is Ambitious						
			Strongly disagree	**Disagree**	**Neutral**	**Agree**	**Strongly agree**	**Don't know**	**Total**
		% of Total	0,9%	0,0%	0,4%	4,3%	8,3%	0,4%	14,3%
Sector	Academia	Count	1	5	9	36	63	6	120
		% within Sector	0,8%	4,2%	7,5%	30,0%	52,5%	5,0%	100,0%
		% within The European Green Deal is Ambitious	16,7%	83,3%	75,0%	54,5%	48,1%	66,7%	52,2%
		% of Total	0,4%	2,2%	3,9%	15,7%	27,4%	2,6%	52,2%
	NGO	Count	0	0	0	1	0	0	1
		% within Sector	0,0%	0,0%	0,0%	100,0%	0,0%	0,0%	100,0%
		% within The European Green Deal is Ambitious	0,0%	0,0%	0,0%	1,5%	0,0%	0,0%	0,4%
		% of Total	0,0%	0,0%	0,0%	0,4%	0,0%	0,0%	0,4%
Total		Count	6	6	12	66	131	9	230
		% within Sector	2,6%	2,6%	5,2%	28,7%	57,0%	3,9%	100,0%
		% within The European Green Deal is Ambitious	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%
		% of Total	2,6%	2,6%	5,2%	28,7%	57,0%	3,9%	100,0%

Table S2-3. Chi-Square test results to show statistically significant difference between groups (sectors) and their given answers on how ambitious the Green Deal is.

Chi-Square Tests			
	Value	**df**	**Asymptotic Significance (2-sided)**
Pearson Chi-Square	19,849[a]	20	,467
Likelihood Ratio	25,043	20	,200
Linear-by-Linear Association	,100	1	,752
N of Valid Cases	230		

a. 21 cells (70,0%) have expected count less than 5. The minimum expected count is ,03.

A Pearson Chi-Square test was performed, with p = 0.467. This tells us there is no statistically significant (α=0.05) association between the Sector someone works in and how ambitious they think the EU Green Deal is.

2.5.3.2 Toxic-Free environment is achievable

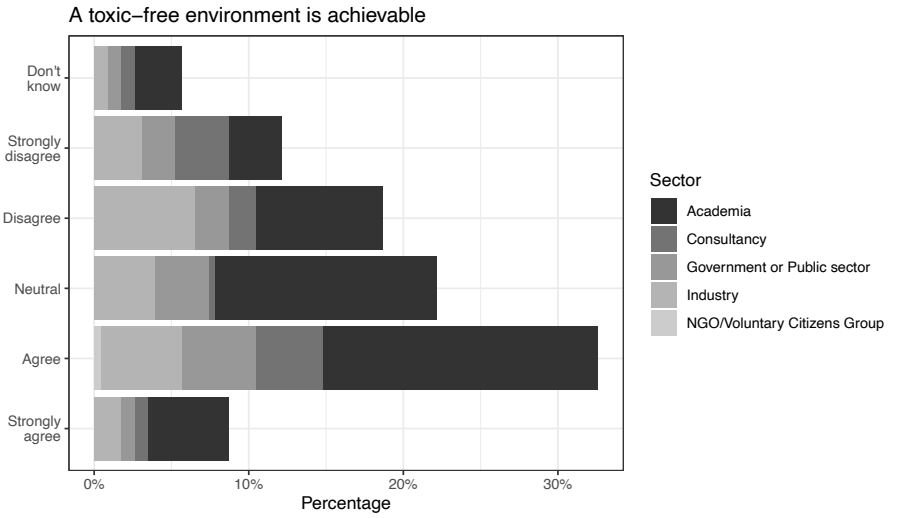

Figure S2-5. Results of how much SETAC members agree with the statement that the EU Green Deal ambition for a toxic-free environment is achievable.

Table S2-4. Amount of respondents (per sector and total) that agree or disagree with the statement that the ambition for a toxic-free environment is achievable.

Sector * A toxic-free environment is achievable Crosstabulation								
			A toxic-free environment is achievable					
			Strongly disagree	Disagree	Neutral	Agree	Strongly agree	Don't know	Total
Sector	Industry	Count	7	15	9	12	4	2	49
		% within Sector	14,3%	30,6%	18,4%	24,5%	8,2%	4,1%	100,0%
		% within A toxic-free environment is achievable	25,0%	34,9%	17,6%	16,0%	20,0%	15,4%	21,3%
		% of Total	3,0%	6,5%	3,9%	5,2%	1,7%	0,9%	21,3%
	Consultancy	Count	8	4	1	10	2	2	27
		% within Sector	29,6%	14,8%	3,7%	37,0%	7,4%	7,4%	100,0%
		% within A toxic-free environment is achievable	28,6%	9,3%	2,0%	13,3%	10,0%	15,4%	11,7%
		% of Total	3,5%	1,7%	0,4%	4,3%	0,9%	0,9%	11,7%
	Government or Public Sector	Count	5	5	8	11	2	2	33
		% within Sector	15,2%	15,2%	24,2%	33,3%	6,1%	6,1%	100,0%
		% within A toxic-free environment is achievable	17,9%	11,6%	15,7%	14,7%	10,0%	15,4%	14,3%
		% of Total	2,2%	2,2%	3,5%	4,8%	0,9%	0,9%	14,3%

Sector * A toxic-free environment is achievable Crosstabulation

			A toxic-free environment is achievable						
			Strongly disagree	**Disagree**	**Neutral**	**Agree**	**Strongly agree**	**Don't know**	**Total**
Sector	Academia	Count	8	19	33	41	12	7	120
		% within Sector	6.7%	15,8%	27,5%	34,2%	10,0%	5,8%	100,0%
		% within A toxic-free environment is achievable	28,6%	44,2%	64,7%	54,7%	60,0%	53,8%	52,2%
		% of Total	3,5%	8,3%	14,3%	17,8%	5,2%	3,0%	52,2%
	NGO	Count	0	0	0	1	0	0	1
		% within Sector	0,0%	0,0%	0,0%	100,0%	0,0%	0,0%	100,0%
		% within A toxic-free environment is achievable	0,0%	0,0%	0,0%	1,3%	0,0%	0,0%	0,4%
		% of Total	0,0%	0,0%	0,0%	0,4%	0,0%	0,0%	0,4%
Total		Count	28	43	51	75	20	13	230
		% within Sector	12,2%	18,7%	22,2%	32,6%	8,7%	5,7%	100,0%
		% within A toxic-free environment is achievable	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%
		% of Total	12,2%	18,7%	22,2%	32,6%	8,7%	5,7%	100,0%

Table S2-5. Chi-Square test results to show statistically significant difference between groups (sectors) and their given answers on the achievability of a toxic-free environment.

Chi-Square Tests			
	Value	**df**	**Asymptotic Significance (2-sided)**
Pearson Chi-Square	25,185[a]	20	,194
Likelihood Ratio	25,696	20	,176
Linear-by-Linear Association	5,687	1	,017
N of Valid Cases	230		

a. 14 cells (46,7%) have expected count less than 5. The minimum expected count is ,06.

A Pearson Chi-Square test was performed, with p = 0.194. This tells us there is no statistically significant (α=0.05) association between the Sector someone works in and how achievable they think a toxic-free environment is.

2.5.3.3 Correlation between ambitiousness and achievability of the Green Deal

A Spearman's rank-order correlation was run to determine the relationship between how achievable a toxic-free environment is and how ambitious the EU Green Deal is perceived. There was a weak, negative correlation, which was statistically significant (rs(229) = -0.163, p = 0.163, a= 0.05). In other words, the more ambitious the EU Green Deal is according to someone, the less achievable it deemed.

Table S2-6. Results of the Spearman's rank-order correlation to show the relationship between how achievable a toxic-free environment is and how ambitious the EU Green Deal is perceived by respondents.

Correlations				
			A toxic-free environment is achievable	**The Europian Green Deal is Ambitious**
Spearman's rho	A toxic-free environment is achievable	Correlation Coefficient	1,000	-,163*
		Sig. (2-tailed)		,013
		N	229	229
	The Europian Green Deal is Ambitious	Correlation Coefficient	-,163*	1,000
		Sig. (2-tailed)	,013	
		N	229	229

**. Correlation is significant at the 0.05 level (2-tailed).*

2.5.4 Consensus on the European Green Deal terminology: interpretation of 'toxic-free'

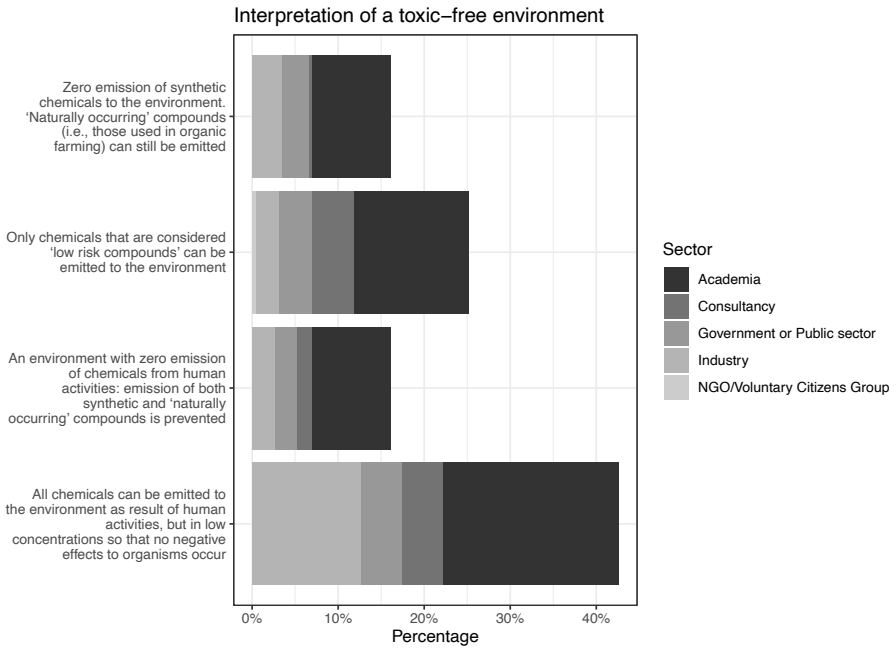

Figure S2-6. Results of how survey respondents interpret a 'toxic-free environment'.

Table S2-7. Results of how respondents (per sector and total) interpret a toxic-free environment.

Interpretation of a Toxic-Free Environment * Sector Crosstabulation								
			Sector					
			Industry	Consultancy	Government or Public Sector	Academia	NGO	Total
Interpretation of a Toxic-Free Environment	Zero emission of synthetic chemicals, natural substances can be emitted	Count	8	1	7	21	0	37
		% within Sector	16,3%	3,7%	21,2%	17,5%	0,0%	16,1%
	Zero emission of any chemical from human activity	Count	6	4	6	21	0	37
		% within Sector	12,2%	14,8%	18,2%	17,5%	0,0%	16,1%
	Low risk compounds can be emitted	Count	6	11	9	31	1	58
		% within Sector	12,2%	40,7%	27,3%	25,8%	100,0%	25,2%
	All chemicals can be emitted, but in low concentrations (no negative effects)	Count	29	11	11	47	0	98
		% within Sector	59,2%	40,7%	33,3%	39,2%	0,0%	42,6%
Total		Count	49	27	33	120	1	230
		% within Sector	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

Table S2-8. Chi-Square test results to show statistically significant difference between groups (sectors) and interpretation of a toxic-free environment.

Chi-Square Tests			
	Value	**df**	**Asymptotic Significance (2-sided)**
Pearson Chi-Square	17,049[a]	12	,148
Likelihood Ratio	18,077	12	,113
Linear-by-Linear Association	2,892	1	,089
N of Valid Cases	230		

a. 6 cells (30,0%) have expected count less than 5. The minimum expected count is ,16.

A Pearson Chi-Square test was performed, with p = 0.148. This tells us there is no statistically significant (α= 0.05) association between the Sector someone works in and their interpretation of a Toxic-Free environment.

2.5.5 An 'one substance-one assessment' principle

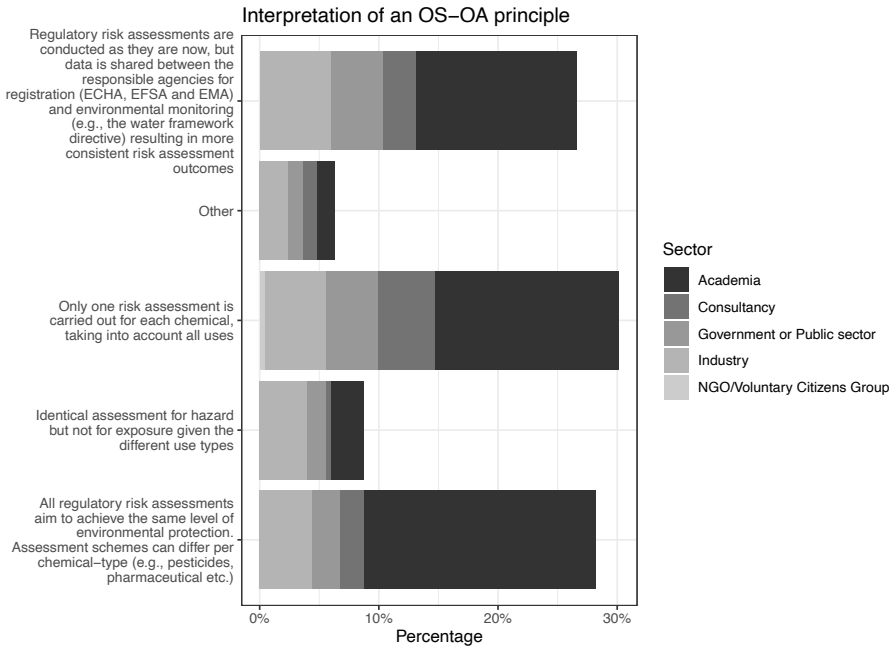

Figure S2-7. Interpretation of the 'one substance-one assessment' approach by the survey respondents.

Table S2-9. Results of how respondents (per sector and total) interpret a 'one substance-one assessment approach'.

Sector * Interpretation of 'one substance - one assessment' Crosstabulation								
			Interpretation of 'one substance - one assessment					
			Regulatory risk Assessments are conducted as they are, but data sharing between EU agencies is improved	All regulatory risk assessments aim for the same level of protection	Regulatory assessments for hazards are identical, but differ for exposure given the different use types	Only one regulatory risk assessment is carried out for each chemical, taking into account all uses	Other	Total
Sector	Industry	Count	12	12	8	11	6	49
		% within Sector	24,5%	24,5%	16,3%	22,4%	12,2%	100%
		% within Interpretation of 'one substance - one assessment	22,6%	16,4%	40,0%	15,9%	40,0%	21,3%
		% of Total	5,2%	5,2%	3,5%	4,8%	2,6%	21,3%
	Consultancy	Count	7	5	1	11	3	27
		% within Sector	25,9%	18,5%	3,7%	40,7%	11,1%	100,0%
		% within Interpretation of 'one substance - one assessment	13,2%	6,8%	5,0%	15,9%	20,0%	11,7%
		% of Total	3,0%	2,2%	0,4%	4,8%	1,3%	11,7%
	Government or Public Sector	Count	9	6	4	11	3	33
		% within Sector	27,3%	18,2%	12,1%	33,3%	9,1%	100,0%
		% within Interpretation of 'one substance - one assessment	17,0%	8,2%	20,0%	15,9%	20,0%	14,3%
		% of Total	3,9%	2,6%	1,7%	4,8%	1,3%	14,3%

Sector * Interpretation of 'one substance - one assessment' Crosstabulation

			Interpretation of 'one substance - one assessment					
			Regulatory risk Assessments are conducted as they are, but data sharing between EU agencies is improved	All regulatory risk assessments aim for the same level of protection	Regulatory assessments for hazards are identical, but differ for exposure given the different use types	Only one regulatory risk assessment is carried out for each chemical, taking into account all uses	Other	Total
Sector	Academia	Count	25	50	7	35	3	120
		% within Sector	20,8%	41,7%	5,8%	29,2%	2,5%	100,0%
		% within Interpretation of 'one substance - one assessment	47,2%	68,5%	35,0%	50,7%	20,0%	52,2%
		% of Total	10,9%	21,7%	3,0%	15,2%	1,3%	52,2%
	NGO	Count	0	0	0	1	0	1
		% within Sector	0,0%	0,0%	0,0%	100,0%	0,0%	100,0%
		% within Interpretation of 'one substance - one assessment	0,0%	0,0%	0,0%	1,4%	0,0%	0,4%
		% of Total	0,0%	0,0%	0,0%	0,4%	0,0%	0,4%
Total		Count	53	73	20	69	15	230
		% within Sector	23,0%	31,7%	8,7%	30,0%	6,5%	100,0%
		% within Interpretation of 'one substance - one assessment	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%
		% of Total	23,0%	31,7%	8,7%	30,0%	6,5%	100,0%

Table S2-10. Chi-Square test results to show statistically significant difference between groups (sectors) and interpretation of a 'one substance-one assessment approach'

Chi-Square Tests			
	Value	**df**	**Asymptotic Significance (2-sided)**
Pearson Chi-Square	25,315[a]	16	,064
Likelihood Ratio	25,566	16	,060
Linear-by-Linear Association	1,543	1	,214
N of Valid Cases	230		

a. 11 cells (44,0%) have expected count less than 5. The minimum expected count is ,07.

A Pearson Chi-Square test was performed, with p = 0.064. This tells us there is no statistically significant association (α= 0.05) between the Sector someone works in and their interpretation of what the 'one substance-one assessment' approach is. In total, 15 respondents (6.2%) voted for 'other', where they could write down their own interpretation of such an approach. It was often highlighted that the 'one substance-one assessment approach' is a vague term yet to be defined by the European Commission.

2.5.6 Science communication

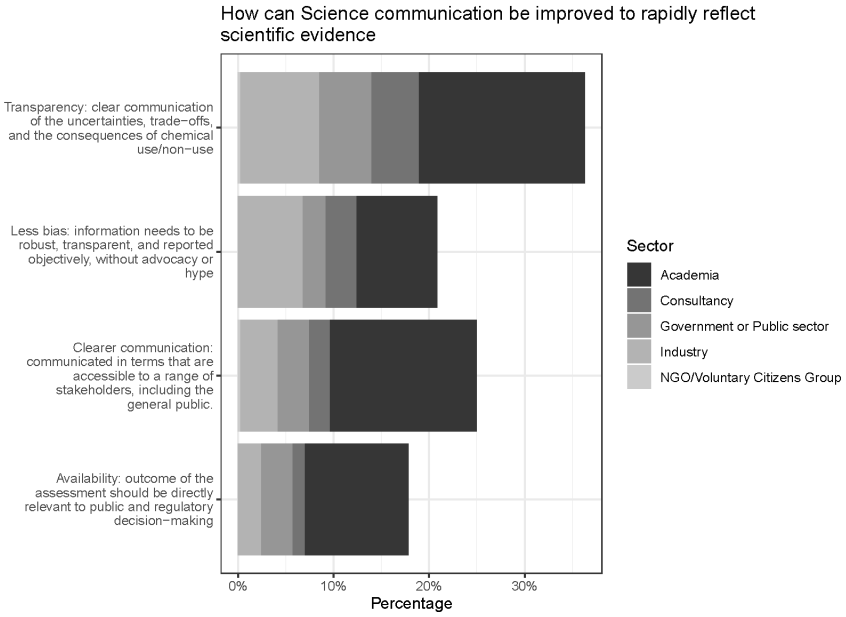

Figure S2-8. Results of how survey respondents think science communication can be improved in order for regulatory and industry to rapidly reflect scientific evidence on chemical hazards and risks.

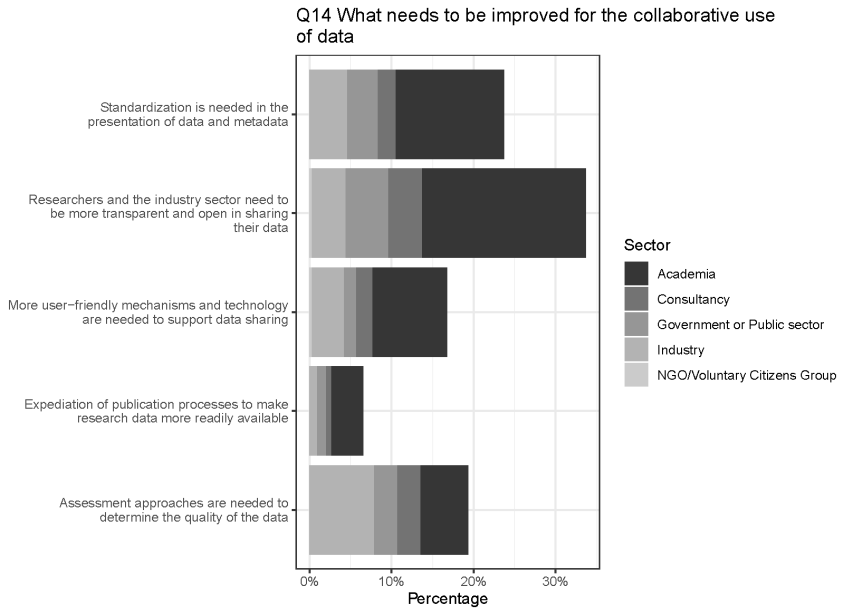

Figure S2-9. Results of what survey respondents think needs to be improved in order the collaborative use of research data.

CHAPTER THREE

CHEMICAL DESIGN AND PRODUCTION | SAFE AND SUSTAINABLE BY DESIGN: A COMPUTER-BASED APPROACH TO REDESIGN CHEMICALS FOR REDUCED ENVIRONMENTAL HAZARDS

Chapter 3 - Chemical Design and Production | Safe and Sustainable by design: a computer-based approach to redesign chemicals for reduced environmental hazards

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Abstract

Persistency of chemicals in the environment is seen as a pressing issue as it results in accumulation of chemicals over time. Persistent chemicals can be an asset in a well-functioning circular economy where products are more durable and can be reused or recycled. This objective can however not always be fulfilled as release of chemicals from products into the environment can be inherently coupled to their use. In these situations, chemicals should be designed for degradation. In this study, a systematic and computer-aided workflow was developed to facilitate the chemical redesign for reduced persistency. The approach includes elements of Essential Use, Alternatives Assessment and Green and Circular Chemistry and ties into goals recently formulated in the context of the EU Green Deal. The organophosphate chemical *triisobutylphosphate* (TiBP) was used as a case study for exploration of the approach, as its emission to the environment was expected to be inevitable when used as a flame retardant. Over 6.3 million alternative structures were created *in silico* and filtered based on QSAR outputs to remove potentially non-readily biodegradable structures. With a multi-criteria analysis based on predicted properties and synthesizability a top 500 of most desirable structures was identified. The target structure (di-*n*-butyl (2-hydroxyethyl) phosphate) was manually selected and synthesized. The approach can be expanded and further verified to reach its full potential in the mitigation of chemical pollution and to help enable a safe circular economy.

Abbreviations

CSS	Chemicals Strategy for Sustainability
MAUT	Multi-Attribute Utility Theory
MCDA	MultiCriteria Decision Analysis
OMG	Open Molecule Generator
PBMTS	Persistent, Bioaccumulative, Mobile, Toxic, Syntehsisability
PMG	Parallel Molecule Generator
QSAR	Quantitative Structure–Activity Relationships
TiBP	Triisobutylphosphate

3.1 Introduction

Synthetic chemicals are pivotal for our society and economy, often contributing to our health and comfort. The overall production and use of these chemicals has been increasing over the past decades (Bernhardt et al., 2017). As a result, these human-made chemicals are omnipresent in the environment where they can cause adverse effects to both humans and other organisms (Naidu et al., 2021; Posthuma et al., 2020). Chemical pollution has consequently been identified as one of five main drivers for global biodiversity loss (IPBES, 2019). Moreover, chemical pollution ('novel entities') is one of the planetary boundaries humanity must not cross in order to avoid unacceptable global change although this specific planetary boundary is still unquantified (Li et al., 2021; Rockström et al., 2009). Recently however it was assumed that this planetary boundary is exceeded as the annual production and release of chemicals outpace the capacity for their assessment and monitoring (Persson et al., 2022). Worldwide, initiatives to reduce the impact of chemicals are lagging behind, underlining the urgent need for more ambitious action (UNEP, 2019a; Wang et al., 2020).

Actions to manage chemical pollution consist for a major part of regulatory and technological (end-of-life) measures. Regulations are in place to register chemicals before market entry and hazard identification is a key part of this process. However, the influx of new chemicals on the market outpaces the speed with which such hazard assessments can be performed and for many chemicals adequate information on (environmental) hazards is lacking (Kristiansson et al., 2021). Consequently, problems are often identified long after the chemical has been approved (Johnson et al., 2020). Additionally, technological measures such as wastewater treatment are considered as resource-intensive and it can be even impossible to remove chemicals once present in waste streams (Kümmerer et al., 2018).

Chemicals can be emitted to the environment during their whole life cycle, from their production to waste phase (Wang and Hellweg, 2021). A combination of strategies covering the whole chemical life cycle will thus be most efficient to tackle the problem of chemical pollution (van Wezel et al., 2017). Technological curative measures will remain relevant at the end-of-life stage when emissions cannot be prevented, but preventive measures could be placed at the outset of the chemical life cycle. Designing Safe and Sustainable chemicals and materials is a promising option as its potential impact is expected to be high whilst costs are low (Peijnenburg et al., 2021; Puhlmann et al., 2021). As part of the EU Green Deal -the new growth strategy to transition the EU economy into a sustainable model and become climate-neutral by 2050- a Chemical Strategy for Sustainability was published. Here, the development of Safe and Sustainable chemicals is identified as a societal urgency and economic opportunity (European Commission, 2020b). Products and materials are ideally designed for a circular economy using Safe and Sustainable chemicals to enable their recycling and reuse and to achieve a society where harm from chemicals is minimized (European Commission, 2020b). The use of Safe and Sustainable chemicals is furthermore important as in many cases the release of substances from products or materials cannot be prevented.

The design of Safe and Sustainable chemicals requires an approach where a chemical's performance is not only seen as the ability to provide a certain function but inherently includes sustainability and hazard mitigation (Zimmerman et al., 2020). The concept of Green Chemistry provides a framework for this, aiming to generate more benign chemicals by taking into account a chemical's life cycle in order to increase resource efficiency and minimize waste (Anastas and Warner, 1998). This concept is further expanded to Circular Chemistry by making chemical processes circular when waste is used as a resource for new products (Keijer et al., 2019a). In order to design chemicals that are not only sustainable but also safe, it is essential to consider the hazards of chemicals in the design phase. This is however seen as one of the least developed areas of Green and Circular Chemistry, and therefore requires urgent attention (Erythropel et al., 2018).

With regard to environmental hazards, substances that are persistent, bioaccumulative and toxic (PBT), or even very persistent and very bioaccumulative (vPvB), pose the highest risks. The mobility (M) of chemicals has been proposed as an additional criterion in order to identify substances that are highly polar as they put the quality of surface waters and drinking water at risk (Hale et al., 2020; Reemtsma et al., 2016; Schulze et al., 2019). These PBMT criteria are inherent properties of chemicals and can therefore be a design choice. Most pesticides and biocides, for example, are designed to be toxic to certain organisms as their desired function, yet their action should be highly selective, not harming other organisms and negatively impacting biodiversity and the environment. Persistency can be an asset for chemicals in closed loops in a functioning circular economy, but is a reason for concern when the emission of chemicals to the environment cannot be prevented (Kümmerer et al., 2020). This can result in accumulation of the chemical with its ongoing usage, increasing the likelihood of long-term exposure that result in adverse effects (Cousins et al., 2019b).

A systems level thinking is required to make choices on chemical design acknowledging that systems on Earth are interconnected (Matlin et al., 2016; Zimmerman, 2020). Systems level design thinking can be applied to design new chemicals, as well as to redesign chemicals that are already in use. By identifying relevant hazards and processes related to the environmental fate and behaviour, the designer can choose to design for circularity, degradation, or in some cases a combination of the two (Cucciniello and Anastas, 2021; Keijer et al., 2019a). Before choosing for a redesign approach, already existing alternatives and the essentiality of the use of the chemical are to be considered according to the frameworks of Essential Use and Alternatives Assessment (Cousins et al., 2019a; Tickner et al., 2015). A chemical can be phased out when suitable alternatives exist or when the chemical fulfils a non-essential function to society.

Redesign of chemicals to minimize persistency is relevant when emissions to the environment cannot be avoided, aiming for complete mineralization of the structure to prevent the generation of possible hazardous transformation products (Puhlmann et al., 2021). Various examples of chemicals designed with reduced persistency exist, including pharmaceuticals, ionic liquids and plasticizers (Erythropel et al., 2018; Jordan et al., 2016; Leder et al., 2015; Rastogi et al., 2015). *In silico* models

such as quantitative structure–activity relationships (QSARs) are important tools in the design process to discover potential unwanted properties such as persistency early on (Erythropel et al., 2018; Gramatica et al., 2016). QSAR models assume that physio-chemical and environmental properties are linked to the chemical structure and molecular properties of a compound and are widely used to fill regulatory data gaps in registration dossiers (Pizzo et al., 2013). Elucidating unwanted effects can also prevent regrettable substitution; replacing a chemical with a structurally similar one that is less-studied, but ends up being equally or even more hazardous than the chemical it replaces (Maertens et al., 2021). Furthermore, *in silico* calculated properties can inform chemical design by prioritizing the most promising structures for further testing (Burello, 2015).

In the present study we aim to develop a framework to select chemicals for redesign and a systematic, computer-aided workflow to facilitate the redesign of these chemicals for reduced environmental and human health (PBMT) hazards with *in silico* generated structure suggestions. The organophosphate compound triisobutylphosphate (TiBP) was selected as case study to which we apply our computer-based approach for redesign. The method section gives an overview of the process to identify chemicals suitable for redesign, which includes considerations of available alternatives and essentiality. Then, the computer-aided redesign process is introduced, comprised of exhaustive structure generation, property prediction using QSARs and multi-criteria analysis of PBMT parameters and synthesizability. The results and implications of applying the developed redesign approach to TiBP are subsequently discussed, as well as the experimental results obtained to verify QSAR predictions. We show how redesign for safety and sustainability can be facilitated by a systematic and exhaustive generation of alternative structure suggestions and assessment of predicted PBMT properties, uncovering the most benign molecules. Current shortcomings and future advancements of our redesign approach are discussed, which will promote further developments according to the principles of Green and Circular Chemistry.

3.2 Methods

Criteria to identify chemicals suitable for redesign were identified, including considerations of available alternatives and essentiality, and presented in Figure 3.1. Following the flowchart, only chemicals which do not provide an essential function for society and/or health and for which no suitable alternatives are available are selected for a redesign approach (Cousins et al., 2019a; Tickner et al., 2015). Dependent on whether environmental emission of the chemical can be prevented or not, a redesign approach for recycling or degradation is chosen (Cucciniello and Anastas, 2021).

After the selection of the chemical for redesign -in our case TiBP- a three-step redesign process inspired on the design-make-test-analyze cycle used in drug discovery was followed (Figure 3.2)(Plowright et al., 2012). First, (I) a set of alternative structure suggestions were generated *in silico*. Then, (II) QSARs were selected and applied to relevant hazardous properties of the

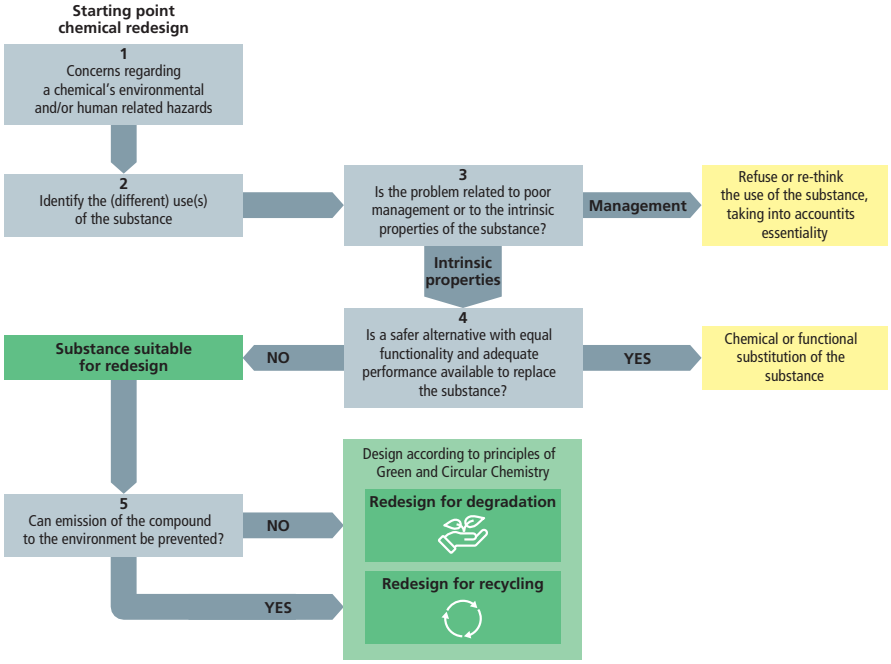


Figure 3.1. Flowchart for selecting chemicals for a redesign approach, inspired by concepts of Essential Use, Alternative Assessment and Green and Circular Chemistry (Anastas and Warner, 1998; Cousins et al., 2019a; Cucciniello and Anastas, 2021; Keijer et al., 2019b; Tickner et al., 2015; Wang and Hellweg, 2021).

generated structure suggestions. Subsequently, (III) the number of alternative structures was reduced by applying a filter for biodegradability followed by an analysis of PBMT properties and synthesizability. The structures were ranked and a target structure was selected manually, after which it was synthesized and tested. The redesign was implemented in python. Jupyter notebooks are available on GitHub (https://github.com/HannahFler/safedesign).

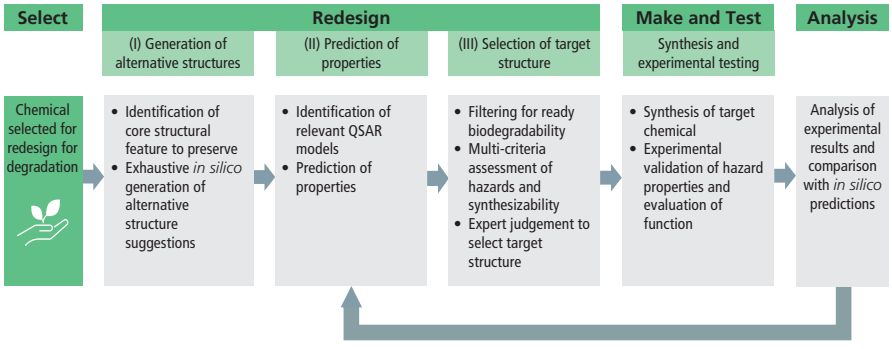


Figure 3.2. Workflow for the systematic, computer aided redesign approach for Safe and Sustainable chemicals.

3.2.1 Generation of alternative structures

2D chemical structures were generated from chemical formulas with the Parallel Molecule Generator (PMG 1.0), the second version of the opensource software Open Molecule Generator (OMG) which allows for parallelization to reduce runtime (Jaghoori et al., 2013; Peironcely et al., 2012). PMG aims at an exhaustive generation of chemical structures, in SDF format, from a given elemental composition (expressed as chemical formula) and core structural fragment, hence generating every structure possible for that composition. It facilitates the systematic generation of alternative structures with moderate computational expense needed. As the software was created for analytics, some chemically unrealistic structures under normal conditions can be generated. The QSARs used in the subsequent steps to predict properties partly filter these out.

Trimethyl phosphate (SDF format, generated with ChemDraw Professional, version 19.0.1.28) was used as core structural fragment for PMG to preserve the organophosphate core as essential structural feature of TiBP for the function of flame retardancy. The phosphate core can form char residue by crosslinking, blocking access to fuel, and form phosphorus containing radicals in the gas phase inhibiting flames, therefore exhibiting flame retardant properties (Velencoso et al., 2018). Chemical formulas were systematically generated to be passed on to PMG. CH_2 units were added to a starting formula, which in turn was varied to include nitrogen or additional oxygen as heteroatoms and double bond equivalents, which result in rings or multiple bonds in the generated structures. For example, the starting formula $C_4H_{11}PO_4$ was used to generate organophosphate structures with different alkyl side chains upon addition of CH_2 units, and the starting formula $C_4H_{11}PO_5$ was used to include one additional oxygen as heteroatom in the side chains. The number of CH_2 units added per starting formula was determined mainly by computation time. An overview of all elemental compositions for which structures were generated and the respective starting formulas is shown in Figure 3.3. Generated enol structures were filtered out, as they would generally tautomerize to their keto form, which were already included in the structure set. The python package RDKit (Landrum et al., 2021) was used to handle chemical structures and translate SDF mol files to SMILES codes to be used in the subsequent steps.

3.2.2 Prediction of properties

A list was compounded with the generated structures as SMILES codes that were used as input to calculate P, B, M and T properties by using QSAR models from EPISuite (Epiweb version 4.1) and models included in the VEGA platform (Benfenati et al., 2019). The applicability domain of the models was manually checked by following the approach described in an OECD Guidance Document (OECD, 2007). Ranges of molecular weight and LogKow were defined for the model training and test data sets. These data sets were also searched for structural similarities to the case

study compound TiBP, of which a summary is presented in Table S3-1. The number of endpoints able to be modelled was constrained, as our dataset fell outside the applicability domain of some QSARs. Some uncertainty regarding the applicability domain remains however, as the models are applied to a large number of diverse *in silico* generated structure suggestions. The QSAR results were thus treated as indications to guide the design.

3.2.3 Multicriteria analysis for selection of target structure

To reduce the size of the dataset, potential non-readily biodegradable substances were filtered out based on the EPISUITE cut-off criteria for combined results from the models BIOWIN 3 and 5, as described in the BIOWIN user manual (BIOWIN 3 ≥ 3.25 and BIOWIN 5 ≥ 0.5, US EPA, 2012). Structures which were predicted to be mutagenic by VEGA Ames test consensus model were also filtered out, as well as structures which were predicted active in estrogen, androgen, thyroid alpha or beta receptor effects. Then, a multi-criteria analysis based on the Multi-Attribute Utility Theory (MAUT) principle was performed on hazard and synthesizability related endpoints. Criteria and endpoints used in the MAUT assessment are shown in Table 3.1. Values of an endpoint were scaled from 0 (worst) to 1 (best) based on results of the whole dataset for that specific endpoint to generate an endpoint subscore. For LogKow and LogKoc, desirability functions were designed to calculate subscores, indicating optimal ranges for the values based on reported criteria and avoiding hard cut-off values (Figure S3-1)(Segall, 2012).

Persistency was calculated based on biodegradability outcomes, which is composed of both aerobic and anaerobic processes. For aerobic degradation, model outputs of BIOWIN 3 and 6 models were combined for the MAUT assessment as this combination of models was shown to have the highest overall predictivity for biodegradation (Posthumus et al., 2005). Anaerobic degradation was predicted with BIOWIN 7. The LogKow, as predicted by KOWWIN, was used as a parameter for bioaccumulation. LogKoc values to estimate mobility were obtained by averaging predictions from KOC OPERA model from VEGA and KOCWIN model from EPISUITE. The BCF, which is used as a parameter to identify bioaccumulative substances under REACH (Regulation (EC) 1907/2009, Annex XIII), was predicted for all substances in our list to be non-concerning and therefore not further taken into account in the analysis. The non-mutagenicity score from VEGA ames test consensus model was included for toxicity. For synthesizability, two scores were created. One by rewarding organophosphate structures with equal side chains (SynSymPoints) as these more symmetric molecules are generally easier to synthesize than those with different side chains which requires more specificity of the synthetic strategy. Structures with no equal side chains received score 0, those with two equal side chains score 0.5 and those with all equal side chains a score of 1. Structures containing three- or four-membered rings were penalized with a score of -1 (SynRingPoints), as these rings are more difficult to synthesize. Furthermore, these rings rarely appear in the training datasets

of the QSAR models used to predict properties, which makes the estimates for this kind of structures less reliable. After assigning scores for every endpoint between 0 to 1, partial scores for PBMTS were calculated by multiplying each criterion with the respective weight (see Table 3.1). All PBMTS criteria had a final weight of 1, treating them as equally important in the MAUT analysis. The partial scores were then summed up and normalized by dividing by the sum of weights to get a final PBMTS score. Accordingly, the alternative structures with the highest PBMTS score were expected to be the most desirable structures regarding their assessed PBMTS properties.

The top 500 structure suggestions according to the scoring were examined manually to select a target molecule. This selection was guided by chemical stability (e.g., no structures with geminal diols, as they would undergo dehydration and form a carbonyl moiety), the identification of potential starting materials, such as the renewable ethylene glycol, and the possibility of systematic structural comparison with the original compound TiBP.

Table 3.1. QSAR models and their application used for the characterization of P, B, M, T and S properties for the MAUT assessment.

Criteria	Endpoint	QSAR model	Application of QSAR: Filter or Ranking (with desired value or range)	Weight for MAUT assessment
P	Ready biodegradability	EPISUITE: BIOWIN 3 and BIOWIN 5	Pre-selection filter	Not used for scoring
	Aerobic biodegradability	EPISUITE: BIOWIN 3 and BIOWIN 6 (average)	Ranking (desired value as high as possible)	0.5
	Anaerobic biodegradability	EPISUITE: BIOWIN 7	Ranking (desired value as high as possible)	0.5
B	BCF	EPISUITE: BCFBAF	All structures predicted non-concerning	Not used for scoring
	LogKow	EPISUITE: KOWWIN	Range between 1 and 3 [1].	1
M	LogKoc	EPISUITE: KOCWIN and VEGA: OPERA KOC (average)	Ranking (undesired below 1, soft lower cutoff between 1 and 2. Desired value between 2 and 4 [2])	1

Criteria	Endpoint	QSAR model	Application of QSAR: Filter or Ranking (with desired value or range)	Weight for MAUT assessment
T	Non-Mutagenicity	VEGA: consensus model	Pre-selection filter and ranking of reliability (desired value as high as possible)	1
	EDC properties: Estrogen, Androgen, Thyroid alpha and beta receptor effects	VEGA: Estrogen (IRFMN/CERAPP), Androgen (IRFMN/COMPARA), Thyroid alpha/beta (NRMEA)	Pre-selection filter with qualitative outputs	Not used for scoring
S	Synthesizability based on chemical symmetry (SynSymPoints)	None, score created using rdkit and SMARTS substructure matching	Ranking (desired value as high as possible)	0.5
	Exclusion of small rings (SynRingPoints)	None, score created using rdkit and SMARTS substructure matching	Ranking (negative value for rings, desired value as high as possible)	0.5

[1] (EU, 2006a)

[2] (Arp and Hale, 2019)

3.3 Results and Discussion

3.3.1 Identifying chemicals for redesign

In the first step to select a substance for a redesign approach (Figure 3.1), chemicals are considered that are present in the environment and for which concerns have been raised regarding risks to humans or ecosystems (Wang and Hellweg, 2021). Within this context, the organophosphate TiBP was selected as an example to showcase our new methodology. TiBP has been detected in water bodies and was added to the NORMAN list of emerging substances (Alygizakis et al., 2019). The second step is to identify the different uses of the substance. At present, there are 8 companies which have a registration for TiBP in the EU, each using between 1.000 – 10.000 tonnes annually as a solvent, plasticizer, anti-foaming agent and additive flame retardant (ECHA, 2020b). Here, we focused on its use as an additive flame retardant for textiles as organophosphate flame retardants are generally known to be a group of concern (Blum et al., 2019; Pantelaki and Voutsa, 2019). Flame retardants are released from their textile matrix and potentially end up in the environment during washing or from wear and tear (Luongo et al., 2016). Emission of TiBP to the environment can thus be

assigned to its intrinsic properties and specific uses, and not to mismanagement (step 3). In this step, the essentiality of the substance is considered as well to phase-out hazardous substances that don't contribute to health or society (Cousins et al., 2019a; European Commission, 2020b). The outcome of this step could change for certain chemicals depending on what uses can be considered essential (Cousins et al., 2021). It will, however, be hard to justify banning chemicals that are considered non-essential, but that contribute to society's comfort. For these functions, improved chemical or product design will play a pivotal role to reduce environmental emissions from manufacturing to end-of-life stages (Wang and Hellweg, 2021). In step 4 it is considered whether the function the chemical provides can be substituted by better alternatives. As no database with an overview of different flame retardants for textiles exists to our knowledge, it is difficult to evaluate for step 4 whether better alternatives for TiBP are already available and what the reasons would be that they are not used industrially. Phosphorus-based flame retardants are however already considered as a better alternative compared to e.g. brominated flame retardants, and therefore offer a promising starting point for the design of a benign additive. Chemicals containing phosphate are also of interest in the context of circularity as phosphate can be well recovered from wastewater effluents and subsequently reused (Jupp et al., 2021). A redesign approach for degradation was chosen, as emission of TiBP as a result of its use as an additive flame retardant cannot be prevented (step 5).

3.3.2 Generation of alternative structures

By repurposing software developed for metabolomics, we enabled a systematic search for alternatives for TiBP with a similar chemical structure. By combining the structure generation with data collection on potential PBMT properties, we aimed to prevent proposing a regrettable substitute as an alternative to TiBP.

More than 6.3 million structures were generated *in silico* to facilitate the redesign of TiBP. The difference in number of structures per elemental composition and in computing time resulted in a heterogenous number of CH_2-units added per starting formula, and thus in number of elemental compositions with the same double bond equivalents and heteroatoms. Figure 3.3 shows the elemental compositions used for the PMG program for the exhaustive generation of structures. The combination of starting formula (x-axis of Figure 3.3) and the total number of carbon atoms (y-axis of Figure 3.3) yields the elemental composition, e.g. at the starting formula $C_4H_{11}PO_4$ (on the x-axis) with 13 carbon atoms (on the y-axis), the elemental composition $C_{13}H_{29}PO_4$ is represented (see left arrow in Figure 3.3) for which PMG generated all possible structures. The starting formula $C_4H_7PO_7$ and 7 carbon atoms denotes the chemical formula $C_7H_{13}PO_7$ (see right arrow in Figure 3.3), for which structures containing three additional oxygen atoms and two double bond equivalents were generated.

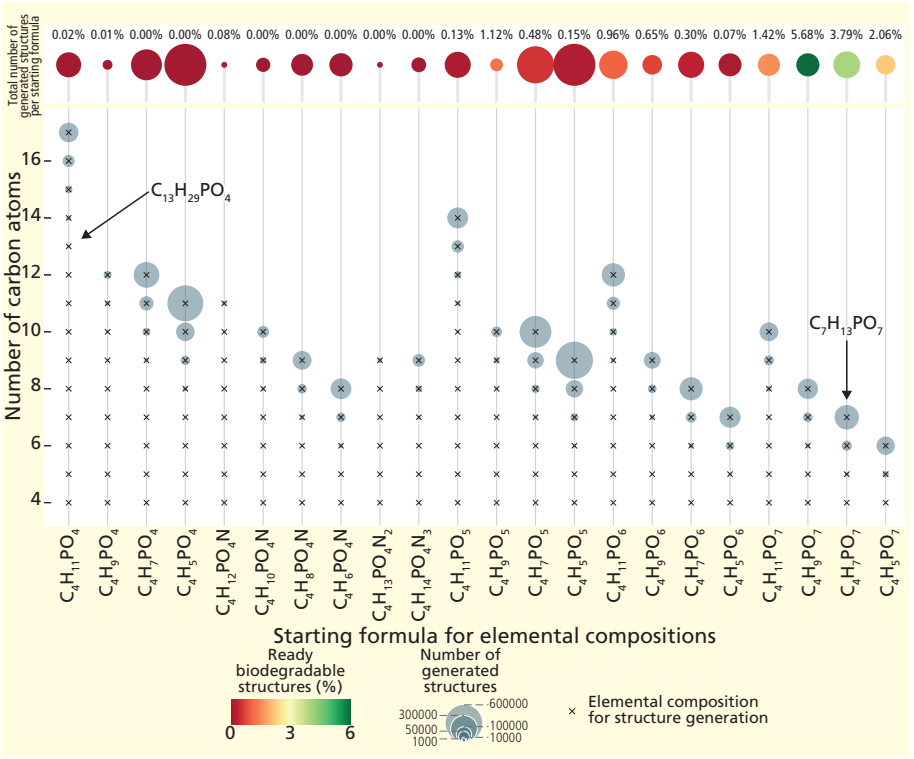


Figure 3.3. Overview of the in silico generated structures and their ready-biodegradability. The starting formula for structure generation is shown on the x-axis. The y-axis shows the number of carbon atoms present in the elemental compositions. Each elemental composition for which structures were generated is marked by an x. Two formulas are shown as examples. The size of the bubbles indicates the number of structures generated for that particular elemental composition. The top plot shows the amount of generated structures per starting formula, and the colours represent the percentage of readily biodegradable structures as predicted by EPISUITE.

3.3.3 QSAR predicted properties

All generated structures were filtered based on their predicted ready-biodegradability according to EPISUITE cut-off criteria (US EPA, 2012), which greatly reduced the dataset from about 6.3 million generated structure suggestions to 32,350 structures. The fraction of structures predicted to be readily biodegradable according to this cut-off was generally highest in sets of structures generated from elemental compositions with more oxygen atoms (Figure 3.3), in accordance with rules of thumb indicating increased biodegradability with the introduction of oxygen handles (Boethling et al., 2007). Structures which were predicted to be mutagenic by the VEGA mutagenicity consensus model were also filtered out (1,057 structures), as well as structures which were predicted to be active in endocrine disruption according to VEGA models listed in Table 3.1 (46 structures).

Other relevant properties for the PBMT assessment were predicted with selected QSAR models from EPISUITE and VEGA platform. Results of all QSAR outcomes can be found on GitHub (https://github.com/HannahFler/safedesign). Uncertainties of QSAR-generated data are higher compared with experimental data, but these were partly addressed here by examining the applicability (Ballabio et al., 2017; Pizzo et al., 2016; Posthumus et al., 2005). It is however important to note that some uncertainty always remains with setting the applicability domain (Netzeva et al., 2005).

Improvement of the reliability of QSAR predictions -especially of biodegradability- is greatly needed (Rücker and Kümmerer, 2012). Concerns have for example been raised regarding the potential (eco)toxicity of organophosphate flame retardants (Blum et al., 2019). Due to their toxic properties, some organophosphate flame retardants (including Trixylyl phosphate and Tris(2-chloroethyl) phosphate) are already included on the candidate list of SVHC for authorization under REACH (ECHA, n.d.). Models to predict endpoints such as carcinogenicity and ecotoxicity could however not yet be included in our approach as their applicability was considered to be unsatisfactory (see SI for further details). In order to improve the reliability of model outcomes in the future, a consensus approach could be applied in which outcomes of multiple models are combined and averaged (Gramatica et al., 2012). The PBT index as reported by Gramatica et al. (2016) offer for example promising tools to strengthen the assessment of persistency, bioaccumulation and toxicity related endpoints (Gramatica et al., 2016). In addition, QSARs to predict functionality as a flame retardant (Gu et al., 2019; Zhang et al., 2020) would be useful to include in order to enhance the approach and filter structures based on their functionality. However, these models currently don't seem suitable for the screening of a large library of structures with limited associated data (SMILES codes). In our framework, the preservation of the organophosphate core retains the key structural feature linked to flame retardancy (Velencoso et al., 2018). Beyond that, properties relating to the interaction with the material matrix are important to the success of an alternative, which depend on the specific application as well as manufacturing techniques.

3.3.4 Multi-criteria analysis

A multi-criteria ranking of the remaining 31,247 structures was made based on PBMTS properties to find the most desirable structures (Figure 3.4). For persistency, the endpoints for aerobic biodegradability and anaerobic biodegradability were evaluated, for bioaccumulation the LogKow was used and for mobility the LogKoc was considered. For toxicity, only the non-mutagenic score given by the VEGA consensus model could be included as our dataset fell outside the applicability domain of other relevant QSAR models. To include the synthesizability in the analysis, identical side chains (SynSymPoints) were rewarded and small rings (SynRingPoints) were penalized (Table 3.1). The distributions of the dataset of alternative structures for each endpoint are presented in the SI.

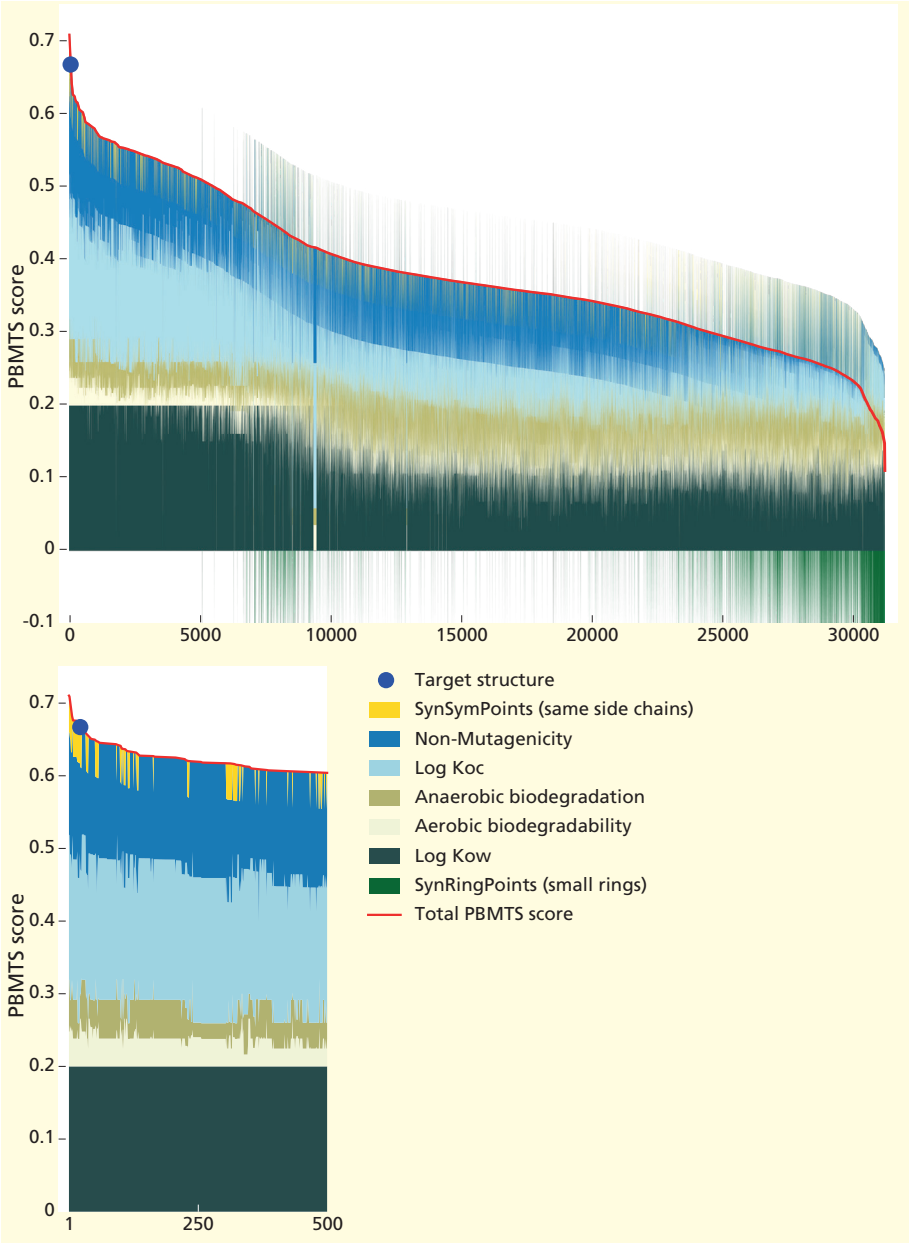


Figure 3.4. Composition of the PBMTS score of the complete set of in silico generated structures which were predicted to be readily biodegradable (A) and the 500 top-scoring structures (B), sorted from highest to lowest ranking structure. Structures containing 3- or 4-membered rings were penalized with a negative sub score (SynRingPoints, plotted in dark grey), leading to a lower total PBMTS score (plotted as red line) for the respective structures. The selected target compound is shown as blue dot.

The combined use of QSAR-generated data and MAUT analysis to identify the most desirable alternative structure has been previously reported (Zheng et al., 2019). The selection of appropriate parameters and QSAR models is a key step in this process, but the type of parameters and models that are useful might differ on a case-by-case basis as the redesign goals and the endpoints that are considered relevant might differ. Furthermore, the weight applied on the parameters in the PBMTS MAUT assessment is a key factor which affects the order of the list of most suitable structures. This emphasizes that the (re)design for Safe and Sustainable chemicals requires a combination of different expertise working together to ensure that all relevant parameters and issues considering a chemical's function and hazard are properly understood and taken into account (Plowright et al., 2012; Zimmerman et al., 2020)

3.3.5 Manual target selection

The top 500 structures according to the PBMTS score ranking were inspected to search for suitable targets. By inspecting the alternative structures based on the PBMTS MAUT ranking, di-*n*-butyl (2-hydroxyethyl) phosphate, which ranked 22nd in the analysis, was selected as the target compound. Figure S3-2 in the supplementary information shows the top 25 structures of the PBMTS scoring for illustrative purposes (see Jupyter notebooks on GitHub for the complete overview). In contrast to many of the top 500 structures, the target compound is chemically stable and has a 2-hydroxyethyl moiety which offers the possibility of using commercially available ethylene glycol and di-*n*-butyl phosphate for the synthesis. The higher ranked structures often contain a hydroxymethyl group which is generally harder to obtain as the C_1-diol building block methanediol is not stable and can oligomerize to $HO(CH_2O)_nH$. Furthermore, the chosen target allows for structural comparison with the original compound TiBP, as the two other side chains have a chain length of four carbon atoms, as compared to higher ranked structures with longer side chains. Moreover, phosphates with C_4 chains are more common in industry, e.g. di-*n*-butyl phosphate is more attainable and economical than di-*n*-pentyl phosphate. The di-*iso*-butyl isomer of the target compound was not predicted to be readily biodegradable and was thus not included in the dataset of possible alternative structures. Consistently, branched hydrocarbon chains are reported to result in lower biodegradation rates compared to similar structures with linear chains (Liang and Liu, 2016). The selected alternative structure was expected to be better water soluble due to its lower LogKow as a result of the added hydroxyl group. Water-soluble substances usually biodegrade faster than substances with a high LogKow, as the latter sorb strongly to the sediment diminishing their bioavailability. In addition, the added hydroxyl group and the linear alkyl chains were expected to increase the biodegradation potential of the structure as well (Boethling et al., 2007).

In addition to the chemical stability and hazard profile of the chemical, attention was paid to the sustainability of potential production routes of the designed alternative. As an organophosphate

chemical, the starting materials could be renewably sourced from P-rich waste streams. Furthermore, the hydroxyethyl side chain of the target could be introduced using ethylene glycol, which is a readily available base chemical with a high potential for sustainable production (Figueiredo, 2020; Kandasamy et al., 2019). The target di-*n*-butyl (2-hydroxyethyl) phosphate is a known compound (CAS 130525-77-8) with mentioned potential applications as a flame retardant and as additive in lubricant oils (Matsumura and Tokuyasu, 1999; Shono and Ogata, 2018). It has also been identified as a metabolite of tri-*n*-butyl phosphate in earthworms (Wang et al., 2018). One preparation of the compound is described in patent literature, starting with di-*n*-butyl phosphate and ethylene oxide (Matsumura and Tokuyasu, 1999) yet no characterization of this compound was reported to date. Furthermore, the compound is not registered in the EU under REACH, nor does it seem to be registered in another region (OECD, n.d.) indicating the compound is currently not produced and used at industrial levels.

3.3.6 Experimental and in silico properties: TiBP vs target compound

We synthesized the target compound from di-*n*-butyl phosphate using oxalyl chloride for activation and subsequent addition of excess ethylene glycol. No attempts were undertaken to optimize the synthesis in this study, but the development of organophosphate synthesis protocols adhering to the principles of Green and Circular Chemistry is ongoing in our laboratories. For example, the design of TiBP can be made circular when degradation products are used as the starting materials for a new cycle (Cucciniello and Anastas, 2021). This can be achieved by mineralization of a structure, generating phosphate that can be retrieved from wastewater and used as a source for the production of new chemicals (Jupp et al., 2021). Mineralization is furthermore desirable as metabolites and transformation products might be equally or even more hazardous than the initial structure (Noguera-Oviedo and Aga, 2016).

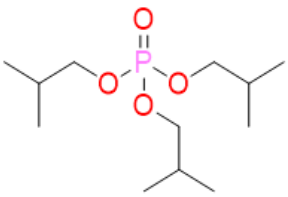
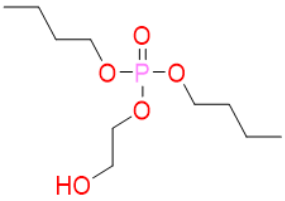
In silico predicted properties and results of experimental testing of TiBP and the target compound are summarized in Table 3.2. The *in-silico* properties of the target compound show an improvement regarding environmental hazards as, contrary to TiBP, it is predicted to be both readily biodegradable and degradable under anaerobic conditions. Furthermore, the predicted LogKow of the target compound is lower than the regulatory trigger value of 3 for bioaccumulation. Model outcomes should be considered with due prudence and need to be validated with relevant experimental testing.

For both TiBP and the target compound, results of the OECD301F test show that degradation is started after an adaptation period of 10 days. The results furthermore suggest that the substances are equally degradable (supplementary information), but neither of them can be considered as readily biodegradable because the degradation rate did not reach 60% within 28 days. Contrary to the *in silico* prediction, the target compound is not more biodegradable than TiBP in this experiment, opening two pathways for further investigation. Following these results, another structure can be selected to

reiterate and continue the design cycle (Figure 3.2). On the other hand, the biodegradation process can be experimentally assessed in more detail to arrive at more definite conclusions for a more limited set of compounds. Many issues can make the outcomes of biodegradation tests difficult to interpret. For example, it is interesting to note that TiBP is considered to be readily biodegradable in the REACH dossier based on an OECD 301 test (ECHA, 2020b). The use of different inocula is shown to yield highly variable biodegradation outcomes, resulting in a lack of reproducibility of these tests (Poursat et al., 2019). This lack of reproducibility could partly be overcome by using chemostats and by introducing an adaptation period of the inoculum to the chemical in future testing (Gresham and Hong, 2015; Poursat et al., 2020). Furthermore, other types of testing such as OECD 308 and 309 tests can be performed to gain better insights on the behavior of a compound in specific environmental media (Seller et al., 2021). These tests could also generate insights into the mechanisms of the degradation process and hint at further possibilities to improve the molecular design process and the predictive tools used in the design process.

Thermogravimetric analyses (TGA) suggest that the function of TiBP as a flame retardant is successfully retained in the designed alternative structure. The TGA monitors the weight loss as a function of temperature and the remaining char yield, which hints both at condensed phase activity for flame retardancy and at reduced emission of potentially combustible gases (Markwart et al., 2019; Rakotomalala et al., 2010). The functionality might even be enhanced due to a higher char yield of 20% for the target compound compared to a yield of 7% for TiBP (Table 3.2). The target compound could exhibit benefits compared to TiBP as, due to its potentially enhanced functionality as a flame retardant, less material might be needed to provide the same level of protection. More extensive testing must be performed to confirm flame retardant properties of the target compound, especially by application to the material that the substance aims to protect. Additionally, environmental fate needs to be further assessed in realistic conditions to evaluate the suitability of the target as a benign alternative to TiBP.

Table 3.2. Comparison of experimental and in silico predicted properties of TiBP and the target compound

	Original compound: TiBP	**Target Compound: di-n-butyl (2-hydroxyethyl) phosphate**
Structure		
CAS number	126-71-6	130525-77-8
SMILES	CC(C)COP(=O)(OCC(C)C)OCC(C)C	CCCCOP(=O)(OCCO)OCCCC
Mw	266.31 g/mol	254.27 g/mol
In silico predicted properties		
LogKow	3.6	1.37
LogKoc	3.15	1.79
BCF	16 (does not bioaccumulate)	2 (does not bioaccumulate)
Readily Biodegradable (BIOWIN 3 & 5)	No	Yes
Anaerobic degradation (BIOWIN 7)	Does not biodegrade fast	Biodegrades fast
Experimental properties		
Biodegradation (OECD301F)	Non-readily biodegradable after 28 days	Non-readily biodegradable after 28 days
Agonistic effects on the hormone system	No	No
Antagonistic effects on the hormone system	No	No
Functionality as FR	Yes (ECHA, 2020b)	Yes (Matsumura and Tokuyasu, 1999)
TGA char yield (Figure S3-6)	7%	20%

3.4 Improvements needed to account for biodegradability in the design process

Despite the need to further improve QSARs that predict ready biodegradability (Mamy et al., 2015), they are useful tools to screen large amounts of substances to guide the (re)design of Safe and Sustainable chemicals in an early stage. Since biodegradation occurs via a variety of different mechanisms, induced by different environmental variables that are currently not completely understood (Fenner et al., 2021), it will remain difficult to accurately predict the biodegradation of a chemical in the environment. The vast number of variables that influence the degradation of a substance in the environment can, for example, not only result in different outcomes between laboratory and field, but also in space and time (Seller et al., 2021). Alternative techniques are being developed that can cope with these aspects (Fenner et al., 2021), yet these methods are all experiment-based and therefore not suitable for incorporation in our redesign approach to screen vast amounts of novel structures. These techniques will provide valuable insights into the various biodegradation processes, however, which we are currently exploiting in our laboratories to advance our *in silico* tools used in the (re)design process.

3.5 Conclusions

Here, we developed a systematic approach to facilitate the design of Safe and Sustainable chemicals in order to reduce hazards whilst the chemical's function is maintained. The approach was applied to TiBP as a case study, yet can be applied to other molecular structures. At first, we evaluated whether TiBP would classify for a redesign approach. By incorporating aspects from the EU Green Deal's Chemicals Strategy for Sustainability, only chemicals that provide an essential function and for which no suitable alternatives are available are of relevance to be selected for redesign. Depending on whether emission of the chemical to the environment can be prevented or not, a redesign approach for recycling or degradation is chosen. Considering that TiBP can leach out of textiles during washing, a redesign approach for degradation was chosen. Next, a three-step redesign process was developed in which alternative structures were generated *in silico* and ranked based on their QSAR-predicted PBMT hazards and synthesizability. Predicted properties of the selected alternative (di-*n*-butyl (2-hydroxyethyl) phosphate) show favorable characteristics compared to TiBP, while first experimental results do not confirm enhanced biodegradability. The implementation of our approach to design chemicals that are functional, safe and sustainable is largely dependent on the availability of suitable tools and methods to predict environmental fate and related hazards. It is therefore key that the knowledge on the mechanisms of biodegradation will be improved so that testing methods can be improved in order to advance the much-needed Chemicals Strategy for Sustainability and help mitigate chemical pollution. Studies like the present can provide valuable input for this strategy and can help taking Green and Circular Chemistry

principles for the design of Safe and Sustainable chemicals into practice. By using future advances of testing methods and by looking beyond a chemical's intended function only, environmental hazards can be minimized to allow chemicals to continue to provide vital functions to society.

3.6 Experimental Section

3.6.1 Synthesis of the Target Compound: Di-n-butyl (2-hydroxyethyl) phosphate

The synthesis was performed with standard Schlenk technique under an atmosphere of dry nitrogen. Dry solvents were obtained from a solvent purification system, where DCM was dried over $CaCl_2$. DMF was dried with $MgSO_4$ or molecular sieves and distilled. Triethylamine was purified by distillation. Other reagents were used as received. NMR spectra were measured with a 400 MHz Bruker Avance NMR spectrometer and calibrated internally to residual solvent resonances (^1H, δ 7.26 ppm (chloroform-d); ^{13}C, 77.36 ppm (chloroform-d)). The software "Bruker TopSpin" (version 4.1.3) was used to analyze the spectra. The IR spectrum was measured with a Bruker Alpha FT-IR spectrometer equipped with a Platinum ATR module. High resolution electrospray ionization (ESI) mass spectra were recorded with flow injection (flow rate 0.01 ml/min) on an AccuTOF LC, JMS-T100LP mass spectrometer (JEOL, Japan) in positive-ion mode with a needle potential of 2500 V. The synthesis protocol was oriented on procedures described in literature (Hilken et al., 2014; Pahor et al., 2016).

Synthesis of di-n-butyl (2-hydroxyethyl) phosphate: A solution of 9.9 mL (10.5 g, 50 mmol) di-*n*-butyl phosphate and 0.5 mL (0.46 g, 6.25 mmol) DMF in 100 mL DCM was added dropwise to a solution of 21.5 mL (31.7 g, 250 mmol) oxalyl chloride in 100 mL DCM at room temperature. Gas evolution was observed. The mixture was stirred for 3 h at room temperature. The solvent and excess oxalyl chloride were removed by vacuum distillation under nitrogen atmosphere. The remaining yellow solid was dissolved in 140 mL DCM. The resulting clear yellow solution was added dropwise over 25 min to a mixture of 14 mL (10.1 g, 100 mmol) triethylamine and 28 mL (31.0 g, 500 mmol) ethylene glycol in 40 mL DCM, while stirring in an ice bath. The mixture was stirred at room temperature for 1.5 h and then refluxed for 18 h. The reaction mixture was quenched with 200 mL water and the aqueous layer was extracted with 2x 100 mL DCM. The combined organic phases were washed (100 mL water, 100 mL sat. aq. NH_4Cl, 100 mL water), dried with $MgSO_4$ and filtered. The solvent was removed in vacuo, leaving 9.53 g (75% crude yield) of an orange oil behind. The product was purified by silica gel column chromatography. Two columns were run using diethyl and diethyl ether:ethanol 98:2 as eluent, respectively, yielding one pure fraction of a pale-yellow oil (2.27 g). Some other fractions containing products and few impurities were combined and purified on a second column (*n*-hexane: ethyl acetate 30:70 to 0:1) giving 2.37 g of a pale yellow oil (4.64 g purified product, 37% yield). R_f(diethyl ether) = 0.18, R_f(*n*-hexane: ethyl

acetate) = 0.43. ^{1}H-NMR (400 MHz, chloroform-d, 298 K): δ 4.11 (m, 2H; CH_2), 4.03 (q, AB-type, ^{3}J(H,H) = 6.7 Hz, 4H; CH_2), 3.78 (m, 2H; CH_2), 3.14 (s, 1H; OH), 1.64 (quintet, ^{3}J(H,H) = 7.1 Hz, 4H; CH_2), 1.38 (sextet, ^{3}J(H,H) = 7.5 Hz, 4H; CH_2), 0.91 (t, ^{3}J(H,H) = 7.4 Hz, 6H; CH_3). ^{13}C-NMR (400 MHz, chloroform-d, 298 K): δ 69.8 (d, ^{3}J(C,P) = 23.4 Hz, 1C; CH_2), 68.1 (d, ^{3}J(C,P) = 24.7 Hz, 2C; CH_2), 62.3 (d, ^{3}J(C,P) = 21.1 Hz, 1C; CH_2), 32.5 (d, ^{3}J(C,P) = 26.6 Hz, 2C; CH_2), 18.9 (s, 2C; CH_2), 13.8 (s, 3C; CH_3). ^{31}P{H}-NMR (400 MHz, chloroform-d, 298 K): δ 0.1 (s, 1P). IR ν (cm^{-1}): 3406 (O-H, s), 2960-2875 (C-H, CH_3, s), 1463-1382 (C-H, CH_2, m), 1252 ($(C\text{-}O)_3P{=}O$), s), 1018 (P-O-C, s), 909-809 (C-C-O, m). HR-MS (70 eV, ESI) calculated for $[C_{10}H_{23}O_5P + H]^+$ 255.1361, found: 255.1350; calculated for $[C_{10}H_{23}O_5P + Na]^+$ 277.1181, found: 277.1221. *m/z*: 143 $[HOC_2H_4PO_4H_2{+}H]^+$, 199 $[HOC_2H_4PO_4HC_4H_9{+}H]^+$.

3.6.2 Testing the Target Compound with regard to functionality and hazard-related properties

To get a first indication about the functionality of the designed and synthesized alternative compound as a flame retardant, a TGA was performed. CALUX (Chemically Activated LUciferase eXpression) assays were performed by the company Bio Detection Systems (BDS) at Amsterdam Science Park to test for agonistic and antagonistic properties on hormone systems. Biodegradation was tested according to the OECD 301F test (OECD, 1992), performed by the company Ibacon GmbH (Rossdorf, Germany). Detailed description of the methods and results are presented in the SI.

Acknowledgements

We thank Bas de Jong for his input for the synthesis of the target compound and Eric Schuler for performing TGA analyses. We thank John Parsons for discussions on the biodegradability tests. This work is part of the Innovative Training Network ECORISK2050 and was supported by the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No [813124], as well as a CE-RUR-08-2018-2019-2020 grant LEX4BIO (grant agreement no. 818309).

3.7 Supplementary information

The supplementary data sheets to this chapter are available via the online publication (van Dijk et al., 2022).

3.7.1 Methods

3.7.1.1 Selection and applicability of QSAR models

In this study, the potential persistency (P), bioaccumulation (B), mobility (M) and toxicity (T) of structures were assessed. These parameters were selected as they are used to identify problematic substances under REACH (Regulation (EC) No. 1907/2006). For the selection of QSAR models, only models were considered that are freely available, able to be used for large sets of structures and that are currently included in Appendix 1 of the Practical Guide - How to use and report (Q)SARs (ECHA, 2016a).

The applicability domain of a (Q)SAR model is the response and chemical structure space in which the model makes predictions with a given reliability, and therefore defined by the nature of the chemicals in the training set (Gramatica et al., 2012; Netzeva et al., 2005). In Table S3-1 the structural and physicochemical parameters used to define the QSAR applicability domains according to the OECD Guidance Document (OECD, 2007) are shown. This guidance is also in accordance with the recommended way of setting the applicability domain as described in the EPISUITE manuals (US EPA, 2012). Models included in VEGA for the prediction of persistency, carcinogenicity and ecotoxicity were not used because the applicability was evaluated to be unsatisfactory. While LogKow and molecular weight (MW) ranges are met for most of these models, the training sets only contain few organophosphates or none in the case of the QSARs for persistency. For carcinogenicity and ecotoxicity models, only few organophosphates were found of which many contained halogens and aromatic side groups, which are mechanistically relevant for these rather complex toxicity endpoints and could lead to a misclassification of organophosphates. Ecotoxicity QSAR Ecosar which is included in EPISUITE does not facilitate the high-throughput prediction of *in silico* generated structures needed for our approach. Thus, persistency was evaluated based on LogKow and biodegradability and toxicity based on mutagenicity and endocrine disruption.

3.7.2 Testing of target compound

3.7.2.1 LC-MS

The LC-MS spectrum of the target compound was measured with an ultrahigh-performance LC system (Nexera Shimadzu, Den Bosch, The Netherlands) coupled to a maXis 4G high resolution quadrupole time-of-flight HRMS (q-ToF/HRMS) with an added HD collision cell (N_2) and an electrospray ionization (ESI) source (Bruker Daltonics, Wormer, The Netherlands). The used chromatography column was a polar reversed-phase core–shell Kinetex biphenyl LC column having 1.7 μm particle size, pore size of 100 Å and dimensions of 150 × 2.1 mm (Phenomenex, Utrecht, The Netherlands). The column was heated at 40 °C. For the mobile phase, pure H_2O (A) and MeOH acidified with 0.05% acetic acid (B) were used at a flow rate of 0.3 mL/min. The LC

Table S3-1. Log Kow and MW range and number of organophosphate structures, number of P containing structures and total number of structures in the training /validation datasets of the used QSAR models.

Attribute	Endpoint kind	Model	Log Kow range (KOWWIN) (exp)	MW range [g mol-1]	n of Organophosphates	n of P containing structures	Total n of structures
P	Biodegradability Mix of expert judgement and experiments	EpiSuite: BIOWIN, Aerobic: Biowin1-6, anaerobic: Biowin7	-4.2 - 8.65	30 - 959	20	45	1263
	Log Kow Experiments	EpiSuite: KOWWIN	-11.96 - 10.2	4 - 1203	66	362	15809
B	BCF Factor/ experiment	EpiSuite BCFBAF	-4.5 - 8.6	68 - 992	21	60	685
M	Log Koc Experiments	VEGA: OPERA KOC	-5.4 - 8.68	32 - 665	9	68	729
		EpiSuite: KOCWIN	-5.4 - 8.68	32 - 1053	13	74	788
T	Mutagenicity	VEGA: Mutagenicity consensus model - CAESAR	-4.22 - 8.65	30 - 3080	42	102	4204
	Experiment (Ames test)	VEGA: Mutagenicity consensus model - ISS	-3.7 - 7.6	30 -1255	8	29	670
		VEGA: Mutagenicity consensus model - KNN	-5.4 - 8.65	28 -1550	42	117	5770
		VEGA: Mutagenicity consensus model - SARPY	-4.22 - 8.65	30 - 3080	42	102	4204

Attribute	Endpoint kind	Model	Log Kow range (KOWWIN) (exp)	MW range [g mol-1]	n of Organophosphates	n of P containing structures	Total n of structures
	Endocrine disruption Expert judgement / experiments	VEGA: Androgen Compara	-3.7 - 8.65	42 - 1701	22	73	1664
		VEGA: Estrogen Cerapp	-3.7 - 8.1	42 - 973	22	64	1529
		VEGA: TRALPHA NRMEA	-5.08 - 9.05	31 - 1638	59	188	5462
		VEGA: TRBETA NRMEA	-5.08 - 9.05	31 - 1638	59	188	5487
			Log Kow range (KOWWIN) (exp)	MW range [g mol-1]	n of Organophosphates	n of P containing structures	Total n of structures
	Database of generated structures		-6.26 – 6.27 (predicted values)	180 - 336	all	all	32350

gradient program was 0% B, 100% A from 0 to 2 min and reached 100% B and 0% A at 17 min. From 17 to 25 min the eluent was kept at 100% B. 20 μL of the sample solution with a concentration of target I of 500 μg L^{-1} in 95% water and 5 % methanol (volume) were injected. The autosampler had a temperature of 15 °C. The MS detector with ESI source was internally calibrated prior to the start of the analysis by infusing a 50 μM sodium acetate solution in H2O:MeOH (1:1, volume) with a loop injection of 20 μL and a loop rinse of 20 μL. A spray voltage of +3.5 kV was used for the positive ESI mode with a resolving power of 30,000–60,000 at full width at half maximum (FWHM). Nitrogen was used as curtain gas to lose neutral compounds. The capillary temperature was 300 °C. MS/MS spectra were recorded in data-dependent acquisition mode with a minimum resolving power of 20,000 at FWHM.

3.7.2.2 CALUX assays

CALUX® assays were performed by BioDetection Systems (BDS), Amsterdam, the Netherlands in order to identify hormone-like properties. The assays were performed according to a similar protocol earlier described by Besselink et al. (2004), to identify both agonistic and antagonistic effects on the estrogen receptor (ER alpha), androgen receptor (AR), progesterone receptor (PR) and thyroid receptor (TR beta). Firstly, cytotoxic effects of TiBP and the target compound on BDS cell line were tested in order to determine suitable concentration for the receptor assays.

For the CALUX assays, cells were cultured in 384 well plates. Subsequently, the cells were exposed to a dilution series of TiBP and the Target Compound. The test was performed in triplicate. Cells were also exposed to a concentration series of a reference compound. After exposure, light production in the wells were quantified. The activity evoked by the TiBP and the Target Compound were derived by interpolation in the response curve of the reference compound.

Additionally, Nrf2, P53, P53 + S9 CALUX assays were performed to elucidate potential genotoxic and/or cytotoxic effects.

3.7.2.3Ready biodegradability tests

The ready biodegradability of the compounds was investigated in a manometric respirometry test (OECD301F) over a period of 28 days (OECD, 1992). The biodegradation was followed by the oxygen uptake of the microorganisms during exposure. As a reference item sodium benzoate was tested simultaneously under the same conditions as the test item, and functioned as a procedure control. Aerobic activated sludge (microorganisms from a domestic wastewater treatment plant) was supplied by the sewage treatment plant of Rossdorf, Germany. Degradation rate of compounds was calculated by the oxygen consumption of the aerobic activated sludge microorganisms after 28 days of incubation. The testing was conducted at 22°C ± 1°C (darkness) according to GLP standards by Ibacon GmHb (Rossdorf, Germany).

3.7.2.4 TGA

To get a first indication about the functionality of the designed and synthesized alternative compound as a flame retardant, thermogravimetric analysis (TGA) was performed (Markwart et al., 2019). The thermogravimetric analysis of TiBP and di-*n*-butyl (2-hydroxyethyl) phosphate (target I) were performed with a Mettler-Toledo TGA/DSC 3+ instrument with autosampler. Ca. 10 mg sample was transferred into a 100 µL aluminum crucible using a micropipette. The lid was pierced with a needle and then used to seal the crucible. The temperature was increased from 25 °C to 600 °C at a rate of 10 K min^{-1}. Both compounds were analyzed in air and in a nitrogen atmosphere at a gas flow of 40 mL min^{-1}. Measurements were performed in duplicate.

3.7.3 Results

3.7.3.1 Top 25 of the PBMTS MAUT analysis

Desirability functions were designed to calculate subscores for LogKoc and LogKow, indicating optimal ranges for the values based on reported criteria, as both very high and very low values are not desirable. The desirability functions for the PBMTS MAUT analysis are shown in Figure S3-1, together with distributions (kernel density) of each endpoint used in the MAUT analysis, both for the whole dataset and for the top 500 structures. The scoring of the selected target structure is visualized by the blue line. It must be noted that the distribution of the anaerobic biodegradability sub score moved to lower values in the set of structures ranked under the top 500 structures compared to the total dataset. For aerobic biodegradability and non-mutagenicity sub scores, the kernel density estimate curve of the top 500 structures shifted to higher scores. Also, the distribution of the LogKow and LogKoc shifted to a more desirable range, as defined by the desirability functions, indicating the effectiveness of the PBMTS scoring approach.

Figure S3-2 shows the top 25 ranked structures from the PBMTS MAUT analysis and their scores are shown. The highest ranked structure has a score of 0.7103. The final selected target structure ranks 22nd and has a score of 0.6673.

3.7.3.2 CALUX assays

As a first step, cytotoxic effects of TiBP and the target compound were tested to determine appropriate concentrations for the CALUX assays to ensure observed effects are not caused by the compound's cytotoxicity (Figure S3-3).

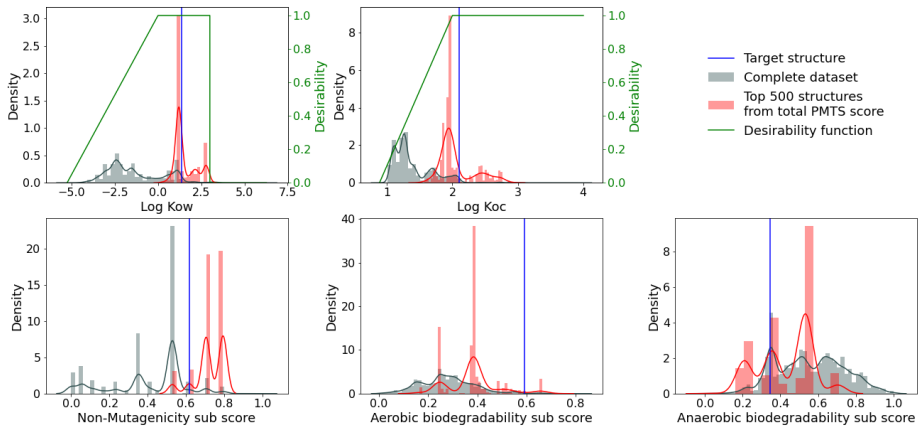


Figure S3-1. Histograms and corresponding kernel density estimates showing the distribution of properties in the complete dataset and the top 500 structures ranked according to the PBMTS score. Desirability functions are plotted in green, values corresponding to the selected target structure are marked with blue vertical lines.

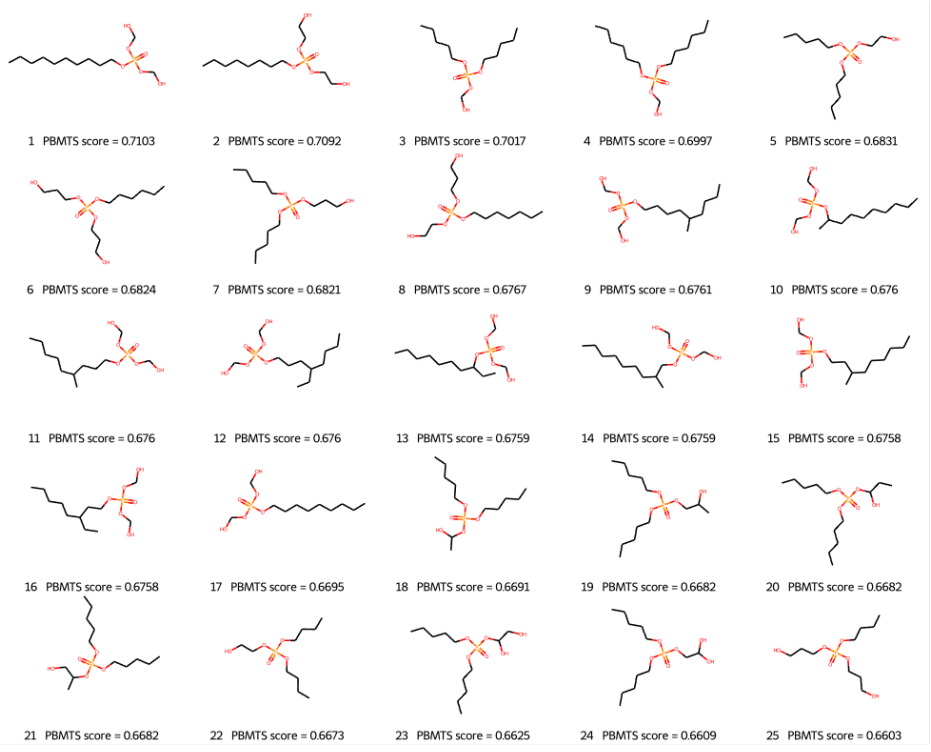


Figure S3-2. The top 25 ranked structures. The final selected target to TiBP was ranked on the 22nd place with a PBMTS score of 0.6673.

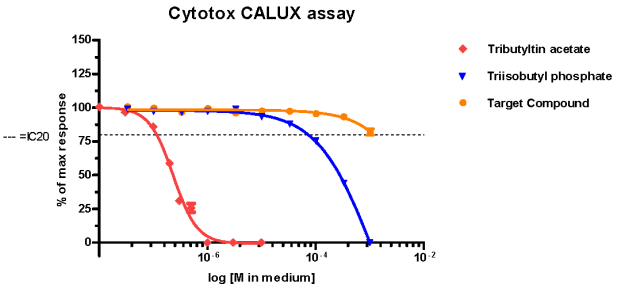
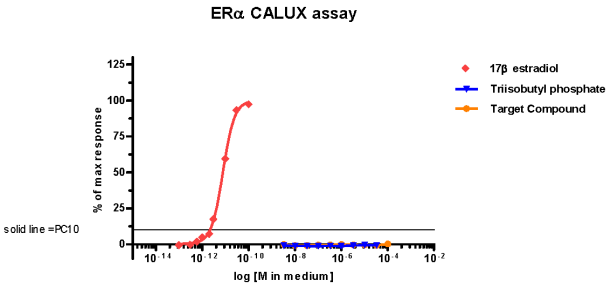
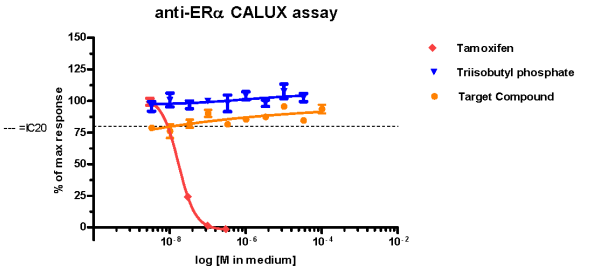
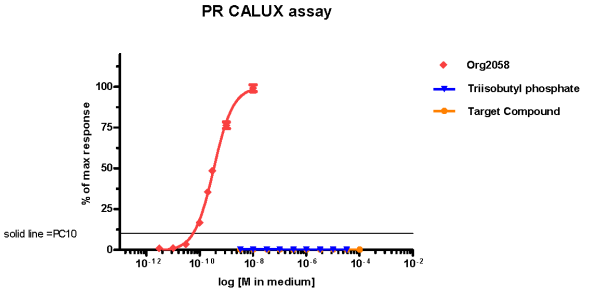
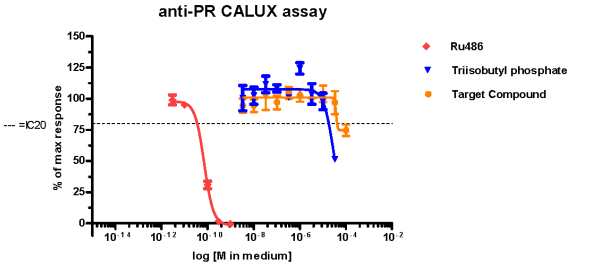


Figure S3-3. Cytotoxic effects of TiBP, the Target Compound and the positive control (Tributyltine acetate).

Table S3-2 shows the results of the CALUX assays used to identify hormone-like properties. For every test a positive control was used (shown in red) to verify the test. Both the TiBP and the target compound seem to have a slight antagonistic effect on the androgen and progesterone receptors in the highest concentrations tested (8.93 mg/L TiBP and 19.6 mg/L target compound). It will however be very unlikely that such high concentrations will be reached inside organisms in real-life, as the highest reported concentration of TiBP detected in organisms is $7.4*10^{-3}$ mg/kg ww (Brandsma et al., 2015). Moreover, both TiBP and the target compound were not found to be genotoxic in the CALUX assays (Table S3-3).

Table S3-2. CALUX results for the identification of potential hormone-like properties.

Receptor	Agonistic effects	Antagonistic effects
Estrogen		
Progesterone		

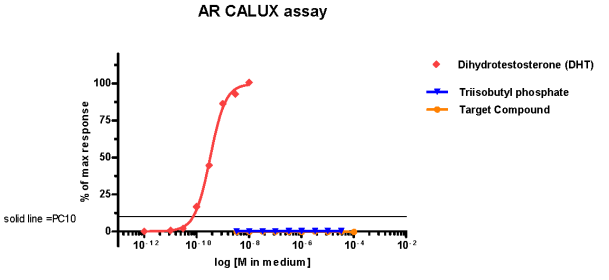
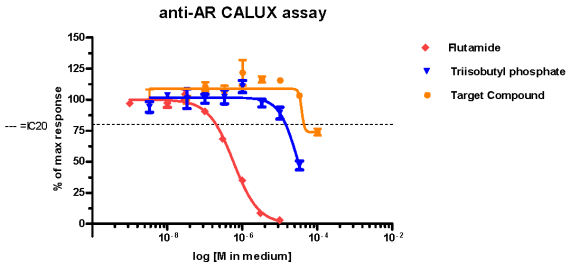
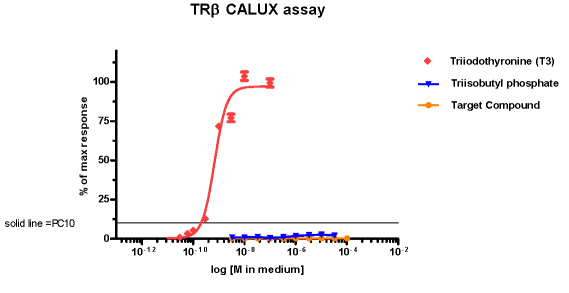
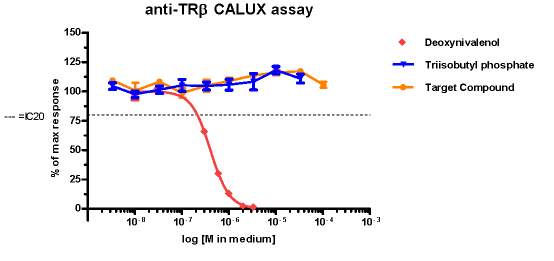
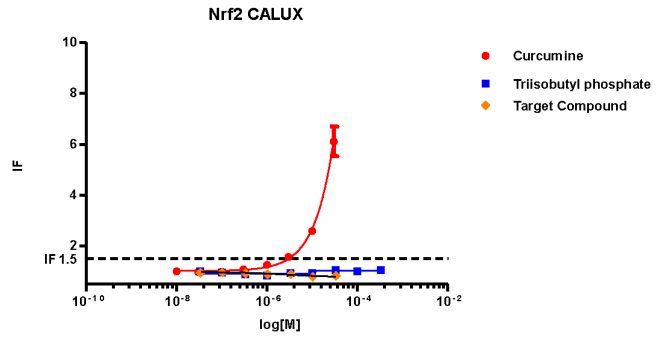
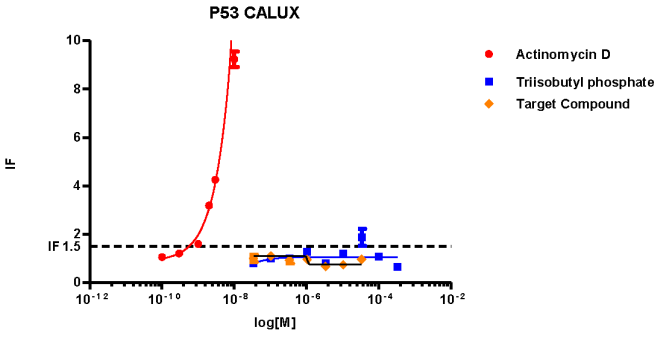
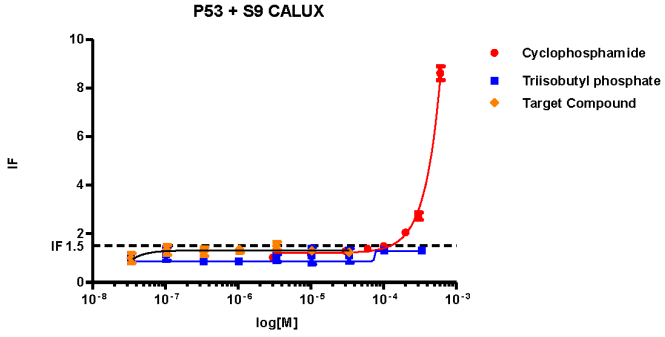
Receptor	Agonistic effects	Antagonistic effects
Androgen		
Thyroid		

Table S3-3. Results from the CALUX assays to identify potential genotoxic properties.

Endpoint	Results
	
	
	

3.7.3.3 Ready biodegradability tests

Results from the OECD301F test are presented in Figure S3-4 (TiBP) and S3-5 (target compound). A mean biodegradation of 10% or more of TiBP was reached at day 15 (mean degradation of 14.5%) and for the target compound at day 18 (the mean degradation of 12%). At the end of the 10-day window at day 28, the mean degradation of TiBP was 41.5% and of the target compound was 27.5%. Therefore, for both substances the 10 day window criterion was not passed. The degradation rate of TiBP and the target compound also did not reach 60% within the 10-day window or after 28 days. Therefore, both TiBP and the target compound are considered to be not readily biodegradable according to the OECD301F test.

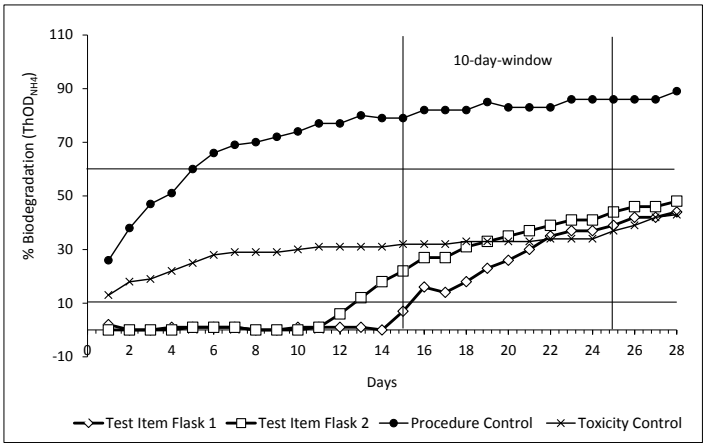


Figure S3-4. Biodegradation during the Exposure Period of 28 days of TiBP (Flask 1 and 2), of the Toxicity Control and of the Reference Item Sodium Benzoate (Procedure Control) related to ThODNH4.

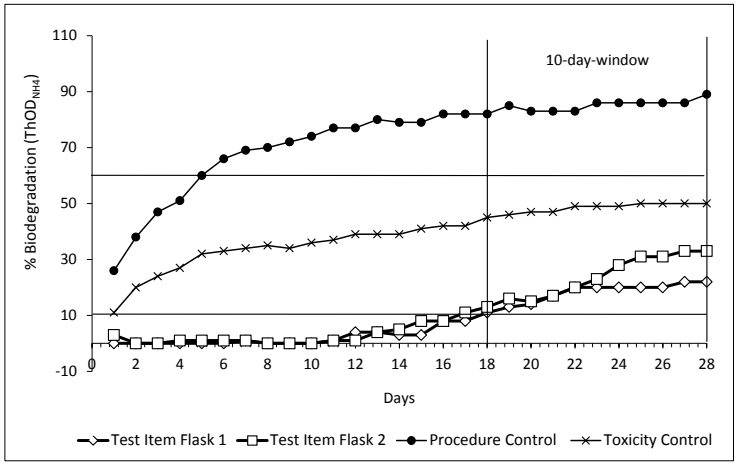


Figure S3-5. Biodegradation during the Exposure Period of 28 days of the Target Compound (Flask 1 and 2), of the Toxicity Control and of the Reference Item Sodium Benzoate (Procedure Control) related to ThODNH4.

3.7.3.4 TGA

The TGA monitors the weight loss as a function of temperature and the remaining char yield, which hints at condensed phase activity for flame retardancy. The char yield was 7% and 20% for TiBP and the target compound, respectively (Figure S3-6).

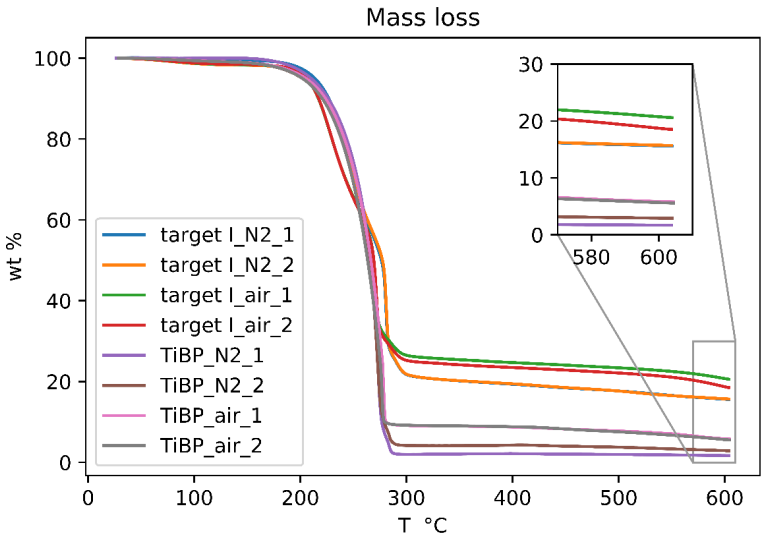


Figure S3-6. Results of the thermogravimetric analysis of the selected target compound and the original compound TiBP show a higher char yield (residue as weight percent after heating, see inset) of the target compound, both in air and in nitrogen atmosphere.

CHAPTER FOUR

REGISTRATION AND MARKET ENTRY | TOWARDS 'ONE SUBSTANCE – ONE ASSESSMENT': AN ANALYSIS OF EU CHEMICAL REGISTRATION AND AQUATIC RISK ASSESSMENT FRAMEWORKS

Chapter 4 - Registration and Market Entry | 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.

Abbreviations

AF	Assessment Factor	WSSD	World Summit on Sustainable Development
OS-OA	One Substance – One Assessment	EC	European Commission
ERA	Environmental Risk Assessment	REACH	Registration, Evaluation and Authorisation of Chemicals
RA	Risk Assessment	MS	Member State
ECHA	European Chemicals Agency	E-PRTR	European Pollutant Release and Transfer Register
EFSA	European Food Safety Authority	CLP	Classification, Labelling and Packaging
EMA	European Food Safety Authority	SVHC	Substance of Very High Concern
PEC	Predicted Environmental Concentration	CfS	Candidate for Substitution
PNEC	Predicted No-Effect Concentration	PBT/vPvB	Persistent, Bioaccumulative, Toxic/very Persistent, very Bioaccumulative
7EAP	7th Environment Action Programme	PMT/vPvM	Persistent, Mobile, Toxic/very Persistent, very Mobile

4.1 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; UNEP, 2019a). 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 1907/2006, Reg (EC) No 1107/2009, Directive 2001/83/EC and Directive 2001/82/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 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., n.d.). Currently, more than 50% of EU water bodies are in poor ecological condition (EEA, 2018a; Posthuma et al., 2019b) 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 Commission, 2016c) 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 (7EAP) 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 7EAP 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 7EAP 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, n.d.), 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 (EU, 2012); (ii) Industrial chemicals (REACH, (EU, 2006a)); (iii) Pesticides (EU, 2009); (iv) Medicines for human use (EU, 2001a); (v) Veterinary medicines (EU, 2001b). 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., 2020a).

4.2 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 4.1). 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.

4.2.1 Exemptions from EU registration

Table 4. 1. Overview of registration criteria and ERAs within different frameworks.

Substance group	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 autumn/ winter 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]

Substance group	Pharmaceuticals	Veterinary pharmaceuticals	Pesticides	Biocides	Industrial chemicals
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 31 December 2023 for registrations in tonnage bands of 100 tonnes or more per year and by 31 December 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 ug/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 ug/L water or <100 ug/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*

All active substances of biocides and pesticides are registered at EU level, but under other frameworks some exemptions for EU-wide registration exist (Table 4.1). 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 (EMA, 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 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., 2019b; 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; S. 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 (EU, 2008), but the safety of the whole mixture often remains unknown. Whole pesticidal and biocidal products are assessed and authorized 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.

4.2.2 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 4.1). Although improvements have been made and the minimum percentage of dossiers to be checked under REACH was recently increased from 5 to 20% (EU, 2020), few chemicals are re-evaluated once they are registered or authorized. 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, 2016b; 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 4.2). 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 4.2

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 biocides and 7 of the banned pesticides were approved under more than one additional framework.

Table 4.2. 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%)

4.3 Risk Assessment for the freshwater environment

RAs 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 4.1). 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.

4.3.1 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 4.1). 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 et al., 2013).

4.3.2 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 et al., 2019; Schäfer et al., 2019).

By comparing all PNECs for industrial chemicals, biocides and pesticides, and PNECs derived for human medicines (see supplementary information) 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 (Figure 4.1, Table 4.3). 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 (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 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 (Figure 4.2). 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 to 5625, with a median difference of 3.6 (Figure 4.3). 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.

Table 4. 3. Summary statistics for the four different regulatory frameworks for which freshwater PNECs were obtained. Further details are provided in the supplementary information.

	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	0	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

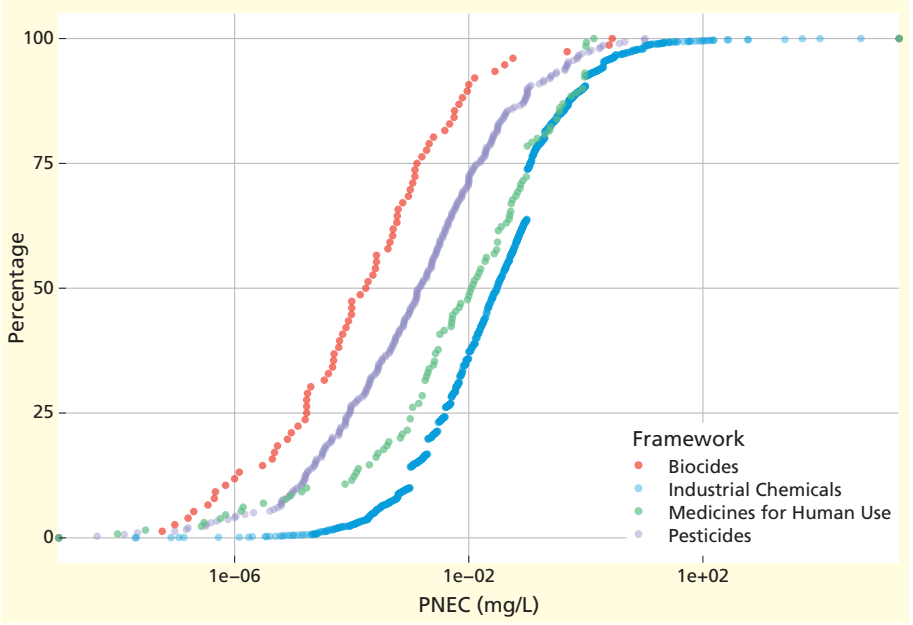

Figure 4.1. Cumulative distribution of PNECs for biocides, industrial chemicals and pesticides as reported in registration dossiers. PNECs from biocides and pesticides dossiers were obtained from Gustavsson et al. (2017), PNECs for medicines for human use were derived from data collected by Gunnarsson et al. (2019). PNECs for industrial chemicals are available online (van Dijk et al., 2020a).

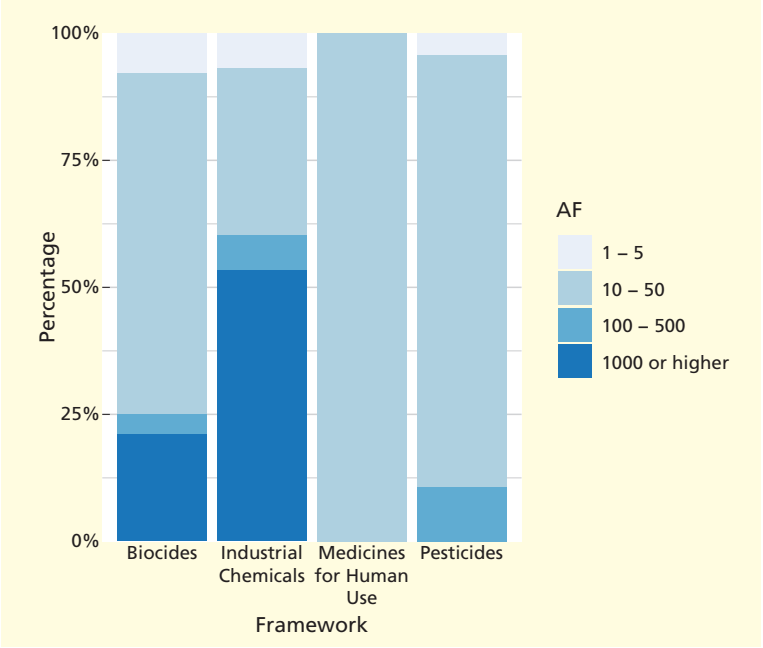

Figure 4.2. AFs used for freshwater PNEC derivations in current regulatory risk assessments.

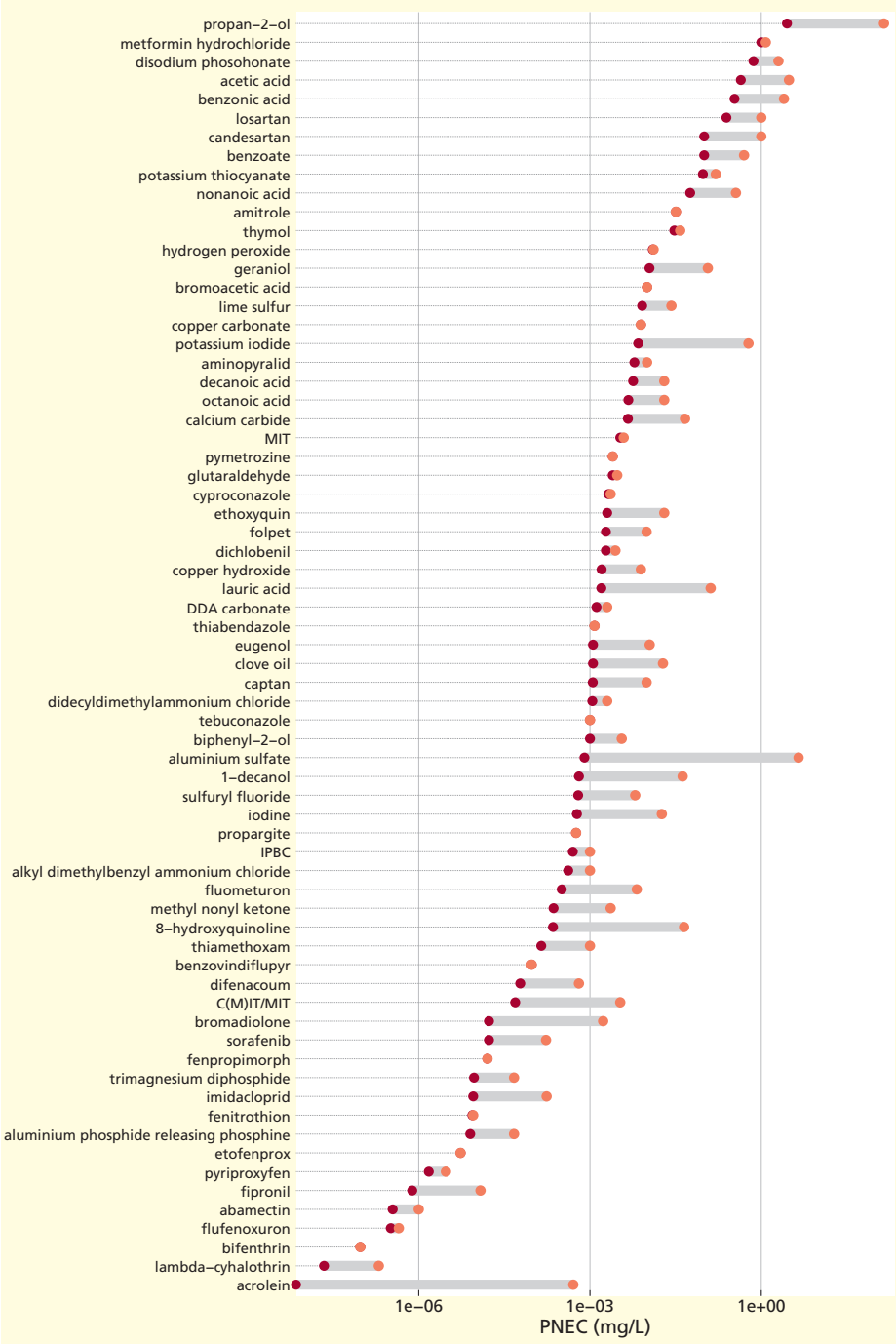

Figure 4.3. Differences between PNEC values for chemicals registered under 2 or more frameworks. The dark red points show the minimum and the orange points the maximum reported PNEC value.

4.3.3 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 4.2.

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, (EU, 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 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).

4.4 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.

4.4.1 Current classification criteria

Currently, SVHCs and CfSs are identified according to the CLP classification (EU, 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. Harmonised 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 4.1). Hence appropriate mitigation efforts to prevent medicines from being released to the environment are often not considered.

4.4.2 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 assessed (Arp and Hale, 2019). Cousins et al. (2019b) 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 exist 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.

4.4.3 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).

4.5 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, (EU, 2000). 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 harmonise 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 (European Commission, n.d.). 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., 2019a) 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.

4.6 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 harmonised, 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 to 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.

Data availability

Supplementary data to this article are available from the open data repository (van Dijk et al., 2020a): https://data.mendeley.com/datasets/9vmwsvsz94

Acknowledgements

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4.7 Supplementary Information: Data generation and processing

4.7.1 CAS numbers and lists of EU registered chemicals

EU-wide databases were used to compile lists of chemicals registered under the EU registration frameworks for medicines for human use (European Commission, n.d.), veterinary medicines (European Commission, n.d.), pesticides (European Commission, n.d.), biocides (ECHA, n.d.)and industrial chemicals . Orphan drugs were excluded from the medicines lists, as well as substances exempted from environmental risk assessments. For industrial chemicals, intermediate substances were excluded as these substances are consumed in or used for chemical processing in order to be transformed into another substance (Article 3(15)(EU, 2006a)). Confidential substances were also excluded from the list as for these substances it is impossible to know if they are on the market.

All data processing was performed using R(Rstudio Team, 2020). CAS numbers for medicines for human use, veterinary medicines and pesticides were initially obtained using the R package webchem (R v1.0.0)(Szöcs et al., 2020) with missing CAS numbers manually added from the drugbank and PubChem databases (NCBI, n.d.; Wishart et al., 2017) (Figure S4-1).

4.7.2 PNEC data

Data from Gustavsson et al. (2017) was used to obtain PNEC values as reported in EU registration dossiers for biocides and pesticides(Gustavsson et al., 2017). PNEC values for medicines for human use were calculated based on data from(Gunnarsson et al., 2019) by selecting medicines

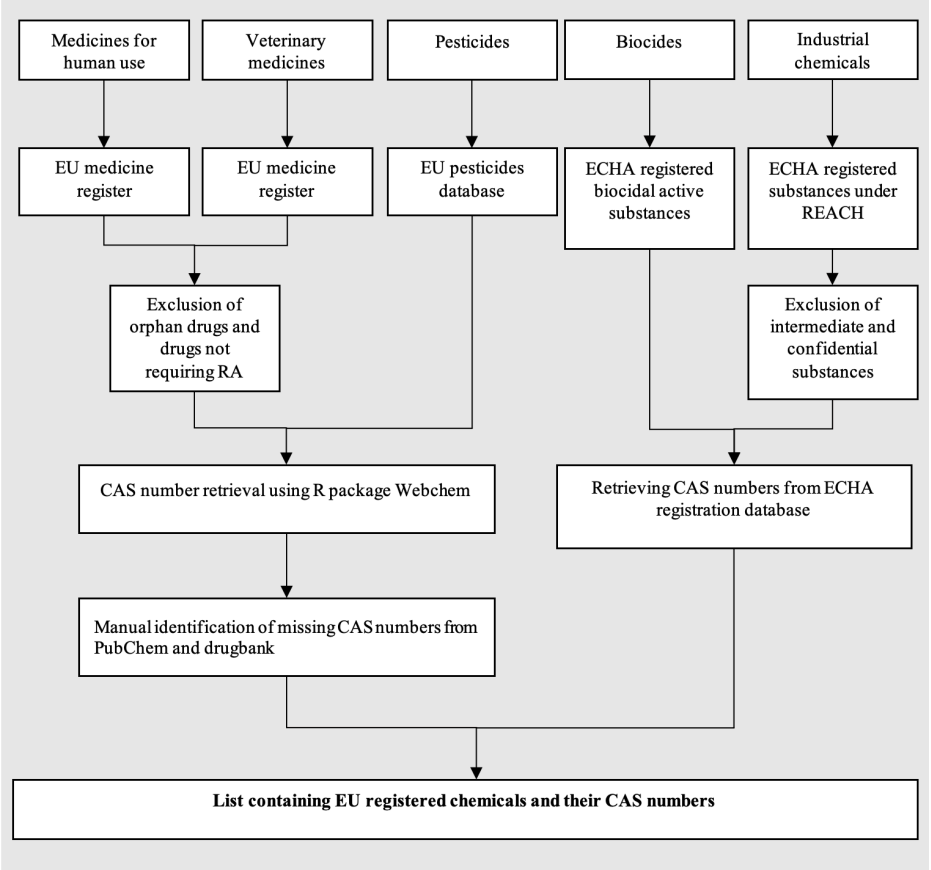

Figure S4-1. Workflow for the generation of a list containing EU registered chemicals and their CAS numbers.

with a complete dataset (i.e. containing a chronic study endpoint for algae, daphnids and fish) and application of an AF of 10 on the lowest available endpoint.

PNECs for industrial chemicals were extracted from the ECHA Database (ECHA, n.d.). The following information was retrieved from this database in April 2020: Substance name, CAS-number, molecular weight, information on production tonnage class, PNEC data for the freshwater environment, and the AF used to determine the PNEC. Distributions of the PNECs and AFs used under every framework were visualized by using R and the R package tidyverse (R v1.3.0) (Wickham et al., 2019). For veterinary medicines no PNEC data was available. Hence, substances registered under Directive 2001/82/EC were excluded in the analyses.

4.7.3 Statistics

4.7.3.1 Analysis

Statistical analyses were performed using SPSS Statistics 25 software (IBM Corp, 2017) to identify statistical difference between PNECs of substances under every framework. Normality of data was tested using Kolmogorov-Smirnov and Shapiro-Wilk tests. PNECs from industrial chemicals and medicines for human use did not follow a (log)normal distribution, hence a non-parametric test was used to show statistical difference between PNEC values reported under the registration frameworks.

4.7.3.2 Results

The null-hypothesis was rejected as a Kruskal-Wallis H test showed that there was a statistically significant difference in PNECs of the different frameworks, $\chi 2(2) = 266{,}837$, $p = 0.000$, with a mean PNEC rank of 1105,16 for biocides, 3277,41 for industrial chemicals, 1883,22 for pesticides and 2859,90 for medicines for human use. Except for Industrial Chemicals compared to Medicines for Human Use (p=0,061), PNECs under the different frameworks are statistically different from each other (p<0,05).

Table S4-1. Kruskal-Wallis H results. Significant values have been adjusted by the Bonferroni correction for multiple tests. *indicates a statistical significant difference between PNEC values of two registration frameworks (p<0,05).

	Kruskal-Wallis H		**Kruskal-Wallis H post-hoc Adjusted Significance**			
	N	**Mean rank**	**Biocides**	**Industrial Chemicals**	**Pesticides**	**Medicines for Human Use**
Biocides	76	1105,16	-	0,000*	0,006*	0,000*
Industrial Chemicals	5850	3277,41	0,000*	-		0,061
Pesticides	298	1883,22	0,006*	0,000*	-	0,000*
Medicines for Human Use	130	2859	0,000*	0,061	0,000*	-

Complete lists of chemicals and their CAS numbers, overlap between EU registration frameworks and freshwater PNECs are available on Mendeley Data .

CHAPTER FIVE

USE STAGE | MANAGING PMT/VPVM SUBSTANCES IN CONSUMER PRODUCTS THROUGH THE CONCEPTS OF ESSENTIAL-USE AND FUNCTIONAL SUBSTITUTION: A CASE-STUDY FOR COSMETICS

Chapter 5 - Use Stage | Managing PMT/vPvM Substances in Consumer Products through the Concepts of Essential-use and Functional Substitution: a Case-Study for Cosmetics

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Abstract

Measures are needed to protect water sources from substances that are mobile, persistent and toxic (PMT) or very persistent and very mobile (vPvM). PMT/vPvM substances are used in a diverse range of applications, including consumer products. The combined application of the essential-use and functional substitution concepts has been proposed to phase out substances of concern and support the transition to safer and more sustainable chemicals, a key goal of the European Commission's Chemicals Strategy for Sustainability. Here, we first identified the market share of PMT/vPvM containing cosmetic products. We found that 6.4% of cosmetic products available on the European market contain PMT or vPvM substances. PMT/vPvM substances were most often found in hair care products. Based on their high occurrence, the substances Allura red (CAS 25956-17-6), Benzophenone-4 (CAS 4065-45-6) and Climbazole (CAS 38083-17-9) were selected as case-studies for assessment of their functionality, availability of safer alternatives and essentiality. Following the functional substitution framework, we found that the technical function of Allura red was not necessary for the performance of some cosmetic products, making the use non-essential. For other applications of Allura red, as well as all applications of Benzophenone-4 and Climbazole, the technical function of the chemical was considered necessary for the performance. Via the alternatives assessment procedure, which used experimental and *in silico* data and three different multicriteria decision analysis (MCDA) strategies, safer alternatives were identified for all case-study chemicals. All assessed uses of PMT/vPvM substances were thus deemed non-essential and should consequently be phased out.

Abbreviations

CAS	Chemical Abstracts Service	MCDA	MultiCriteria Decision Analysis
C&L	Classification and Labelling	PBT/vPvB	Persistent, Bioaccumulative, Toxic/very Persistent, very Bioaccumulative
CPR	Cosmetic Product Regulation	PMT/vPvM	Persistent, Bioaccumulative, Toxic/very Persistent, very Bioaccumulative
CSS	Chemicals Strategy for Sustainability	QSAR	Quantitative Structure-Activity Relationship
ECHA	European Chemicals Agengy	REACH	Registration, Evaluation and Authorisation of Chemicals
MAUT	Multi-Attribute Utility Theory	SVHC	Substances of Very High Concern

5.1 Introduction

Synthetic chemicals are present in approximately 95% of all manufactured goods and are considered as indispensable for modern societies (Oxford Economics, 2019). Over 350,000 chemicals and mixtures are reportedly registered for usage and production globally (Wang et al., 2020). Chemical production, use and disposal result, however, in pollution of the environment, affecting both human and environmental health (Naidu et al., 2021; Posthuma et al., 2020). Furthermore, pollution, including from chemicals, has been identified as one out of five main drivers for global biodiversity loss (IPBES, 2019). Chemical pollution (now known as "novel identities") is also one of the planetary boundaries which humanity has already crossed (Persson et al., 2022; Steffen et al., 2015).

Driven by safety concerns, regulations are in place world-wide in order to reduce the risks associated with the use of chemicals. In the EU, the main chemical legislation REACH (Reg. No. 1907/2006 EC) should '*ensure a high level of protection of human health and the environment as well as the free movement of substances... while enhancing competitiveness and innovation*'. REACH should also promote the development of alternative methods for the assessment of hazards of substances. Under REACH, substances that are persistent, bioaccumulative and toxic (PBT) and substances that are very persistent and very bioaccumulative (vPvB) are identified as substances of very high concern (SVHC), resulting in a limit or ban of their production and consumption. Current SVHC classification criteria, however, do not capture all potentially hazardous substances, including substances that negatively impact water resources. The so-called mobile substances are readily transported in water, soil layers, river banks, aquifers, or , pass through natural or artificial barriers (e.g. in wastewater treatment plants). When combined with persistence, these mobile substances accumulate in the aquatic environment and drinking water sources (Hale et al., 2020; Rüdel et al., 2020; Schulze et al., 2019). Mobility (M) has therefore been proposed as an additional hazard criterion to identify SVHCs, as substances that are mobile, persistent and toxic (PMT) or very persistent and very mobile (vPvM) (European Commission, 2020d, 2022a).

PMT/vPvM substances are currently used in a diverse range of applications, including in cosmetic products (Schulze et al., 2019). An estimated 2320 thousand tonnes of cosmetic products are sold per year in the European Economic Area (Winkens Pütz et al., 2021). Furthermore, it has been reported that cosmetic products contain a large number of chemicals with potential hazardous properties (Bilal et al., 2020). Environmental risks are currently not taken into account for market approval of cosmetics under the Cosmetic Products Regulation (CPR, Regulation (EC) No 1223/2009) (Kättström et al., 2022), despite the use of cosmetic products contributing to the occurrence of chemicals in the environment (Winkens Pütz et al., 2021). Several improvements are expected, however, in light of the European Green Deal's Chemicals Strategy for Sustainability (CSS) (European Commission, 2020d). As part of the CSS, a new legislative proposal to amend

the CPR will be presented. This will include an aim to minimise and substitute the use of chemicals that have a chronic effect on human health and the environment, and incorporation of the essential-use concept in order to phase out the most hazardous chemicals (European Commission, 2021).

The essential-use concept was first introduced in 1987 as part of the Montreal Protocol to phase-out ozone-depleting chlorofluorocarbons. Under the Montreal Protocol, a use of a substance is considered essential if: "(1) it is necessary for the health, safety or is critical for the functioning of society; and (2) there no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of environment and health". More recently, the essential-use concept was proposed as a tool to guide the phase-out of PFAS(Cousins et al., 2021, 2019a). Following this approach, uses of PFAS can be classified into three different categories: 1) Essential and non-substitutable, 2) Essential but substitutable by safer chemicals and 3) Non-essential; and only the uses that would be judged as being essential and non-substitutable should be authorised (Cousins et al., 2021, 2019a).

Essentiality assessments have been proposed to focus on the technical function provided by a chemical for a specific use. Hence, it was recently suggested to combine the essential-use concept with the functional substitution approach (Cousins et al., 2021; Roy et al., 2022). The identification of non-essential uses is key to prevent the continued use of hazardous substances. In order to identify uses that are substitutable, the implementation of the essential-use concept requires a sufficient understanding of the current uses of substances, but also of the availability, suitability, and hazardous properties of alternatives (Cousins et al., 2021; Glüge et al., 2021). Identifying alternative non-hazardous chemicals that are functional and affordable is key to prevent regrettable substitution of chemicals (Jacobs et al., 2016; Sackmann et al., 2018).

First described by Tickner et al. (2015), functional substitution aims to evaluate whether the function of a chemical is necessary for the application, and then examines through alternatives assessment whether safer and effective chemicals, product/process design, or product service alternatives exist to provide similar function. By combing the essential-use and functional substitution concepts, and thus focussing on both the essentiality, function and performance of substances of concern, a solution-oriented approach is obtained that can help to effectively support the transition to safer and more sustainable chemicals (Roy et al., 2022).

The aim of this study is to explore the potential of the combined application of the essential-use and functional substitution concepts to facilitate the phase-out PMT/vPvM substances in cosmetic products. First, the market share of PMT/vPvM-containing cosmetic products is identified through database searches. Then, the most frequently occurring substances are selected as case-study chemicals for which an assessment is performed per use case by 1) assessing the functional use of these chemicals, 2) identifying suitable and safer alternatives through the process of alternatives assessment and 3) considering whether the use of the chemical is necessary for health, safety or critical for the functioning of society, in case no suitable and safer chemical alternatives are available.

5.2 Methods

An overview of the method used to determine the essentiality of specific potential PMT/vPvM substances used in cosmetic products is presented in Figure 5.1. An integrated method has been developed based on the concepts of essential-use (Cousins et al., 2019a), function substitution (Tickner et al., 2015) and the decision tree suggested by Roy et al. (2022). The hazard assessment of alternatives was based on ECHA (2021) and OECD (2021). Each step is explained in more detail below.

5.2.1 Identifying PMT/vPvM substances in cosmetic products

The most comprehensive analysis of PMT/vPvM substances registered under REACH has been published by the German Environment Agency in which any substance with a logarithm of the organic carbon-water partition coefficient (log K_{OC}) lower than 4 is classified as being mobile (Arp and Hale, 2019). In total, 211 substances have been identified as potential PMT/vPvM substances. Those substances were compared with entries in the cosmetic ingredient database (CosIng) in order to identify substances which can be used in cosmetic products (European Commission, n.d.). As of November 2021, CosIng had a total of 53,028 entries. These entries contained many substances without CAS numbers. In addition, the list contains substances that are mentioned twice or more, due to their multiple functions. When substances without a CAS number are removed and substances with multiple functions are merged, this results in 10,000 unique CAS numbers.

PMT/vPvM substances listed in the CosIng database were screened in The Danish Consumer Council Think Chemicals (Kemiluppen, screened in November 2021) and Cosmethics (screened in December 2021) databases to identify cosmetic products containing PMT/vPvM substances. Kemiluppen is an initiative under the Danish Consumer Council and contains information on cosmetic products available on the Danish market. A full database search was performed for this study, only leaving out outdated products as these are no longer on the market. Cosmethics is a company that has a data repository of cosmetic products. For our study, 1,000 products registered in Cosmethics in 2021 were randomly selected and analysed for PMT/vPvM substances. Data beyond the publicly available information of these databases were obtained via personal communication with Stine Müller (Kemiluppen) and Katariina Rantanen (Cosmethics). The three highest occurring substances in the datasets were selected as case studies for the assessment of alternatives and for further analysis of essentiality.

5.2.2 Technical function and application of substances

The general technical function(s) provided by the case-study chemicals was derived from the CosIng database. Interviews with Gerald Renner (Cosmetic Europe) and Héloïse Le Levier (IDUN

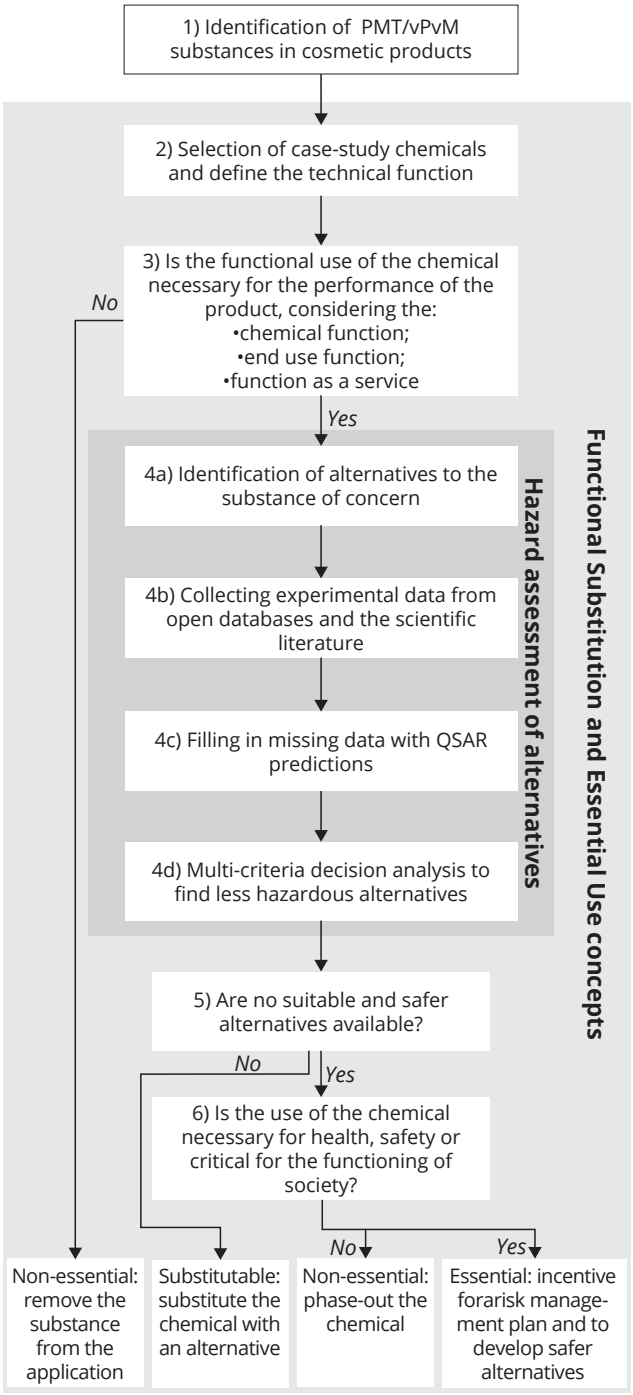

Figure 5.1. Integrated methodology for the identification and assessment of chemical alternatives to PMT/vPvM substances in cosmetics, incorporating aspects from the concepts of functional substitution, essential-use and alternatives assessment (Cousins et al., 2019a; OECD, 2021a; Roy et al., 2022; Tickner et al., 2015).

Minerals) helped to provide a better understanding of the precise technical function provided by the substances of interest and their necessity for the performance in each application.

5.2.3 Investigating the availability of suitable alternatives

A suitable alternative includes any type of alternative (i.e., chemical, material, process and/or product alternative) which is safer for the environment and human health, and technically and economically feasible (ECHA, 2021). To determine whether suitable alternatives to each case-study chemical were available, an alternative assessment based on chemical hazards (PBMT) was performed following the framework described in the ECHA guidance on the preparation for application for authorisation, and the suggestions provided in the OECD guidance on key considerations for the identification and selection of safer chemical alternatives (ECHA, 2021; OECD, 2021a).

5.2.3.1 Identification of potential alternatives

Potential chemical alternatives with a similar technical function to the case-study chemicals were identified via the CosIng database, the cosmetics ingredients database (SpecialChem, n.d.), the list of authorised substances under the CPR and approved food additives, as approved food additives can also be used in cosmetic products (Regulation (EC) No 1333/2008). In addition, literature searches (e.g., reports from industry, industry organisations and suppliers' website) were performed. Only substances with a CAS number were considered in this study.

The potential chemical alternatives were shortlisted in order to filter out substances known (or suspected) to be hazardous. To achieve that goal, the potential alternatives were screened in the SUBSPORT database, which includes 32 lists of substances from industry, authorities and non-governmental organisations (NGOs) that are legally or voluntarily restricted, or are recommended for restriction due to their hazard properties (BAuA, n.d.). All the lists screened in the SUBSPORT database are listed in the supplementary information. Annex III to the CPR (listing restricted substances in cosmetic products) was used as an additional priority list to filter out substances. The ECHA database of registered substances was screened to identify classifications under CLP (Classification, labelling and Packaging) and C&L (Classification and Labelling) notifications for the potential alternatives. Lastly, the REACH Annex III inventory was screened to determine if the potential alternatives are suspected to present CMR (Carcinogenic, Mutagenic or Reprotoxic), PBT and ED (Endocrine Disruption) properties based on QSAR outcomes. The precise workflow, which has been followed to shortlist chemical alternatives for further assessment, is presented in the supplementary information. Other types of potential alternatives (e.g., change in product, change in material) were identified based on the information collected during semi-structured interviews with Gerald Renner (Cosmetic Europe) and Héloïse Le Levier (IDUN Minerals).

5.2.3.2 Hazard assessment of the shortlisted alternatives

A hazard assessment was performed for the shortlisted chemical alternatives following the recommendations of the OECD guidance (OECD, 2021). To that end, 26 hazard endpoints were selected. These cover PBMT properties, consisting of environmental fate and behaviour endpoints (P = persistency, B = bioaccumulation, and M = mobility) and human health (Thuman), ecotoxicity (Tenv) endpoints (Supplementary Information). First, experimental data were collected via the OECD QSAR toolbox, ECHA registration database, US EPA CompTox and EcoTox databases, and the EFSA Foodtox database (ECHA, n.d., n.d.; Kovarich et al., 2020; OECD and ECHA, n.d.). The data set was supplemented with experimental data from the open literature when possible. The search strategy is explained in more detail in the supplementary information. When no experimental data were found, quantitative structure-activity relationship QSAR models were used to attempt to fill in data gaps. Only models fulfilling criteria, as laid down in Annex XI to the REACH regulation, were used (Regulation (EC) No 1907/2006). To that end, models available in the OECD QSAR Toolbox and the VEGA platform were used. Only predictions from models for which the compounds of interest fall in the applicability domain were kept. An average value was calculated when multiple models were available. Predictions from classification models were transformed into quantitative data by calculating the ratio of models returning a "positive" outcome over the total number of models for which the compound of interest fall in the applicability domain (for a given endpoint). Further details on the collection of hazard data are providing in the supplementary information.

5.2.3.3 Comparison of the alternatives

5.2.3.3.1 Heatmap

Hazard profiles of each alternative were compared by using a heatmap. The range of values for each hazard endpoints was divided into four colour-coded categories. The threshold values to define the categories for each hazard endpoint were taken from Zheng et al. (2019), who used CLP and PBT classification criteria to assign hazard categories. All threshold values used in this study are available in the supplementary information. In order to compare the hazard profiles of the potential alternatives, a score was assigned to each alternative following the recommendations of the OECD guidance. In short, for a given alternative, a score of 1 was assigned for every endpoint coloured green (low hazard), of 2 for endpoints coloured yellow (moderate hazard), of 3 for endpoints coloured orange (high hazard), and 4 for endpoints coloured red (hazard criterion exceeded). To test the sensitivity of the approach to the data gaps, three different scenarios were tested (i.e., risk neutral, risk seeking, and risk averse scenarios) as has been done in previous studies (Zheng et al., 2021, 2019). For the risk neutral scenario, data gaps were assigned a score of 2.5. The method to assign the score to data gaps under the other scenarios is detailed in the supplementary information. The final score of the alternative was obtained by summing up the scores of each endpoint. The alternative with the lowest score was considered to be the potential safest alternative.

5.2.3.3.2 MAUT and ELECTREIII

A multi-criteria analysis based on the Multi-Attribute Utility Theory (MAUT) principle was performed on the hazard endpoints in a similar manner as Zheng et al. (2019). In short, the data collected for all alternatives were normalised from 0 to 1 for each endpoint considered in the assessment, 0 corresponding to the worst level, and 1 the best level for a given endpoint. As for the heatmap, three different scenarios were used to test the sensitivity of the approach to the data gaps. Under the risk neutral scenario, data gaps were assigned a value of 0.5. Further information on the approach is provided in the supplementary information.

The scores for P, B, M, Thuman, Tenv were considered as equally important (equal weight approach) and added up to obtain a final MAUT score for a chemical. The chemical with the highest MAUT score was assumed to be the most preferred alternative. The MAUT assessment was complemented with ELECTREIII (an outranking method), for which calculations were done according to Zheng et al. (2021, 2019). The determination of the thresholds for the pairwise comparison for each endpoint is detailed in the supplementary information.

5.2.4 Necessity of the use of the compound of concern for health, safety, and functioning of society

As no clear criteria to evaluate the necessity of the use of a chemical for health, safety and functioning of society are available at the time of the study, only a qualitative assessment was performed.

5.3 Results

5.3.1 Occurrence of PMT/vPvM substances in cosmetic products

50 PMT/vPvM substances were identified in CosIng. These include REACH registered substances and the pharmaceuticals Ibuprofen, Naproxen, Progesterone and the biocidal active substance, Triclosan. Six substances (Dimethoxydiglycol, Pigment orange 5, Progesterone, Chloroform, DMSO and Methylthiophenyl morpholino isobutanone) on this list were listed as Annex II substances, meaning their use in cosmetic products is prohibited. These six substances were subsequently not considered for further analysis as they should not be present in cosmetic products. The remaining 44 substances were screened in the cosmetic product databases. Out of these substances, 21 were identified in cosmetic products. In total, 20 of these substances were found in 6.6% (897) of the cosmetic products listed in Kemiluppen, and 8 substances were found in 6.2% (62) of the cosmetic products screened in the Cosmethics database (Figure 5.2). In both databases, the product group containing the most PMT/vPvM substances was hair care products. A overview of all PMT/vPvM substances which have been identified in the Cosing database along with their technical function(s), and the type of cosmetic products they are used in are presented

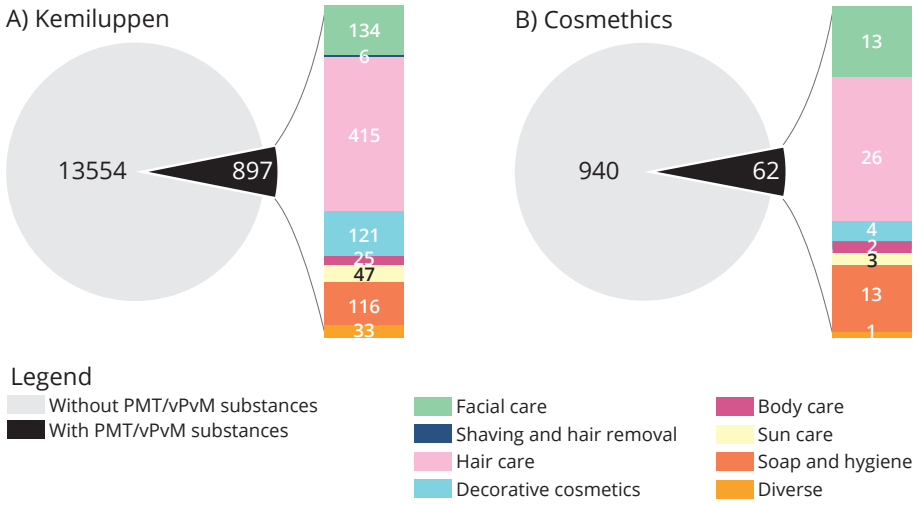

Figure 5.2. Total number of cosmetic products with and without PMT/vPvM substances in the databases from A) Kemiluppen and B) Cosmethics.

in the supplementary information. Based on their high occurrence, Allura red (CAS 25956-17-6), Benzophenone-4 (CAS 4065-45-6) and Climbazole (CAS 38083-17-9) were selected as case-studies chemicals for the assessment of alternatives and essentiality.

5.3.2 Technical function provided by case-study chemicals

5.3.2.1 Allura red

Allura red is a red pigment used to provide colour to cosmetic products, drugs and food and beverages (IACM, n.d.). In the database analyses, Allura red was found in all types of cosmetic products. Some of these products aim to change the appearance of certain body parts (e.g. hair colour products, make-up). In those type of products, it has been assumed that the chemical function of Allura red is necessary for the technical performance of the cosmetic product (Table 5.3). However, according to the industry stakeholders, a pigment can also be incorporated into formulations in order to make the cosmetic product more attractive to the consumer (e.g. providing a red colour to a soap formulation that smells like cherries). According to industry stakeholders, similar results could be achieved by, for example, changing the colour of the packaging. Therefore, it has been assumed that the pigment is not necessary for the technical performance of the product and could be removed from the formulation.

5.3.2.2 Benzophenone-4

Benzophenone-4 is a so-called broad spectrum UV-filter and can adsorb both UVB and short UVA range rays (Heurung et al., 2014), and was found in all types of products. In sun care products,

Benzophenone-4 is added to protect the human skin from UV radiation, whilst in other products Benzophenone-4 is added to protect the cosmetic product from degradation by light and therefore to increase the shelf-life. In both applications the technical function of Benzophenone-4 was considered necessary for the technical performance of the cosmetic products (Table 5.3).

5.3.2.3 Climbazole

Climbazole is a halogenated preservative and exhibits a strong activity against fungi. Halogenated preservatives are commonly added to personal hygiene products (Polati et al., 2007). However, Climbazole was only found in shampoos. The chemical is also listed as an anti-seborrheic agent in anti-dandruff shampoos to treat a common chronic inflammatory skin condition called seborrheic dermatitis. Due to these chemical functions, Climbazole was considered to be necessary for the technical performance of the products (Table 5.3).

5.3.3 Identifying suitable chemical alternatives

5.3.3.1 Identification and short listing of potential alternatives

For Allura Red at time of the analysis, 47 substances with a CAS number that provide a red colour were allowed to be used as alternatives in cosmetic products (Annex IV to Regulation 1223/2009/EC). Some of these substances were inorganic substances, which are exempted from PBT/vPvB assessments under REACH. Hence, no information on these properties is contained in the REACH database. In addition, QSAR models cannot be used to predict chemical properties of inorganic substances. Subsequently, only organic compounds were selected for the alternatives assessment. Based on known hazard and classification data (BAuA, n.d.; ECHA, n.d., n.d.; European Commission, 2023), six of these colourants were shortlisted for the alternative assessment for Allura red (Table 5.1).

For Benzophenone-4, 39 potential alternatives were selected from annex VI of the CPR (allowed UV-filters). Six of these substances were selected for the alternative assessment based on known hazard data, classification, and by compromising of both low priority substances for environmental assessment (Brooke et al., 2008) and UV filters with a similar absorbance compared to benzophenone-4 (Jesus et al., 2022).

As Climbazole was only found in shampoos, only its anti-seborrheic functionality was considered for which 10 potential alternatives were identified. Based on known hazard data and classification five of these substances were selected for the alternative assessment.

The exact process to shortlist chemical alternatives for further assessment is presented in the supplementary information. All case-study chemicals and the alternatives selected for this study are presented in Table 5.1. The supplementary information available via the online publication provides further information on the chemical structure, physico-chemical of the shortlisted alternatives.

Table 5.1. Overview of the studied case-study chemicals and short-listed alternatives and their Chemical Abstract Service (CAS) registry number. Further details of the assessed substances are presented in the supplementary information.

Use case	Chemical name	CAS number
Pigment	**Allura red**	**25956-17-6**
	Malvidin chloride	643-84-5
	Beetroot red	7659-95-2
	Pigment red 51	5850-87-3
	Pigment red 68	5850-80-6
	Acid red 180	6408-26-0
	Pigment red 122	980-26-7
UV- filter	**Benzophenone-4**	**4065-45-6**
	Ensulizole	27503-81-7
	Benzylidene camphor sulfonic acid	56039-58-8
	Bisdisulizole disodium	180898-37-7
	Bemotrizinol	187393-00-6
	Bornelone	2226-11-01
	Phenylemenis-diphenyltriazine	55514-22-2
Anti-seborrheic	**Climbazole**	**38083-17-9**
	Octanoic acid	102731-54-4
	Caprylylglycine	14246-53-8
	Shikimic acid	138-59-0
	Ciclopirox olamine	41621-49-2
	Hexamidine diisethionate	659-40-5

5.3.3.2 Data collection of hazard endpoints for the alternatives assessment

All the hazard data collected for the hazard assessment of the shortlisted alternatives are presented in the supplementary information available via the online publication. An overview of the type of hazard data which have been collected are presented in Figure 5.3. The ECHA database of registered substances was the most important source for collecting experimental data. No or few experimental data were found for substances not registered under REACH. QSAR models were used to fill in missing data, but some data gaps for human and environmental toxicity endpoints still remain for all substances. Data gaps were mainly found for acute and chronic toxicity for exposure via inhalation and dermal application. More information on how hazard data were harmonized and predictions from QSAR models were handled are presented in the supplementary information.

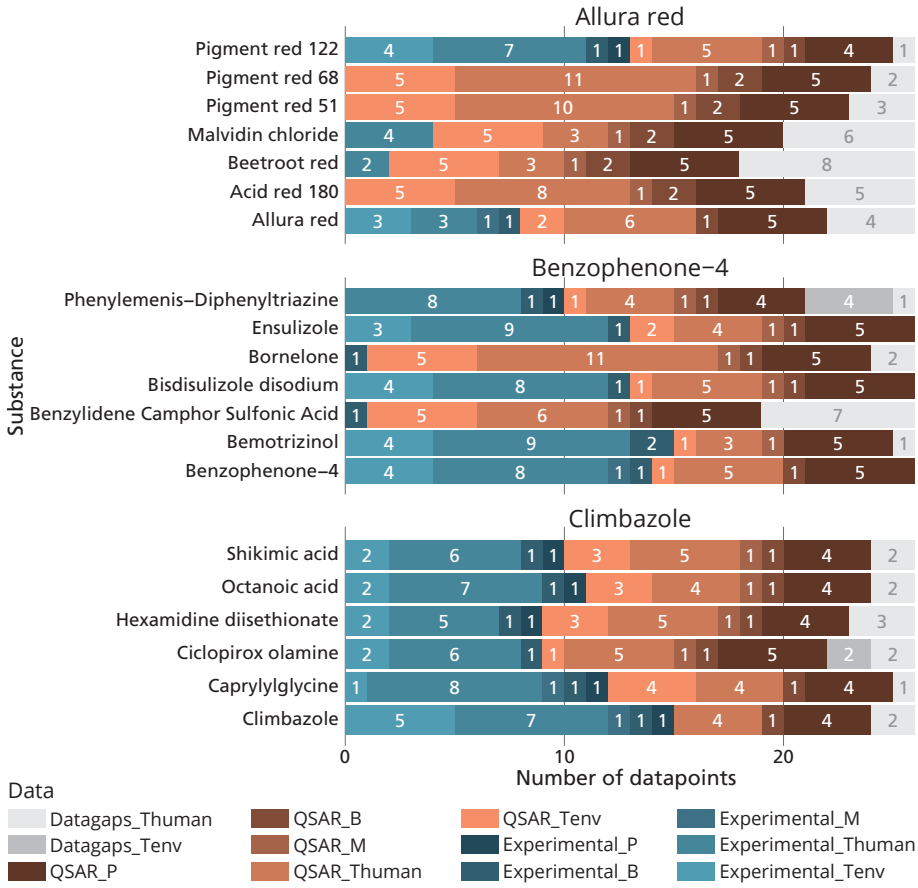

Figure 5.3. Total amount of experimental data, QSAR data and data gaps for the 26 PMBT endpoints considered for the alternatives assessment, consisting of environmental fate and behaviour endpoints (P = persistency, B = bioaccumulation, and M = mobility) and human health (Thuman), ecotoxicity (Tenv) endpoints.

5.3.3.3 Heat map and scoring based on regulatory criteria

The heat map shows that all assessed chemicals obtained at least one red endpoint, indicating that none of the chemical alternatives can be considered as "non-hazardous" according to current (regulatory) criteria (Figure 5.4). When looking at the total obtained hazard scores, the most favourable alternative for Allura red is Beetroot red with a score of 44.5. Beetroot red obtained the fewest number of red indicators, but also has most data gaps. Allura red, as well as all assessed alternatives, were assigned a red indicator for mobility. Moreover, with the exception of Beetroot red, all substances were assigned multiple red indicators for persistency.

For Benzophenone-4, all substances were assigned at least one red indicator for persistency and, except for Bemotrizinol, the mobility hazard criterium was met for all substances. The lowest total hazard score of 37 was obtained for Ensulizole, making this the most preferred alternative.

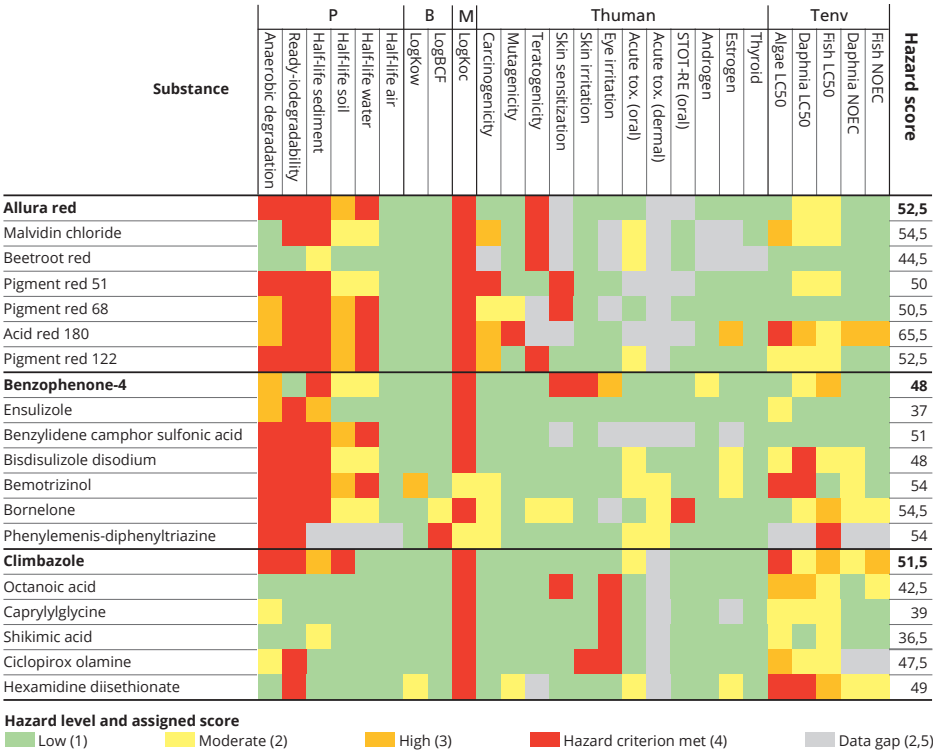

Figure 5.4. Heat map and total hazard score of the three case-study chemicals and their potential alternatives for the P (persistency), B (bioaccumulation), M (mobility), human toxicity (Thuman) and ecotoxicity (Tenv) endpoints. The thresholds for the colour codes were based on (Zheng et al., 2019) and the scores were based on (OECD, 2021a). Colour codes indicate whether a hazard criterion is exceeded according to current regulatory standards and a very high hazard (red) is assigned. When hazard criteria fell below regulatory standards a high (orange), moderate (yellow) or a low (green) hazard level is assigned. Chemicals with lower hazard scores compared to the case-study chemical are potentially safer alternatives.

Climbazole and potential alternatives were all assigned a red indicator for mobility as well. The lowest hazard score was obtained for Shikimic acid, which obtained a score of 36.5.

Heat maps for the other scenarios (i.e. risk seeking and risk averse scenarios) to test the sensitivity of the approach to the data gaps are available in the data sheets available via the online publication. The ranking of the most favourable alternative compared to the case-study chemical did not change in any of the scenarios.

5.3.3.4 Multi-Attribute Utility Theory and ELECTREIII

All the data and results of the MAUT and ELECTRE III methods are available in the data sheets available via the online publication. In agreement with the heat-map, also the MAUT analysis showed that for every case-study chemical a safer alternative is available (Figure 5.5). In order to test

the sensitivity of the approach, the assigned value for data gaps was varied under the 'risk averse' and 'risk seeking' scenarios. This, however, did not seem to change the ranking of alternatives compared to the case-study chemical, as shown in the supplementary information.

Similar ranking of the alternatives was furthermore observed in the ELECTREIII method, which was performed to complement MAUT results. From Figure 5.5, it can be observed that, even though the total MAUT score is higher for some potential alternatives, the individual criteria do not always have a better score. For example, Benzophenone-4 has a P score of 0.51, but most assessed alternatives are more persistent based on the available data and therefore have a lower P score.

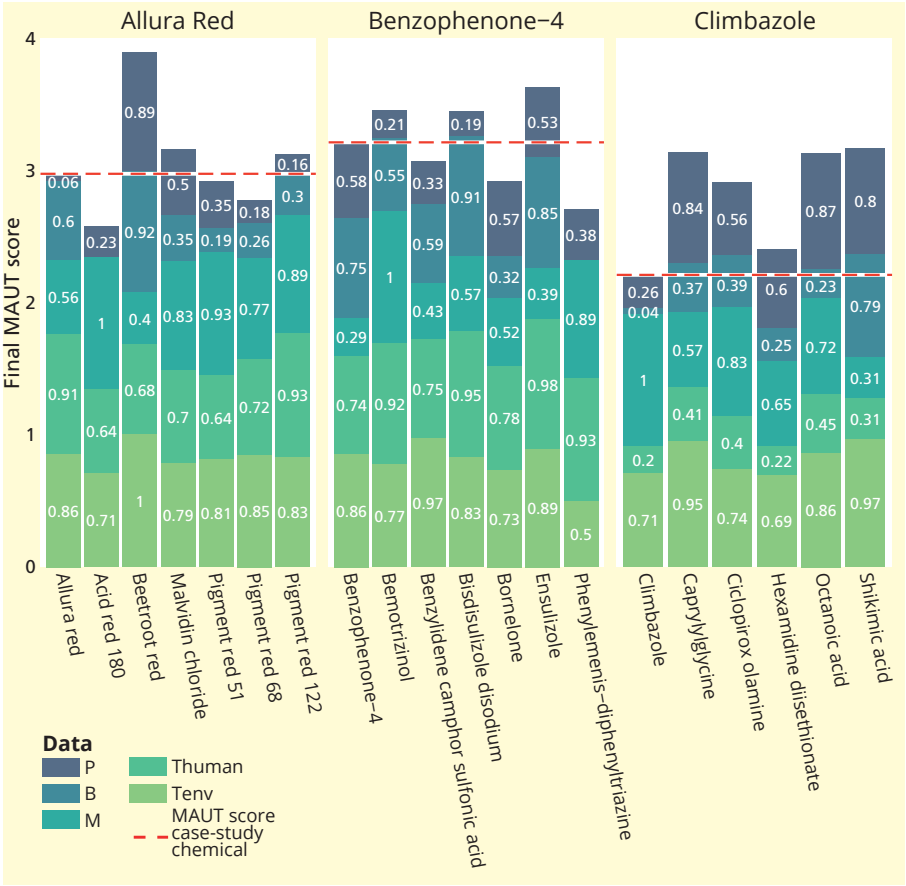

Figure 5.5. Results of the MAUT assessment of the three case-study chemicals and shortlisted alternatives. The target line shows the total MAUT score for the case-study chemical, alternatives with a higher score are potential safer alternatives. (P = persistency, B = bioaccumulation, and M = mobility) and human health (Thuman), ecotoxicity (Tenv) endpoints

5.3.3.5 Comparison of MCDA approaches

The final ranking of the potential alternatives according to the three multicriteria decision analysis (MCDA) approaches considered in this study is shown in Table 5.2. In the cases of the pigment and the UV-filter, although the final ranking of the alternatives differs according to the MCDA method which is being used, it is possible to identify one substance which is consistently ranked first in both cases (i.e. Beetroot red in the case of Allura Red; Ensulizole in the case of Benzophenone-4). Furthermore, it is also possible to identify substances which are consistently ranked lower than the substance to phase-out (i.e. Pigment red 51 and Acid red 180 in the case of Allura Red; Benzylidene camphor sulfonic acid, Bornelone, and Phenylemenis-diphenyltriazine in the case

Table 5.2. Final ranking of the potential alternatives according to the heatmap, MAUT, and ELECTRE III approaches for the safest (ranked 1) and least safe (ranked 6 or 7) substances.

Use case	Chemical name	Heatmap OECD scoring	MAUT	ELECTREIII
Pigment	Allura red	2	4	3
	Malvidin chloride	4	2	2
	Beetroot red	1	1	1
	Pigment red 51	6	5	5
	Pigment red 68	4	6	3
	Acid red 180	7	7	7
	Pigment red 122	3	3	5
UV- filter	Benzophenone-4	2	4	3
	Ensulizole	1	1	1
	Benzylidene camphor sulfonic acid	5	5	7
	Bisdisulizole disodium	2	3	5
	Bemotrizinol	4	2	2
	Bornelone	7	6	5
	Phenylemenis-diphenyltriazine	6	7	3
Anti-seborrheic	Climbazole	6	6	5
	Octanoic acid	3	2	1
	Caprylylglycine	2	3	2
	Shikimic acid	1	1	4
	Ciclopirox olamine	4	4	2
	Hexamidine diisethionate	5	5	6

of Benzophenone-4). In the case of the anti-seborrheic, four potential alternatives (i.e., octanoic acid, caprylylglycine, shikimic acid, and ciclopirox olamine) are consistently ranked higher than climbazole with every MCDA approach considered. However, none of these potential alternatives is ranked first with all of the methods.

5.3.4 Chemical management step based on functionality and essentiality

The technical function of Allura red was not considered necessary for the performance of some cosmetic products and thus considered as non-essential. The chemical should therefore be removed from those cosmetic products where its function is unnecessary (Table 5.3). For other applications of Allura red, as well as all applications of Climbazole and Benzophenone-4, the technical function of the chemical was considered as necessary for the desired performance of cosmetic products. Even though no hazard-free alternatives exist, potentially better alternatives were identified for all case-study chemicals in the alternatives assessment of hazards. This assessment indicated that Allura red, Benzophenone-4 and Climbazole can be substituted. Following the concept of essential-use, the use of these chemicals of concern is considered as non-essential for those products, as they can be substituted.

Table 5.3. Summary table of the approach from Roy et al. (2022) to assess the functionality and essentiality of the case-study chemicals in cosmetic products in order to identify appropriate management actions.

Case-study chemical	Cosmetic products in which the chemical is present, ordered per product group	Technical function of the substance in the cosmetic products	Is the functional use of the chemical necessary for the performance of the product?	Are there no alternatives available?	Is the use of the chemical necessary for health, safety or critical for the functioning of society?	Management of substance in product
Benzo phenone-4	Bath and Body Products: Body wash/shower gel, Body scrub, Body oil, Bath salt	UV protection	Yes, find drop-in chemical replacement	No	Not relevant	Substitute
	Facial Care: Cleansers Hair Care: Conditioner, Hair spray, Shampoo, Styling cream		Yes, find drop-in chemical replacement	No	Not relevant	Substitute
	Hands and Nails: Hand wash		Yes, find drop-in chemical replacement	No	Not relevant	Substitute
	Make-up: Lipstick/ lip gloss / lip pencil		Yes, find drop-in chemical replacement	No	Not relevant	Substitute
	Suncare: Self-tanning, Suncream/lotion/ gel		Yes, find drop-in chemical replacement	No	Not relevant	Substitute
Climbazole	Hair Care: Shampoo	Anti-dandruff agent	Yes, find drop-in chemical replacement	No	Not relevant	Substitute

Case-study chemical	Cosmetic products in which the chemical is present, ordered per product group	Technical function of the substance in the cosmetic products	Is the functional use of the chemical necessary for the performance of the product?	Are there no alternatives available?	Is the use of the chemical necessary for health, safety or critical for the functioning of society?	Management of substance in product
Allura red	Bath and Body Products: Shower gel, Bath bomb		No, redesign product or packaging	Not relevant	Not relevant	Remove from application
	Facial Care: Cleansers, Eye makeup remover, Face mask, Lip balm, Scrub/peeling		No, redesign product or packaging	Not relevant	Not relevant	Remove from application
	Hair Care: Conditioner, Hair spray, Shampoo, Hair colour, Hair mask		Hair colours: Yes, find drop-in chemical replacement All other products: No, redesign product or packaging	No	Not relevant	Substitute in hair colour. Remove from all other formulations
	Foot care: Foot wash/bath		No, redesign product or packaging	Not relevant	Not relevant	Remove from application
	Fragrances: Parfum / eau de toilette / bodymist	Colourant	No, redesign product or packaging	Not relevant	Not relevant	Remove from application
	Hands and Nails: Hand disinfection, Hand wash, Nail polish remover		No, redesign product or packaging	Not relevant	Not relevant	Remove from application
	Make-up: Pressed powders, (foundation, bronzer, primer, blush and eye make-up), Eyebrow pencil, Eyeliner, Lipstick/ lip gloss / lip pencil, Mascara, nail polish		Yes, find drop-in chemical replacement	No	Not relevant	Substitute
	Mouth/toothcare: Mouthwash, Toothpaste		No, redesign product or packaging	Not relevant	Not relevant	Remove from application
	Suncare: Self-tanning, Suncream/lotion/ gel, Sunspray		No, redesign product or packaging	Not relevant	Not relevant	Remove from application

5.4 Discussion and conclusion

5.4.1 PMT/vPvM substances in cosmetics

Our analysis revealed that approximately 6.4% of all cosmetic products contain PMT or vPvM substances, and that these substances have a wide variety of functions in cosmetics. The highest share of PMT/vPvM substances was found for hair care products, followed by facial care products. The list of (potential) PMT/vPvM substances from Arp and Hale (2019) was used as a starting point in this study which classified substances as mobile if the Log K_{oc} is 4.5 or lower. In the proposed CLP revision, the mobility criterion, however, is set as Log K_{oc} ≤3 (European Commission, 2022b), so a more stringent analysis can be considered. Thus, the list from Arp and Hale (2019) might not provide an accurate overview of all relevant PMT/vPvM substances. Previous studies ranked PMT/vPvM substances based on their emission potential to the environment (Schulze et al., 2018) or their mobility through waste water treatments (Fries et al., 2022). By comparing these rankings we observe that approximately half of the PMT/vPvM substances identified in the CosIng database are also listed in the rankings from Schulze et al. (2018) and Fries et al. (2022)(SI2). This emphasises that, whilst we selected the most frequently occurring PMT/vPvM substances in cosmetics based on data from Kemiluppen and Cosmethics, many other relevant substances, uses (see e.g. Groh et al., 2021) and consequent emissions need to be addressed in future studies.

5.4.2 Assessing functionality and identifying alternatives

In this study, only chemical-by-chemical substitution was assessed as no assessment could be performed to compare chemicals to other types of alternatives for functional substitution, such as a change of material and system changes (Tickner et al., 2015). It is key that an alternative chemical provides the same chemical function to preserve the overall performance of a products, whilst lowering hazards. An extensive search was conducted to identify candidate alternatives with a known chemical function. However, this search might not be exhaustive as other, perhaps better, alternatives exist that are not listed in open databases. In addition, inorganic substances and substances without a CAS number were purposely left out as no hazard data were available. The other identified substances were short-listed based on already known hazard and classification data (BAuA, n.d.; ECHA, n.d., n.d.; European Commission, 2023). Chemicals that are not classified as hazardous under current regulations are however not necessarily safer compared to classified chemicals, as effects of many chemicals are not sufficiently studied, both in the scientific literature and within REACH due to varying information requirements based on the annual tonnage (Coria et al., 2022; Kristiansson et al., 2021; Sobek et al., 2016). In addition, information on the specific end function (i.e. function of the chemical in the product) is often unknown, for many types of

chemical uses. Information contained in the CosIng database provided a generic function such as UV filter, but detailed information on the functionality (such as the UV absorbance spectrum) is not given. Approaches to predict chemical function based on structural and physicochemical descriptors exist (Isaacs et al., 2016; Phillips et al., 2017), but to our knowledge only provide generic classifications. Hence, better open data on the different uses and functionalities of chemicals in products would be helpful in the future to support chemical substitution.

5.4.3 Collection and evaluation of hazard data

Most experimental data used in our study was obtained from REACH dossiers, and no, or only few, experimental endpoints were found for substances not registered under REACH. Data contained in REACH dossiers, however, are not always compliant, and issues regarding REACH data reliability have been raised before (Ingre-Khans et al., 2019a; UBA, 2018). Future studies assessing safer alternatives using REACH data might therefore need to incorporate reliability assessments in order to communicate and deal with uncertainties, which will subsequently increase the transparency of the alternatives assessment (Ingre-Khans et al., 2019b; Moermond et al., 2016). Experimental data can furthermore be less reliable when only one study for an endpoint is available. In these cases, it might be better to use a set of QSAR predictions to define an endpoint instead of using this single experimental value (Li et al., 2022). However, for many endpoints no experimental data were found and QSAR methods were used for all chemicals in order to fill in data gaps. Modelled results also need to be interpreted with caution, especially when results from different QSARs could not be combined as only one model for a specific endpoint was available. Thus, it is also important to generate confidence scores for QSAR results to reflect uncertainties in alternatives assessments (Myatt et al., 2022). Future studies need to explore better how both experimental and QSAR data can be combined in MCDAs and how confidence scores can be incorporated in these approaches. Furthermore, data gaps were found for all chemicals and included in the MCDA approaches by assigning standard scores. Methods on how to handle data gaps can influence the alternatives assessment outcomes greatly (Malloy et al., 2013). However, there is not yet an agreed method on how this should be done (Jacobs et al., 2016; Tickner et al., 2019a). Data gaps were mainly found for long-term exposure endpoints, emphasising the need of data generation and/or developments of *in silico* methods in these areas.

5.4.4 Comparing and selecting safer alternatives

We were able to show that safer alternatives for Allura red, Benzophenone-4 and Climbazole exist, based on an assessment of hazards. However, none of the assessed alternatives fully satisfy the criteria for the set of 26 hazard endpoints, meaning that no 'hazard-free' alternatives are available. For the MCDA approaches, endpoints were selected based on OECD recommendations and weighted

using an equal weighting approach. As the vast majority of low molecular weight substances that are neutral or weakly to non-polar will be either bioaccumulative or mobile (Neumann and Schliebner, 2019), many chemicals will receive similar scores for the combined bioaccumulation and mobility criteria. A few polar, ionisable or ionic substances can on the other hand be classified as both bioaccumulative and mobile, as is the case for some PFAS (e.g. perfluorooctanoic acid (PFOA)). Furthermore, a classification of a substance as bioaccumulative or mobile should not be reason for concern alone, but should always be combined with persistency; the higher the persistence of a substance, the higher the concern for potential long-lasting effects on human health and the environment (Cousins et al., 2019b). The MCDA method used in this study can thus be refined by applying higher weights to the most important endpoints, such as persistency.

The relevance of other individual hazard endpoints varies according to chemical and product type. A certain hazard might sometimes even be needed for the functionality of a chemical. For example, poorly degradable (i.e. persistent) UV-filters have a higher efficacy as they can protect of the skin from UV radiation for a longer time (Giokas et al., 2007). In addition, certain hazards are legally allowed for one use, but not for another. Category 1 and 2 CMR substances can for example be used in cosmetic products if the Scientific Committee on Consumer Safety deems the reasonably foreseen uses as safe (Art. 15 Regulation (EC) No 1223/2009). Different stakeholders need to be involved in order to refine alternatives assessments by e.g. selecting relevant endpoints, weighting endpoints in MCDAs and dealing with trade-offs (Grant et al., 2022; Jacobs et al., 2016; Tickner et al., 2019a, 2019b).

It is furthermore important to note that the present analysis solely focused on hazard assessments of the potential alternatives to the substances of concern. Further work is needed to characterize the relevant exposure routes for humans and the environment resulting from the use of the alternatives. This might change the level of concern for the assessed alternatives. Such assessment could be performed qualitatively, as outlined in the OECD guidance (OECD, 2021a).

5.4.5 MCDA approaches for chemical alternatives assessments

In this study, three different MCDA approaches were used to compare hazards and select a safer alternative to the case-study chemicals, which generally yielded similar results in identifying the top ranked alternatives. Even though the combined use of multiple MCDA approaches has been advised (e.g. Yatsalo et al., 2007), it might not always be feasible to use multiple (complex) methods due to time and other resource constraints. Limitations and benefits of the heatmap, MAUT and ELECTRE approaches have previously been documented by e.g. Zheng et al. (2019). We also found the heat map to be the most helpful in rapidly comparing burden-shifting of hazards across case-study chemicals and potential alternatives, and by applying the OECD scoring approach a hazard ranking is obtained by which the most preferred chemical is identified. This ranking, however, is for a large part determined by the toxicity to human health, relating to 12 out of 26 endpoints. This is circumvented

by using aggregated scores for PBMT, as done for the MAUT and ELECTRE ranking. Of these two methods, the MAUT method is the most user friendly. The ELECTRE method is an outranking technique where superior performance on some criteria can compensate for inferior performance on other criteria. Even though ELECTRE is best able to deal with data uncertainty, a potential downside, however, is that the method does not always reflect the magnitude of relative superior or under performance of individual criteria (Jacobs et al., 2016). Selection of the most suitable approach will depend greatly on the information needs of decision makers, but guidance is currently lacking to select and successfully implement MCDA approaches (Beaudrie et al., 2021; Rowley et al., 2012).

5.4.6 Managing hazardous substances in cosmetic products

Following the combined application of the concepts of functional substitution and essential-use (Roy et al., 2022), none of the assessed uses of PMT/vPvM substances were found to be essential. Starting with considerations of the function, some uses of Allura red were found not to be needed for the performance of cosmetic products. For other uses of Allura red and all uses of Benzophenone-4 and Climbazole, as the chemical function was considered necessary for product technical performance, the essentiality depended on the availability of suitable alternatives. As safer alternatives are available, the use of the PMT/vPvM substances was non-essential and should be substituted (Cousins et al., 2019a). This also meant that the question whether use of the chemical is necessary for health, safety or functioning of society did not need to be answered. It might, however, be argued that, based on essentiality criteria defined earlier (Cousins et al., 2021, 2019a), the use of hazardous substances in cosmetic products can always be classified as non-essential. Given that chemical risks are currently not adequately managed due to the many different chemicals and uses existing (Fenner and Scheringer, 2021; Persson et al., 2022), discussions about the essentiality of chemical uses might help to decide whether the continued widespread use of chemicals for certain uses is desirable in the first place.

5.4.7 Looking beyond chemical hazards

This work focussed mainly on the hazard assessment of chemical alternatives due to data limitations regarding the technical and economic feasibility. These other aspects should, however, be included in order to make an informed choice on the substitution of chemicals. The technical and economic feasibility of a specific alternative can depend highly on the type of actor performing the alternative assessment, and on the type of product in which the compound of concern is used. Similarly, due to lack of open data and resources, the availability of an alternative can be dependent on the actor who is attempting to phase-out a hazardous substance and could therefore not be evaluated with certainty in the context of this study.

Human health and the environment might not sufficiently be protected when only hazards

are considered (Greggs et al., 2019; Jolliet et al., 2021), emphasising the need to include exposure assessments. In order to estimate emission and exposure, information on the different uses of chemicals and their volume in products is needed. However, to our knowledge this information is not yet openly available, and modelling approaches will be needed instead, e.g. to estimate chemical weight fractions (Isaacs et al., 2018; Jolliet et al., 2021). Furthermore, it is important to consider environmental impacts beyond chemical effects, as emphasised by e.g. the planetary boundaries concept and the ambition laid down in the CSS to transition towards safe and sustainable chemicals (European Commission, 2020d; Rockström et al., 2009). Environmental impact assessments covering the whole product life cycle can potentially be used to obtain a complete overview of all potential advantages and disadvantages of using a certain substance (Fantke et al., 2020; Greggs et al., 2019).

As alternative assessments are a core element to phase out hazardous substances via the essential-use concept, it is key that these methods combine hazard-based considerations with broader life cycle impacts to prevent burden shifting and assure that chemicals are used in a safe and sustainable manner. Such assessments might affect the ranking of most preferred alternatives found in this study. For example, Beetroot red was in our analysis the best alternative to Allura red. However, the use of plant extracts in consumer products can result in a larger environmental footprint due to increased water depletion and CO_2 emissions (Holmquist et al., 2021; Secchi et al., 2016). Incorporation of sustainability assessments will add an additional layer of complexity to chemicals assessment. Further methods are therefore required that combine safety and sustainability considerations in an accessible and transparent way.

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5.5 Supplementary Information

In this section, more details are given about the methods used in Chapter 5. An overview is also presented of the supplementary data files, which can be obtained via the online publication.

5.5.1 List of PMT/vPvM substances contained in cosmetic products

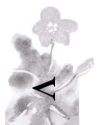
The table S5-1 is listing the substances from the Cosing database which have been identified as PMT or vPvM according to the analysis from the German Environmental Agency (Arp and Hale, 2019) along with their chemical functions, and the type of cosmetic products they are sued based on the information contained in Kemiluppen and Cosmethics databases.

Table S5-1. List of PMT/vPvM substances listed in Cosing database, showing their INCI name, CAS number, Technical function, presence in products and their prioritization rank based on Schulze et al. (2018) and Fries et al (2022). NA = Not Available.

Substance Name	CAS number	Technical function	Listed in products database		Products Type		Prioritization rank based on Schulze et al. (2018)	Prioritization rank based on Fries et al. (2022)
			Kemiluppen	Cosmethics	Products category	Subcategory		
TRICLOSAN	3380-34-5	Antimicrobial/ Deodorant/ Preservative	YES	NO	Soap and hygiene	Toothpaste	215	75
BENZOTRIAZOLE	95-14-7	Antimicrobial	YES	NO	Suncare	Sun cream	Not found	95
BENZOPHENONE-3	131-57-7	Light stabilizer/ UV absorber/ UV filter	YES	YES	Facial care	Make-up remover, Day cream, Colored day cream, Lip balm, Moisturisers	Not found	58
					Hair care	Hair cream, Hairspray, Wax, Serum		
					Make-up	Foundation cream, Blush, Powder, Lipstick, Lip gloss, Nail polish, Nail care, Nail polish remover, Perfume		
					Body care	Oil		
					Suncare	Self-tanner, Sun cream, Sun spray, Sun stick		
					Soap and hygiene	Body shampoo, Body wash		

Substance Name	CAS number	Technical function	Listed in products database		Products Type		Prioritization rank based on Schulze et al. (2018)	Prioritization rank based on Fries et al. (2022)
			Kemiluppen	Cosmethics	Products category	Subcategory		
BENZOPHENONE-4	4065-45-6	Light stabilizer/ UV absorber/ UV filter	YES	YES	Facial care	Cleansers	428	Not found
					Hair care	Conditioner, Shampoo, Hair spray, Styling cream		
					Make-up	Lipstick, Lip gloss		
					Body care	Ointment, Scrub, Hand care		
					Sun care	Self-tanner		
					Soap and hygiene	Bath salts, Body shampoo, Liquid hand soap, Wet wipes, Body wash, Shower gel		

Substance Name	CAS number	Technical function	Listed in products database		Products Type		Prioritization rank based on Schulze et al. (2018)	Prioritization rank based on Fries et al. (2022)
			Kemiluppen	Cosmethics	Products category	Subcategory		
CI 16035	25956-17-6	Colourant/ Hair dyeing	YES	YES	Facial care	Make-up remover (skin and eye), day cream, lip balm, mask, scrub, skintonic, eye care	500	Not found
					Hair care	Conditioner, Hair cream, Hair color, Hairspray, Shampoo, Wax		
					Make-up	Blush, Concealer, powder, Lipstick/Lip gloss, Nail polish, nail care, perfume, eyeliner, eye shadows		
					Body care	Cream, Hand care, Scrub, Foot care		
					Sun care	Self-tanner, Sun cream, Sun spray		
					Soap and hygiene	Bubble bath, Body shampoo, Hand disinfection, Liquid hand soap, Mouthwash, Toothpaste		
					Other	Gift boxes, Theatre make-up		
CLIMBAZOLE	38083-17-9	Anti-seborrheic/ Preservative	YES	YES	Hair care	Conditioner, Shampoo, Scalp care	563	Not found



Substance Name	CAS number	Technical function	Listed in products database		Products Type		Prioritization rank based on Schulze et al. (2018)	Prioritization rank based on Fries et al. (2022)
			Kemiluppen	Cosmethics	Products category	Subcategory		
DIMETHYL ETHER	115-10-6	Propellant/ Solvent/ Viscosity Controlling	YES	YES	Facial care	Skintonic	Not found	84
					Hair care	Conditioner, Hair color, Hairspray, Hair mousse, Shampoo, Wax		
					Sun care	Self-tanner, Sun cream, Sun spray		
					Soap and hygiene	Deodorant spray, Hand disinfection		
DISILOXANE	107-46-0	Antifoaming/ Skin conditioning	YES	NO	Facial care	Mask	Not found	114
					Hair care	Conditioner, Hair oil, Shampoo		
					Make-up	Lipstick, Lip gloss, Nail polish, Nail care, Primer		
					Body care	Oil		
EDTA	60-00-4	Chelating	YES	YES	Facial care	Make-up remover, Day cream, Scrub, Moisturisers	Not found	87
					Hair care	Conditioner, Hair colour, Hairspray, Shampoo, Wax		
					Make-up	Cream, Mascara, Primer, Eyebrows		
					Body care	Cream, Scrub		
					Soap and hygiene	Deodorant spray and stick, Liquid hand soap, Teeth whitening		

Substance Name	CAS number	Technical function	Listed in products database		Products Type		Prioritization rank based on Schulze et al. (2018)	Prioritization rank based on Fries et al. (2022)
			Kemiluppen	Cosmethics	Products category	Subcategory		
GUANIDINE CARBONATE	593-85-1	Buffering/ Skin conditioning	YES	NO	Facial care	Day cream	178	Not found
					Hair care	Shampoo		
					Body care	Cream, Ointment		
					Soap and hygiene	Deodorant roll-on		
HYDROXYETHYLPIPERAZINE ETHANE SULFONIC ACID	7365-45-9	Buffering	YES	YES	Facial care	Day cream, Mask, Night cream, Scrub, Serum, Skintonic, Eye care, Moisturisers	439	Not found
					Make-up	Foundation liquid		
					Body care	Cream, Hand care, Ointment		
PENTASODIUM PENTETATE	140-01-2	Chelating	YES	YES	Facial care	Day cream, Night cream	42	Not found
					Shaving and hair removal	Razor		
					Hair care	Jelly, Hair bleaching, Hair color, Shampoo		
					Make-up	Lash color		
					Body care	Cream, Hand care		
					Soap and hygiene	Solid hand soap		

Substance Name	CAS number	Technical function	Listed in products database		Products Type		Prioritization rank based on Schulze et al. (2018)	Prioritization rank based on Fries et al. (2022)
			Kemiluppen	Cosmethics	Products category	Subcategory		
PHENYLETHYL RESORCINOL	85-27-8	Antioxidant	YES	NO	Facial care Sun care	Day cream, Serum Sun cream	734	Not found
POTASSIUM ACESULFAME	55589-62-3	Fragrance	YES	NO	Soap and hygiene	Mouthwash	277	Not found
BENZOGUANAMINE	91-76-9	Antioxidant/ Fragrance	YES	NO	Make-up	Nail polish	67	Not found
BIS-TRIMETHYLBENZOYL PHENYLPHOSPHINE OXIDE	162881-26-7	Light stabilizer	YES	NO	Make-up	Nail polish	299	88
ACETAMINOPHEN	103-90-2	Skin conditioning	YES	NO	Hair care	Hair spray	Not found	48
CHLORHEXIDINE	55-56-1	Oral care/ Preservative	YES	NO	Hair care	Conditioner, Hair colour	Not found	Not found
P-AMINOPHENOL	123-30-8	Hair dyeing	YES	NO	Hair care	Hair colour	Not found	67
BENZOPHENONE	119-61-9	Fragrance/ Light Stabilizer	YES	NO	Hair care, Soap and hygiene	Deodorant spray, Hair Spray	Not found	64
2-ACRYLAMIDO-2-METHYLPROPANE SULFONIC ACID	15214-89-8	Not reported	NO	NO	NA	NA	257	66
4,4'-ISOPROPYLIDENEDIPHENOL/ EPICHLOROHYDRIN COPOLYMER	25068-38-6	Film forming	NO	NO	NA	NA	Not found	Not found
AZOBISISOBUTYRONITRILE	78-67-1	Not reported	NO	NO	NA	NA	176	34
BENZOTHIAZOLE	95-16-9	Perfuming	NO	NO	NA	NA	43	39

Substance Name	CAS number	Technical function	Listed in products database		Products Type		Prioritization rank based on Schulze et al. (2018)	Prioritization rank based on Fries et al. (2022)
			Kemiluppen	Cosmethics	Products category	Subcategory		
CI 21108	5567-15-7	Colourant	NO	NO	NA	NA	118	5
CI 73000	482-89-3	Colourant	NO	NO	NA	NA	80	41
DICYCLOHEXYL SODIUM SULFOSUCCINATE	23386-52-9	Cleansing/ Foam boosting/ Surfactant/ Hydrotrope	NO	NO	NA	NA	304	Not found
DIMETHYL 2,6-NAPHTHALATE	840-65-3	Skin conditioning	NO	NO	NA	NA	Not found	Not found
DIMETHYL IMIDAZOLIDINONE	80-73-9	Hair conditioning/ Humectant/ Skin conditioning	NO	NO	NA	NA	Not found	Not found
DIMETHYLACRYLAMIDE	284-95-7, 2680-03-7	Not reported	NO	NO	NA	NA	Not found	50
FORMAMIDINE SULFINIC ACID	1758-73-2	Reducing	NO	NO	NA	NA	Not found	Not found
HYDROXY TETRAMETHYLPIPERIDINE OXIDE	2226-96-2	Antioxidant	NO	NO	NA	NA	286	Not found
IBUPROFEN	15687-27-1	Skin conditioning	NO	NO	NA	NA	Not found	Not found
MESITYLENE	108-67-8	Solvent	NO	NO	NA	NA	Not found	109
METHENAMINE	100-97-0	Antimicrobial/ Preservative	NO	NO	NA	NA	Not found	4

Substance Name	CAS number	Technical function	Listed in products database		Products Type		Prioritization rank based on Schulze et al. (2018)	Prioritization rank based on Fries et al. (2022)
			Kemiluppen	Cosmethics	Products category	Subcategory		
NAPROXEN	22204-53-1	Skin conditioning	NO	NO	NA	NA	Not found	Not found
P-CHLOROPHENOL	106-48-9	Antimicrobial	NO	NO	NA	NA	Not found	Not found
PENTETIC ACID	67-43-6	Chelating	NO	NO	NA	NA	187	83
PHOSPHONOBUTANETRICARBOXYLIC ACID	37971-36-1	Anticorrosive/ Buffering/ Chelating	NO	NO	NA	NA	Not found	Not found
SODIUM DIETHYLENETRIAMINE PENTAMETHYLENE PHOSPHONATE	22042-96-2	Chelating	NO	NO	NA	NA	Not found	Not found
T-BUTYL METHYL ETHER	1634-04-4	Solvent	NO	NO	NA	NA	3	92
TRICHLOROETHANE	71-55-6	Solvent	NO	NO	NA	NA	Not found	115
TRIETHYL PHOSPHATE	78-40-0	Solvent	NO	NO	NA	NA	Not found	80
TRIFLUOROACETIC ACID	1-5-1976	pH Adjusters	NO	NO	NA	NA	218	42

5.5.2 Shortlisting of alternatives for further assessment

The Figure S5-1 below presents the workflow which has been followed to shortlist chemical alternatives for further hazard assessment. In short, the Annex III of the Cosmetic Products Regulation (CPR) lists the substances subject to restriction of use under the CPR; SUBSPORT portal is a database which gathers 32 lists from authorities, industry or NGOs of substances for which the uses are restricted either legally or voluntarily; the PACT tool is a tool provided by ECHA which summarize risk assessment and risk management activities in the EU; and the REACH Annex III Inventory compiles a list of substances which are likely to meet the criteria of Annex III of REACH based on QSAR data.

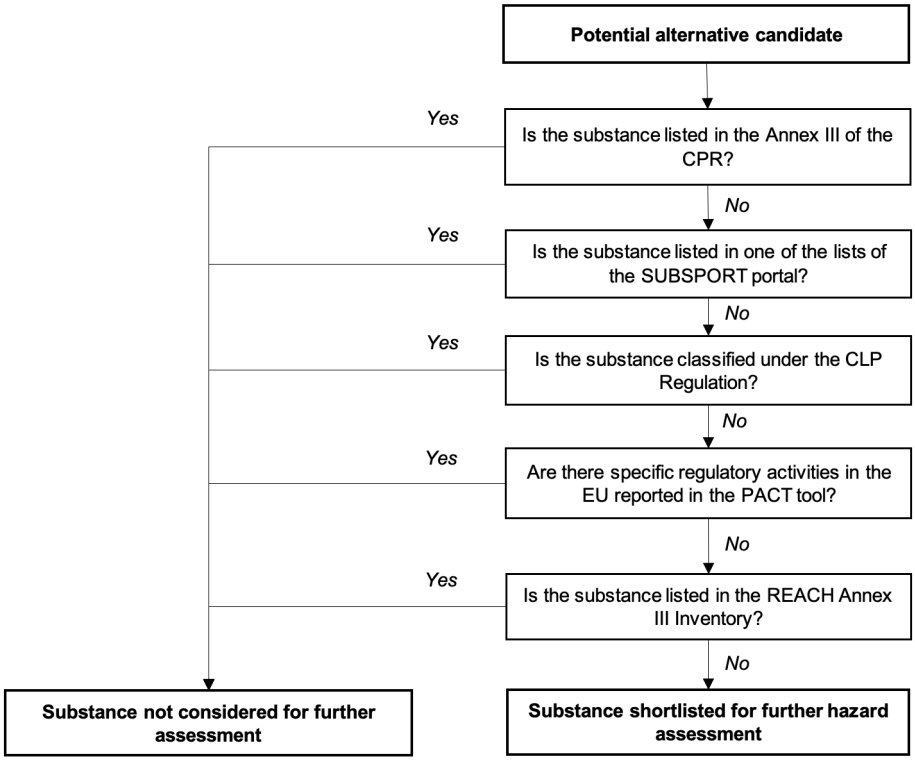


Figure S5-1. Workflow for selecting shortlisted chemical alternative for further hazard assessment: Annex III of the Cosmetic Products Regulation (CPR) lists the substances subject to restriction of use under the CPR; SUBSPORT portal is a database which gathers 32 lists from authorities, industry or NGOs of substances for which the uses are restricted either legally or voluntarily (the lists available are compiled in table 1); the PACT tool is a tool provided by ECHA which summarize risk assessment and risk management activities in the EU; and the REACH Annex III Inventory compiles a list of substances which are likely to meet the criteria of Annex III of REACH based on QSAR data.

The following data is included in SI3 (datasheet is available in the online publication):

- A full table of lists included in the SUBSPORT portal:
  - Table S3.1: list of restricted substances from authorities, industry or non-governmental organisations (NGOs) included in the SUBSPORT portal
- All the information which has been gathered to identify shortlisted candidates for further hazard assessment:
  - Table S2.2.1: Authoritative list screening of potential alternatives to the substances of interest
- Shortlisted chemical alternative which have been selected for further hazard assessment, along with their CAS number, molecular structure and physico-chemical properties:
  - Table S2.2.2: List of shorlisted potential alternatives for further assessment (see separated Excel file SI2)

5.5.3 Hazard profiling of the shortlisted alternatives

In SI4 (available via the online publication), all the hazard data which have been collected for all hazard endpoints and all shortlisted chemical alternatives are presented. More detailed information on the considered endpoints and how data was collected is given below.

5.5.3.1 Hazard endpoints considered

Table S5-2 below lists the hazard endpoints which have been considered to perform the hazard assessment of the shortlisted alternatives.

Table S5-2. Hazard endpoints considered for the hazard assessment. P = Persistency; B = Bioaccumulation potential; M = Mobility; T human = Toxicity to human health; T env = Toxicity to the environment

Parameter	Endpoint considered
P	Ready biodegradability
	Anaerobic degradation
	Half-life soil
	Half-life sediment
	Half-life water
	Half-life air
B	Octanol-water partition coefficient
	Bioconcentration factor

Parameter	Endpoint considered
M	Organic carbon-water partition coefficient
T human	Carcinogenicity
	Mutagenicity
	Teratogenicity
	Acute toxicity – Oral
	Acute toxicity – Dermal*
	Skin sensitisation
	Skin irritation
	Eye irritation
	Specific Target Organ Toxicity – Repeated Exposure – Oral
	Endocrine disruption: a) Androgenic b) Estrogenic c) Thyroid
T env	Acute toxicity – Algae
	Acute toxicity – Daphnia
	Acute toxicity – Fish
	Chronic toxicity – Daphnia
	Chronic toxicity – Daphnia

**: Acute toxicity via dermal exposure has been considered only for the assessment of alternatives to benzophenone-4 as no data was available for this endpoint for the other alternatives.*

5.5.3.2 Gathering of hazard data

Experimental hazard data were collected from the sources below (organised by order of preferences):

i. ECHA Registration database (https://echa.europa.eu/information-on-chemicals/registered-substances)
ii. CompTox database (https://comptox.epa.gov/dashboard/)
iii. EcoTox database (https://cfpub.epa.gov/ecotox/)
iv. OECD eChemPortal (https://www.echemportal.org/echemportal/)
v. EFSA publications (https://www.efsa.europa.eu/en)
vi. Open scientific literature. The terms used for the open literature search are listed per endpoints in Table S5-3.

Table S5-3. Terms for open scientific literature search for every hazard endpoint considered

Parameter	Endpoint considered	Search terms
P	Ready biodegradability	"biodegradation"
	Anaerobic degradation	NA
	Half-life soil	"half life" "soil"
	Half-life sediment	"half life" "sediments"
	Half-life water	"half life" "water"
	Half-life air	"half life" "air"
B	Octanol-water partition coefficient	"Kow"
	Bioconcentration factor	"BCF"
M	Organic carbon-water partition coefficient	"Koc"
T human	Carcinogenicity	"Carcinogenic*" "in vitro"
	Mutagenicity	"Mutagenic*" "in vitro"
	Teratogenicity	"reproduction" "toxicity" "in vitro" "reprotoxic"
	Acute toxicity – Oral	"toxicity" "oral" "rats" "mice" "roddens" "in vitro"
	Acute toxicity – Dermal*	"toxicity" "dermal" "rats" "mice" "roddens" "in vitro"
	Skin sensitisation	NA
	Skin irritation	NA
	Eye irritation	NA
	Specific Target Organ Toxicity – Repeated Exposure – Oral	"organ" "chronic" "toxicity" "rats" "mice" "rodent" "in vitro" "mammalian"
	Endocrine disruption: d) Androgenic e) Estrogenic f) Thyroid	"endocrine*"
T env	Acute toxicity – Algae	"green algae" "toxicity"
	Acute toxicity – Daphnia	"daphnia magna" "toxicity" "invertebrate"
	Acute toxicity – Fish	"Danio rerio" "Toxicity" "zebrafish" "rainbow trout" "Pimaphales promelas" "in vitro" "embryo test"
	Chronic toxicity – Daphnia	"daphnia magna" "toxicity" "invertebrate"
	Chronic toxicity – Daphnia	"Danio rerio" "Toxicity" "zebrafish" "rainbow trout" "Pimaphales promelas" "in vitro" "embryo test"

If different sources provided different effect concentrations for a same hazard endpoint, the lowest concentration was kept for the assessment.

If experimental data was not available, QSAR models available in the OECD QSAR Toolbox (v 4.5) and the VEGA platform were used to fill in further data gaps according to the ECHA guidance on how to use QSAR models (ECHA, 2016a). According to the point 1.3 of the Annex VI to Regulation (EC) No 1907/2006, results of QSARs may be used instead of testing when the following conditions are met:

1. results are derived from a QSAR model whose scientific validity has been established;
2. the substance falls within the applicability domain of the QSAR model;
3. results are adequate for the purpose of classification and labelling and/or risk assessment, and;
4. adequate and reliable documentation of the applied method is provided.

It has been assumed that 1st, 3rd and 4th points are automatically met for models available in the OECD QSAR toolbox and the VEGA platform. The Table S5-4 below lists the number of models available for each hazard endpoints considered in this study. QSAR predictions from a specific model were used only if the substance was within the applicability domain of the model.

If several QSAR models were available for a quantitative hazard endpoint (e.g. acute toxicity to algae), the average of the predictions from models for which the substance was within the applicability domain was kept for further assessment. In case of qualitative hazard endpoint (e.g. carcinogenicity), a hazard endpoint score was determined for a specific substance by calculating the ratio of the number of models returning a negative outcome over the total number of model available for which the substance was within the applicability domain (AD).

The equation illustrates the calculation of the mutagenicity score for Bornelone (CAS: 2226-11-1).

$$Mutagenicity\ score_{Bornelone} = \frac{Number\ of\ models\ predicting\ a\ negative\ outcome}{Number\ of\ models\ for\ which\ Bornelone\ is\ in\ the\ AD} = \frac{55}{58} = 0.94$$

Table S5-4. Number of QSAR models available for each hazard endpoint.

Parameter	Assessment criteria	Number of models	Software platforms
P	Ready biodegradability	6	OECD QSAR Toolbox & VEGA
	Half-life soil	1	OECD QSAR Toolbox
	Half-life sediment	1	OECD QSAR Toolbox
	Half-life water	1	OECD QSAR Toolbox
	Half-life air	1	OECD QSAR Toolbox
	Anaerobic degradation	1	OECD QSAR Toolbox
B	LogKow	4	OECD QSAR Toolbox & VEGA
	BCF	11	OECD QSAR Toolbox & VEGA
M	LogKoc	3	OECD QSAR Toolbox & VEGA
T human	Carcinogenicity	23	OECD QSAR Toolbox & VEGA
	Mutagenicity	74	OECD QSAR Toolbox & VEGA
	Reprotoxicity (teratogenicity)	7	OECD QSAR Toolbox & VEGA
	Acute toxicity (oral, dermal exposure)	3	OECD QSAR Toolbox & VEGA
	Skin sensitisation	8	OECD QSAR Toolbox & VEGA
	Skin irritation	5	OECD QSAR Toolbox
	Eye irritation	1	OECD QSAR Toolbox
	Specific Target Organ Toxicity -Repeated Exposure (oral)	4	OECD QSAR Toolbox
	Endocrine disruption: *Androgenic* *Estrogenic* *Thyroid*	29 *5* *14* *10*	OECD QSAR Toolbox & VEGA
T env	Algae (EC50)	6	OECD QSAR Toolbox & VEGA
	Daphnids acute	8	OECD QSAR Toolbox & VEGA
	Fish acute	14	OECD QSAR Toolbox & VEGA
	Daphnids chronic	2	OECD QSAR Toolbox & VEGA
	Fish chronic	2	OECD QSAR Toolbox & VEGA

5.5.4 Hazard assessment and comparison of the alternatives

5.5.4.1 Harmonization of the hazard data

For some hazard endpoints, the experimental results and/or QSAR predictions were documented as qualitative data. In order to compare hazard profiles of alternatives it was necessary to transform these qualitative results into a quantitative score. Furthermore, for some endpoints, it was necessary to log-transformed the quantitative results so the distribution of the data would be closer to a normal distribution.

This part is summarizing all the changes which have been made to the data for each hazard endpoint considered.

- Ready biodegradability

Experimental data were documented qualitatively. The results were transformed into quantitative data by assigning a score equalled to 0 if the substance is not readily biodegradable or 1 if the substance is readily biodegradable.

If experimental data were not available, a combined prediction from BIOWIN3 and BIOWIN5 models was used. The results were transformed in similar manner as for experimental data.

- Half-life in soil

No transformation of the data was made for this endpoint.

- Half-life in sediments

No transformation of the data was made for this endpoint.

- Half-life in water

No transformation of the data was made for this endpoint.

- Half-life in air

No transformation of the data was made for this endpoint.

- Anaerobic biodegradation

No transformation of the data was made for this endpoint.

- Octanol-water partition coefficient (Kow)

The data on octanol-water partition coefficient were log-transformed in order to have a distribution of the data closer to a normal distribution.

- Bioconcentration factor (BCF)

The data on the bioconcentration factor were log-transformed in order to have a distribution of the data closer to a normal distribution.

- Octanol-water partition coefficient (Koc)

The data on organic carbon-water partition coefficient were log-transformed in order to have a distribution of the data closer to a normal distribution.

- Carcinogenicity

Qualitative results were transformed into quantitative data by assigning a score equalled to 0 if the substance is carcinogenic or 1 if the substance is not carcinogenic. In some cases, the experimental results were expressed quantitatively. In those cases, the final conclusion of the study on carcinogenicity potential was documented and transformed as explained above.

The predictions from QSAR models for carcinogenicity were qualitative. The carcinogenicity score of a specific substance was then calculated by calculating the ratio of the number of models returning a negative outcome over the total number of model available for which the substance was within the applicability domain.

- Mutagenicity

Qualitative results were transformed into quantitative data by assigning a score equalled to 0 if the substance is mutagenic or 1 if the substance is not mutagenic.

The predictions from QSAR models for mutagenicity were qualitative. The mutagenicity score of a specific substance was then calculated by calculating the ratio of the number of models returning a negative outcome over the total number of model available for which the substance was within the applicability domain.

- Teratogenicity

The predictions from QSAR models for teratogenicity were qualitative. The teratogenicity score of a specific substance was then calculated by calculating the ratio of the number of models returning a negative outcome over the total number of model available for which the substance was within the applicability domain.

The experimental data to evaluate the teratogenicity of a specific substance were quantitative. In those cases, the final qualitative conclusion of the study on the teratogenicity potential of the substance was documented. A score of 0 was assigned to the substance if it was concluded that it presented a teratogenic potential, and a score of 1 if it was concluded that the substance is not teratogenic.

- Acute toxicity – Oral exposure

The data on acute toxicity were log-transformed in order to have a distribution of the data closer to a normal distribution.

- Acute toxicity – Dermal exposure

The data on acute toxicity were log-transformed in order to have a distribution of the data closer to a normal distribution.

- Skin sensitization

Qualitative results were transformed into quantitative data by assigning a score equalled to 0 if the substance is skin sensitizing or 1 if the substance is not skin sensitizing.

The predictions from QSAR models for skin sensitizing were qualitative. The skin sensitizing score of a specific substance was then calculated by calculating the ratio of the number of models returning a negative outcome over the total number of model available for which the substance was within the applicability domain.

- Skin irritation

Qualitative results were transformed into quantitative data by assigning a score equalled to 0 if the substance is skin irritating or 1 if the substance is not skin irritating.

The predictions from QSAR models for skin sensitizing were qualitative. The skin irritation score of a specific substance was then calculated by calculating the ratio of the number of models returning a negative outcome over the total number of model available for which the substance was within the applicability domain.

- Eyes irritation

Qualitative results were transformed into quantitative data by assigning a score equalled to 0 if the substance is eyes irritating or 1 if the substance is not eyes irritating. If the data suggested that the substance was possibly irritating to the eyes, a score of 0.5 was assigned.

The predictions from QSAR models for skin sensitizing were qualitative. The skin irritation score of a specific substance was then calculated by calculating the ratio of the number of models returning a negative outcome over the total number of model available for which the substance was within the applicability domain.

- Specific Targeted Organ Toxicity – Repetitive Exposure (STOT RE)

The predictions from QSAR models for STOT-RE were qualitative. The STOT-RE score of a specific substance was then calculated by calculating the ratio of the number of models returning a negative outcome over the total number of model available for which the substance was within the applicability domain.

Based on the information provided on the development of the model available, the model returns a "positive" result if the predicted effect concentration is within the range 0.0167-2.69 mg/kg bw/day, and a "negative" result if the predicted concentration is within the range 5-1000 mg/kg bw/day. These categories were used to expressed the experimental results qualitatively.

- Endocrine disruption potential – Androgen, Estrogen or Thyroid

The predictions from QSAR models for endocrine disruption potential were qualitative. The endocrine disruption to androgen, estrogen and thyroid activities score of a specific substance were then calculated by calculating the ratio of the number of models returning a negative outcome over the total number of model available for which the substance was within the applicability domain.

- Acute toxicity to algae

The data on acute toxicity to algae were log-transformed in order to have a distribution of the data closer to a normal distribution.

- Acute toxicity to daphnia

The data on acute toxicity to daphnia were log-transformed in order to have a distribution of the data closer to a normal distribution.

- Acute toxicity to fish

The data on acute toxicity to fish were log-transformed in order to have a distribution of the data closer to a normal distribution.

- Chronic toxicity to daphnia

The data on acute toxicity to daphnia were log-transformed in order to have a distribution of the data closer to a normal distribution.

- Chronic toxicity to fish

The data on acute toxicity to fish were log-transformed in order to have a distribution of the data closer to a normal distribution.

5.5.4.2 Normalization of the data and handling of data gaps

5.5.4.2.1 Normalization of the hazard data

In order to compare the hazard profiles of the chemical alternatives with certain multi-criteria decision analysis (MCDA) methods, it was necessary to normalise the hazard data. Therefore, for a specific endpoint, the hazard data were transformed so it is within the range 0 – 1, with 0 representing the worst level, and 1 representing the best level, as it has been done in previous studies (Zheng et al., 2019). Table S5-5 below specifies to what 0 and 1 in normalised data correspond to in the original data, for each hazard endpoint.

Table S5-5. Levels for each hazard endpoint for normalisation of the data

Parameter	Endpoint	Level 0	Level 1
P	Ready biodegradability	0 [b]	1 [b]
	Half-life soil	Maximum among alternatives [a]	0 [a]
	Half-life sediment	Maximum among alternatives [a]	0 [a]
	Half-life water	Maximum among alternatives [a]	0 [a]
	Half-life air	Maximum among alternatives [a]	0 [a]
	Anaerobic degradation	Minimum among alternatives [c]	1.5 [c]
B	LogKow	Maximum among alternatives [d]	-3 [d]
	BCF	Maximum among alternatives [a]	-1 [a]
M	LogKoc	-2 [a]	Maximum among alternatives [a]
T human	Carcinogenicity	0 [b]	1 [b]
	Mutagenicity	0 [b]	1 [b]
	Reprotoxicity (teratogenicity)	0 [b]	1 [b]
	Acute toxicity (oral, dermal exposure)	1 [a]	Maximum among alternatives [a]
	Skin sensitisation	0 [b]	1 [b]
	Skin irritation	0 [b]	1 [b]
	Eye irritation	0 [b]	1 [b]
	Specific Target Organ Toxicity -Repeated Exposure (oral)	0 [b]	1 [b]
	Endocrine disruption:		1 [b]
	Androgenic	0 [b]	1 [b]
	Estrogenic	0 [b]	1 [b]
	Thyroid	0 [b]	

Parameter	Endpoint	Level 0	Level 1
T env	Algae (EC50)	$1x10^{-6}$ [a]	Maximum among alternatives [a]
	Daphnids acute	$1x10^{-6}$ [a]	Maximum among alternatives [a]
	Fish acute	$1x10^{-6}$ [a]	Maximum among alternatives [a]
	Daphnids chronic	$1x10^{-6}$	Maximum among alternatives
	Fish chronic	$1x10^{-6}$	Maximum among alternatives

a: Same approach as in Zheng et al., 2019; b: for hazard endpoint for which results were expressed qualitatively, the hazard endpoints scores were already normalized, so no transformation was needed; c: for anaerobic degradation, the "best level" was considered to 1.5 as it is the maximum prediction from the QSAR model which was used; d: for log(Kow), it has been considered that a high log(Kow) would represent a greater concern, and the "best level" was assigned arbitrarily to ensure that all the data would be included within the range.

5.5.4.2.2 Data gaps and sensitivity analysis

As it has been done by to Zheng et al. (2019), three different scenarios were considered in order to evaluate the sensitivity of the MCDA models to data gaps. In each scenario, data gaps were replaced by a different value in the normalised data (Zheng et al., 2019):

- A risk neutral scenario, in which the data gaps were replaced by the value 0.5;
- A risk averse scenario, in which data gaps were replaced by the value 0.8;
- A risk seeking scenario, in which data gaps were replaced by the value 0.2.

5.5.4.3 Multicriteria decision analysis methods

5.5.4.3.1 Heatmap

For the heat map, the thresholds of the different categories were determined according to legislation levels (i.e. CLP Regulation) or literature, as suggested by Zheng et al. (2019). For qualitative hazard endpoint which were not considered by Zheng et al. (2019) (e.g. endocrine disruption potential), a similar approach as for other qualitative hazard endpoint (e.g. carcinogenicity) was taken to determine the thresholds. For chronic toxicity on daphnia and fish endpoints, the same threshold as for acute toxicity endpoints were taken. For log(Kow), the threshold were determined based on a report from ECETOC which is linking the bioconcentration factor with the value of log(Kow). Hence, the threshold of log(BCF) were used to determine the threshold for log(Kow). For anaerobic degradation, values from the BIOWIN user guide were taken to set thresholds (US EPA, 2012). Table S5-5 below presents the thresholds of each categories for every hazard endpoints considered.

Table S5-6. Threshold for each colour category to create the heat map

Parameter	Endpoint	RED	ORANGE	YELLOW	GREEN
P	Ready biodegradability[b]	0 – 0.2	0.2 – 0.5	0.5 – 0.8	0.8 – 1
	Half-life soil (days)[a]	>180	120 – 180	60 – 120	<60
	Half-life sediment (days)[a]	>180	120 – 180	60 – 120	<60
	Half-life water (days)[a]	>180	120 – 180	60 – 120	<60
	Half-life air (days)[a]	>180	120 – 180	60 – 120	<60
	Anaerobic degradation[b]	<-0.5	-0.5 – 0	0 – 0.5	>0.5
B	LogKow[b]	[5.71;781]	[5.20;7.71] [7.81;8.10]	[4.41;5.20] [8.10;8.54]	logKow < 4.41 logKow > 8.54
	LogBCF[a]	>3.70	3.30 – 3.70	2.70 – 3.30	<2.70
M	LogKoc[a]	<4.5	4.5 – 6.5	6.5 – 9	>9
T human	Carcinogenicity[a]	0 – 0.2	0.2 – 0.5	0.5 – 0.8	0.8 – 1
	Mutagenicity[a]	0 – 0.2	0.2 – 0.5	0.5 – 0.8	0.8 – 1
	Reprotoxicity (teratogenicity)[a]	0 – 0.2	0.2 – 0.5	0.5 – 0.8	0.8 – 1
	Acute toxicity (oral, dermal) (mg/kg bw)[a]	<50	300 – 50	300 – 2000	>2000
	Skin sensitisation[a]	0 – 0.2	0.2 – 0.5	0.5 – 0.8	0.8 – 1
	Skin irritation[a]	0 – 0.2	0.2 – 0.5	0.5 – 0.8	0.8 – 1
	Eye irritation[a]	0 – 0.2	0.2 – 0.5	0.5 – 0.8	0.8 – 1
	Specific Target Organ Toxicity -Repeated Exposure (oral)[b]	0 – 0.2	0.2 – 0.5	0.5 – 0.8	0.8 – 1
	Endocrine disruption: *Androgenic*[b] *Estrogenic*[b] *Thyroid*[b]	0 – 0.2	0.2 – 0.5	0.5 – 0.8	0.8 – 1
T env	Algae (EC50)[a]	<1	1 – 10	10 – 100	>100
	Daphnids acute[a]	<1	1 – 10	10 – 100	>100
	Fish acute[a]	<1	1 – 10	10 – 100	>100
	Daphnids chronic[b]	<1	1 – 10	10 – 100	>100
	Fish chronic[b]	<1	1 – 10	10 – 100	>100

a: The threshold was taken from Zheng et al. (2019); b: See explanations above

A hazard score was calculated for each alternative by assigning a value to the colour categories in the heat map: red category was scored 4; orange category was scored 3; yellow category was scored 2; green category was scored 1. The final hazard score of an alternative was obtained by summing up

the scores of every hazard endpoint considered. Data gaps were scored 2.5, 3.4 and 1.6 in the risk neutral, risk averse and risk seeking scenarios, respectively.

The resulting heatmaps and the total hazard scores for all alternatives for each case study chemicals and for every scenarios (i.e. risk neutral, risk averse and risk seeking) are presented in Table S5.1 (see online publication for the excel datasheet).

Table S5.1: Heatmap of chemical alternatives for each case study chemical for risk neutral, risk averse and risk seeking scenarios

5.5.4.3.2 Multi-attribute utility theory (MAUT)

In the MAUT approach, partial scores for persistency (P), bioaccumulation potential (B), mobility (M), toxicity to human health and toxicity to the environment (T) were determined by calculating the average value normalised data of the corresponding hazard endpoints. In this study it was assumed that every hazard endpoint is equally important and therefore have the same weight in the decision-making. Hence, the final PBMT scores of each alternative was determined by summing up all partial scores for P, B, M and T. Potential alternatives were then compared between each other and with the substance to phase out based on their final PBMT score. It was assumed that the alternative with a higher PBMT score could be considered as safer. Figure S5-2 below is presenting the final PBMT scores for every alternative to each case study chemicals in the risk neutral, risk averse and risk seeking scenarios.

The data used for the MAUT approach are presented in Tables S5.2A, 2B and 2C (datasheets available in the online publication) .

Table S5.2A: Data used in the MAUT approach to identify safer alternatives to Allura Red
Table S5.2A: Data used in the MAUT approach to identify safer alternatives to Benzophenone-4
Table S5.2A: Data used in the MAUT approach to identify safer alternatives to Climbazole

Data for the risk neutral, risk averse and risk seeking scenarios is presented on the same sheet.

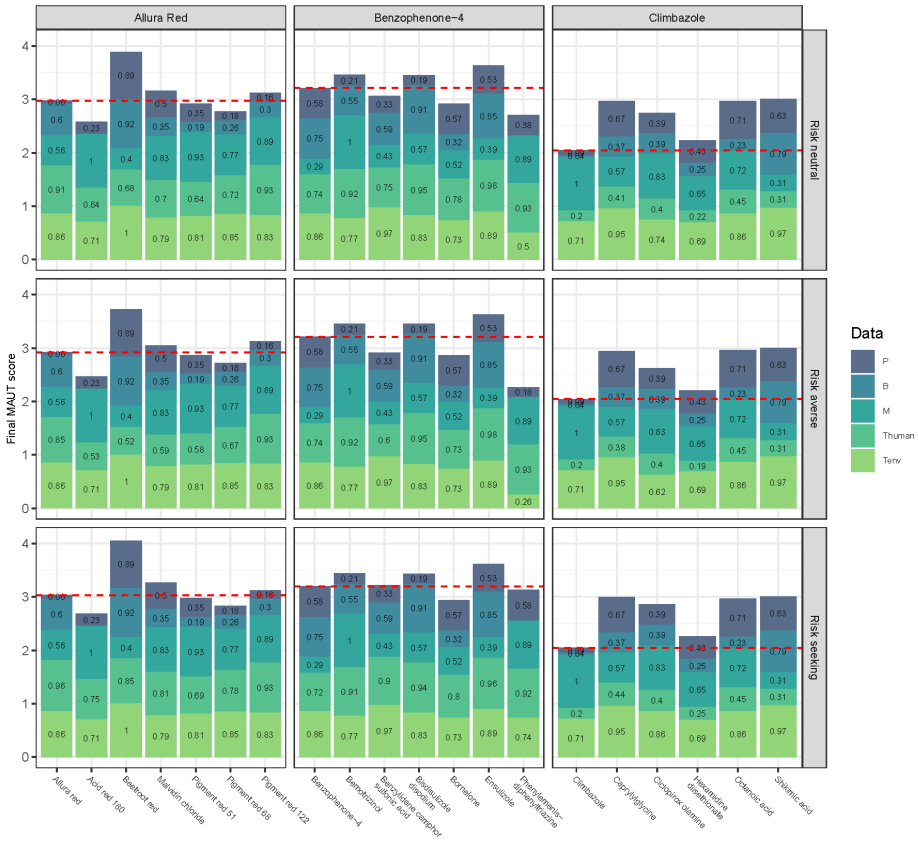


Figure S5-3. Results of the MAUT assessment of the three different case-study chemicals and shortlisted alternative substances for three different scenarios to treat data gaps. In the risk neutral, risk averse and risk seeking scenario data gaps were assigned a value of 0.5, 0.2 and 0.8, respectively. The red dashed line represent the final PBMT score of the substance to phase out. Every alternatives with a higher PBMT socre were considered as safer.

5.5.4.3.3 ELECTREIII

ELECTRE III is an outranking approach that compares different alternatives with each other (Rowley et al., 2012). Three important thresholds for each hazard endpoint are necessary for this method: the indifference threshold (*a*), the preference threshold (*b*), and the veto threshold (*c*). In short, when comparing to alternatives for one hazard endpoint, if the difference between the two alternatives is lower than *a*, then the weight of the hazard endpoint is set to 0; if the difference is greater than *b,* then the full weight of the hazard endpoint considered is awarded to the superior alternative. At last, if the difference is as large as *c*, the ELECTRE III method eliminates the underperforming alternative from contention.

The method to determine the value of each threshold for every hazard endpoint was inspired by Zheng et al. (2019). The thresholds for a specific hazard endpoint were determined based on the difference between the level 0 and the level 1 in the MAUT approach for the endpoint. The equations to determine each threshold are provided below.

$$Indifference_{Endpoint\ A} = 0.25 * (Endpoint\ A_{Level\ 1\ in\ MAUT} - Endpoint\ A_{Level\ 0\ in\ MAUT})$$

$$Preference_{Endpoint\ A} = 0.5 * (Endpoint\ A_{Level\ 1\ in\ MAUT} - Endpoint\ A_{Level\ 0\ in\ MAUT})$$

$$Veto_{Endpoint\ A} = 0.5 * (Endpoint\ A_{Level\ 1\ in\ MAUT} - Endpoint\ A_{Level\ 0\ in\ MAUT})$$

The alternatives were then ranked based on the results of the comparison on P, B, M, and T. In this study it was assumed that every hazard endpoint is equally important and therefore have the same weight in the decision-making. The alternative with a higher rank was considered as safer.

The data used for the MAUT approach are presented in the datasheets available via the online publication in Tables S5.3A, 3B and 3C.

Table S5.3A: Data used in the ELECTRE III approach to identify safer alternatives to Allura Red
Table S5.3B: Data used in the ELECTRE III approach to identify safer alternatives to Benzophenone-4
Table S5.3C: Data used in the ELECTRE III approach to identify safer alternatives to Climbazole

Each table is separated into three Excel sheets to present data for the risk neutral, risk averse and risk seeking scenarios.

CHAPTER SIX

WASTE STAGE | EUROPEAN-WIDE SPATIAL ANALYSIS OF SEWAGE TREATMENT PLANTS AND THE POSSIBLE BENEFITS OF ADVANCED TREATMENT TO REDUCE PHARMACEUTICAL EMISSIONS

Chapter 6 - Waste Stage | European-wide spatial analysis of sewage treatment plants and the possible benefits of advanced treatment to reduce pharmaceutical emissions

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Abstract

Pharmaceuticals are known to widely occur in the environment and to affect the health of ecosystems. Sewage treatment plants (STPs) are main emission pathways for pharmaceuticals, which are often not sufficiently removed during wastewater treatment. In Europe, STP treatment requirements are specified under the Urban WasteWater Treatment Directive (UWWTD). The introduction of advanced treatment techniques, such as ozonation and activated carbon, under the UWWTD is expected to be an important option to reduce pharmaceutical emissions. In this study, we present a European-wide analysis of STPs reported under the UWWTD, their current treatment level and potential to remove a set of 58 prioritised pharmaceuticals. Three different scenarios were analysed to show 1) UWWTD present effectiveness, 2) the effectiveness at full UWWTD compliance, and 3) the effectiveness when advanced treatment is implemented at STPs with a treatment capacity of >100.000 person equivalents. Based on a literature study, the potential of individual STPs to reduce pharmaceutical emissions ranged from an average of 9% for STPs with primary treatment to 84% for STPs applying advanced treatment. Results of our calculations show that European-wide emission of pharmaceuticals can be reduced with 68% when large STPs are updated with advanced treatment, but spatial differences exist. We argue that adequate attention should also be paid with regards to preventing environmental impacts of STPs with a capacity <100.000 p.e.. Circa 44% of total STP effluent is emitted near Natura2000 sites (EU nature protection areas). Of all surface waters receiving STP effluent for which the ecological status has been assessed under the Water Framework Directive, 77% have a status of less than good. Relatively often only primary treatment is applied to wastewater emitted into coastal waters. This analysis can be used to further model pharmaceutical concentrations in European surface waters, to identify STPs for which more advanced treatment might be required and to protect EU aquatic biodiversity.

Abbreviations

EEA	European Environment Agency	STP	Sewage Treatment Plants
p.e.	Population Equivalent	UWWTD	Urban WasteWater Treatment Directive
RBD	River Basin District	WFD	Water Framework Directive

6.1 Introduction

Pharmaceuticals help to increase the longevity and quality of life for many people. However, the widespread use of human and veterinary pharmaceuticals also results in releases to the aquatic environment (aus der Beek et al., 2016). This is of concern as most pharmaceuticals are designed to be highly active at low concentrations and resistant to biodegradation (Khetan and Collins, 2007). Active pharmaceutical ingredients and their transformation products have widely been detected in surface water, groundwater and drinking water (Houtman et al., 2014; Schulze et al., 2019; Zhou et al., 2019). At some locations pharmaceuticals are already present at levels deemed unsafe, classifying them as a global threat to both human and environmental health (Wilkinson et al., 2022). The global consumption of pharmaceuticals has increased over the last decades (E. Y. Klein et al., 2018) and is expected to rise further due to multiple factors, including changes and innovations in clinical practices, aging populations and higher market availability, potentially amplifying already existing environmental concentrations (Belloni et al., 2016; Bernhardt et al., 2017; Bunke et al., 2019; Nagesh et al., 2022; OECD, 2021b).

Pharmaceuticals may be emitted as a result from production, patient excretion and incorrect disposal (Straub, 2016). In order to protect water sources from pharmaceutical pollution, multiple actions can be taken over the whole chemical life cycle (OECD, 2019; van Wezel et al., 2017). Options early in the chemical life cycle, include the design of Safe and Sustainable substances and personalised healthcare, are often preferred as they are more cost-effective (Puhlmann et al., 2021). Via patient excrements, pharmaceuticals and their metabolites can enter the wastewater systems where they are not sufficiently removed and are consequently released into the environment (Luo et al., 2014). End-of-pipe measures such as the treatment of wastewater will remain indispensable, as it is clear that pharmaceuticals will continue to be needed and will thus continue to be released into the wastewater (Kümmerer et al., 2018). Sewage treatment plants (STPs) are of special relevance as households are seen as one of the most important emission sources of pharmaceuticals to wastewater (Adeleye et al., 2022; Comber et al., 2015; Michael et al., 2013), except for specific types of pharmaceuticals which are mainly emitted via hospitals and health institutions (Herrmann et al., 2015; Le Corre et al., 2012).

In the EU, the Water Framework Directive (WFD) is implemented to protect surface waters, transitional waters, coastal waters and groundwater (Directive 2000/60/EC). A key aim of the WFD is to achieve a 'good ecological status' for all water bodies, which is influenced among others by water quality. Measurements according to the WFD regularly take place within Natura2000 sites; a network of key breeding and resting sites for rare and threatened species, and some rare natural habitat types that the WFD (Annex V No. 1.3.5) specifically refers to. A good ecological condition of aquatic systems is important to ensure delivery of ecosystem services in the future (Grizzetti et al., 2019), and an important aim of the EU Biodiversity Strategy (European

Commission, 2020e). According to the latest assessment, however, a good ecological status has only been achieved for 40% of European surface waters, and chemicals released via STPs are identified as one of the main pressures on these surface water bodies (EEA, 2018a; Lemm et al., 2021).

The WFD also links to the EU Urban Wastewater Treatment Directive (UWWTD, 91/271/EEC). The objective of this Directive is to protect the environment against adverse effects of urban waste water, and concerns its collection, treatment and discharge. The UWWTD sets maximum concentrations for the nitrogen, phosphorous and organic matter content for treated wastewater, but does not address micropollutants such as pharmaceuticals yet. The WFD does include several pharmaceutical substances on the so-called 'Watch List' (European Commission, 2022c). In the proposal for a revised UWWTD, the European Commission lays down the aim to implement advanced treatment to STPs treating a load equal to or greater than 100.000 person equivalents (p.e.) by 31 December 2035 at the latest (European Commission, 2022d). As also mentioned in the Strategic Approach to Pharmaceuticals in the Environment, the European Commission will investigate the feasibility of upgrading selected STPs to more advanced treatment technologies (European Commission, 2020f).

A wide range of advanced treatment methods have been investigated for the removal of pharmaceuticals from wastewater, for which either ozonation or activated carbon treatment are reported to be the best performing and most cost-effective (Kosek et al., 2020; Logar et al., 2014; Rout et al., 2021). Advanced treatment techniques have already been implemented in Switzerland at selected STPs as part of the Swiss water conservation legislation introduced in 2016 (Stamm et al., 2015). By following this approach, the pressure of pollution on Swiss surface waters is estimated to be reduced by 50% (FOEN, 2015). A recent study by (Pistocchi et al., 2022a) estimates that by following a similar approach in the entire EU, the cumulative toxicity of STP effluent will be reduced by circa 36%. Certain knowledge gaps however still remain. For example, removal rates as used in the Pistocchi et al. (2022) study were mainly assumed using models. This results in high uncertainties as it is still difficult to generically model the fate of chemicals in advanced treatment processes due to the influence of, amongst others, specific process conditions (Fischer et al., 2019). Inclusion of experimental data might provide better insights in the removal of chemicals in STPs and reduce uncertainties (Pistocchi et al., 2022).

In this study, experimental removal rates are derived from an extensive literature research. Next, we aim to assess the effectiveness of European STPs to reduce pharmaceutical emissions for a 1) Present, 2) Full Compliance and 3) Advanced Treatment scenario. In addition, spatial variation between European STPs are assessed for all European river basins taking into account their ecological status as assessed under the WFD, as well as proximity to Natura 2000 sites. For the Advanced Treatment scenario, we follow the approach by Pistocchi et al. (2022) in order to show the present effectiveness and the possible value of introducing advanced treatment at large STPs (>100 000 p.e.).

6.2 Methods

6.2.1 Waste water treatment scenarios

Three different scenarios were analysed in this study. For every STP in the EU, we considered 1) the present level of treatment (Present scenario), 2) full compliance with the UWWTD in its current form (Full Compliance scenario) and 3) a scenario where more advanced treatment, either with ozonation or activated carbon, is required at large STPs (Advanced Treatment scenario). For the Full Compliance scenario, envisioned changes to non-compliant STPs as reported under article 17 of the UWWTD were used to calculate the total capacity (in p.e.) per treatment level (EEA, 2022a). For the Full Compliance and the Advanced Treatment scenarios, it was also assumed that 100% of the population is connected to a STP. In addition, for the Advanced Treatment scenario, all STPs with a capacity of ≥100.000 p.e. were assigned with advanced treatment (ozonation or activated carbon).

In Figure 6.1 a workflow is presented to calculate the population (in p.e.) per treatment level. First, data collected under Article 15 of the UWWTD for the year 2020 and reported in Waterbase v8 (EEA, 2022a) was used to assign treatment levels to individual STPs for the present scenario. Waterbase contains information on the location and characteristics of urban STPs with generated wastewater loads above 2 000 population equivalents (p.e.) for all EU member states. Based on availability of data, 23.568 STPs were selected for our assessment. See SI1 for more detailed description on steps taken to filter the data. Treatment levels were defined following UWWTD and OECD definitions

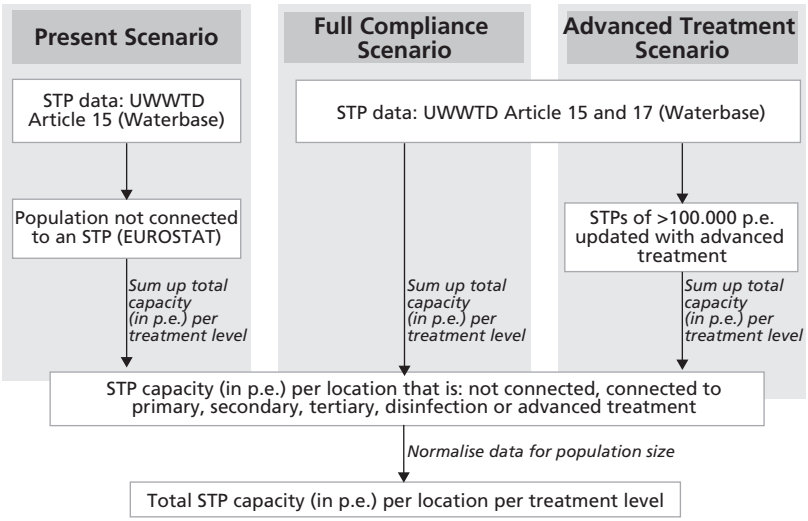

Figure 6. 1. Workflow for calculating the total population per European region that is connected to a certain treatment level under the Present, Full Compliance and Advanced Treatment Scenarios.

Table 6. 1. Overview of the different European regions defined in this study

Region	Countries	Total population (in 2020 or 2019)
North	Norway, Sweden, Finland	16.387.131
Central	Austria, Belgium, Denmark, Germany, Ireland, Luxembourg, the Netherlands, the United Kingdom	200.242.146
South	Cyprus, Greece, France, Italy, Malta, Spain, Portugal	197.187.604
East	Czechia, Estonia, Hungary, Latvia, Lithuania, Poland, Slovenia, Slovakia	71.990.553
South-East	Bulgaria, Croatia, Romania	30.286.952

(OECD, 2003) as primary, secondary, tertiary, disinfection or advanced treatment (ozonation or activated carbon). Next, the total capacity (in p.e.) per treatment level was calculated for 5 regions in Europe (see Table 6.1), defined according to divisions used in the EEA indicator assessment (EEA, 2017). Data on the total STP capacity per treatment level was combined with Eurostat data on the percentage of residents that is not connected to STPs (Eurostat, 2022a). At time of the analysis, Eurostat contained data till 2019. Hence, for most countries data for the year 2019 was used or the latest data available in the database. Details on the percentage of residents per member state that are not connected an STP are shown in the supplementary information (Table S6-1).

6.2.2 Selected pharmaceuticals and their STP removal rates

A list of 58 pharmaceuticals posing the highest risk to aquatic systems was compiled based on already existing prioritisation lists, including both parent compounds and metabolites (de Voogt et al., 2009; European Commission, 2020g; FOEN, 2015; NORMAN Network, 2014; Zhou et al., 2019). Removal efficiencies of these substances by different wastewater treatment techniques were collected in the scientific literature. According to the approach first introduced in Switzerland, upgraded STPs will contain either ozonation or activated carbon treatment. The removal rates of STPs that apply ozonation or activated carbon were combined in this study and averaged to obtain the removal rate for advanced treatment. Based on the identified references (63 in total), removal rates were calculated per pharmaceutical per STP with a specific treatment type. Only total removal rates were used from full scale STPs which apply a combination of techniques. Next, the average removal rate over all substances was used to estimate the fraction being released to the environment and being removed per treatment level. A more extensive description of the literature search and calculation method is given in the supplementary information.

6.2.3 Spatial analysis

The location of STPs and their proximity to Natura2000 sites was assessed by using a buffer of 2.000 meter as in line with an earlier defined non-binding buffer zone (EEA, 2018b). Natura2000 sites were available for all countries except Norway and the United Kingdom (EEA, 2022b).

STP data was also combined with data on the ecological status (or potential) of water bodies in order to assess the total STP effluent (in p.e.) emitted into water bodies with a good or less than good ecological status. The ecological status of water bodies as defined under the 2nd River Basin Management Plans was derived from the WISE Water Framework Directive Database (EEA, 2021). Out of the 23.568 STPs reported under the UWWTD, information on the ecological status of water bodies into which effluent is emitted was available for 15.950 STPs. A more detailed description on how the datasets were combined is provided in the supplementary information. All data analysis was performed in R and QGIS.

6.3 Results and Discussion

6.3.1 Removal rates of pharmaceuticals in STPs

The removal rates of the 58 pharmaceuticals taken into account in this study for different STP treatment levels are shown in Figure 6.2. For a couple of substances (e.g. acetaminophen, atenolol, carbamazepine, diclofenac, ibuprofen and sulfamethoxazole) relatively many data were available, whereas for other substances only few studies or no data could be found. Details on removal rates for individual substances can be found in the online data repository (van Dijk et al., 2023). Specifically for primary and tertiary treatment, up to 50% of individual pharmaceutical the literature search did not yield removal rates (black cells in Figure 6.2). This can impact the validity and reliability of our analysis and potentially bias the calculated average STP removal rates. The calculated removal rates are furthermore biased by the compounds selected in this study. In the future, data gaps might be partly filled by using modelling approaches such as SimpleTreat (Struijs, 2014). However, SimpleTreat can only be used to calculate removal for primary and secondary treatment. Data gaps from the literature were partly found due to incomplete reporting of measured data on STP substance removal in the studies. Future studies would benefit from more transparent and accessible data on STP removal efficiencies (Fischer et al., 2019). It's important to acknowledge that our assessment may not cover all relevant pharmaceuticals, as pollution can vary by location and time, and there are a multitude of factors that can influence which pharmaceuticals are present in wastewater (Bunke et al., 2019; Massei et al., 2018; van Gils et al., 2019). Furthermore, it should be noted that this study focused solely on pharmaceuticals, and did not consider other types of substances such as biocides and chemicals registered under REACH. These substances can however also be important sources of pollution in surface waters (Posthuma et

al., 2018; van Gils et al., 2020). When averaging the collected removal rates of all 58 pharmaceuticals per treatment and excluding data gaps, primary treatment has a removal potential of circa 9% (±11), secondary treatment of 42% (±27), tertiary treatment of 42% (±27), disinfection of 66% (±29) and advanced treatment of 84% (±20) (Table 2). Average removal rates of advanced treatment lie above the removal criteria of ≥80% earlier laid down in Switzerland (FOEN, 2015). Based on our analysis, six substances (Cyclophosphamide, Fluconazole, Gabapentin, Irbesartan, Oxypurinol, Sulfadiazine) are however expected to not be well removed by ozonation or activated carbon treatment (Figure 6.2). No significant difference (p value of 0.05) between ozonation and active carbon treatment was found (supplementary Information). Furthermore, no significant difference between removal efficiencies of secondary and tertiary treatment was found, as well as between tertiary and disinfection treatment (supplementary information, Table SI6-5). These findings can help to generate a better picture of pharmaceutical emissions to water bodies as most modelling exercises to date (e.g. in Oldenkamp et al., 2018; van Gils et al., 2020) rely on STP models such SimpleTreat and therefore only consider the fate and removal during primary and secondary treatment (Lautz et al., 2017; Struijs, 2014).

Table 6.2. Descriptive statistical parameters for STPs applying Primary, Secondary, Tertiary, Disinfection, Ozonation, Activated Carbon and Advanced treatments. Advanced treatment was calculated as the average from ozonation and activated carbon.

Treatment Level	Number of substances with data (out of 58)	Average removal (%)	Stdv (%)	Min. removal (%)	Max removal (%)	Median removal (%)
Primary	26	9	11	0	41	5
Secondary	55	42	27	0	99	42
Tertiary	33	42	27	5	99	40
Disinfection	43	66	29	0	100	68
Ozonation	50	87	16	27	100	93
Activated carbon	41	81	18	27	99	88
Advanced	50	84	20	27	100	89

6.3.2 Removal rates and substance characteristics

Primary treatment intends to reduce the solid content of the wastewater (oils and fats, grease, sand, grit and settleable solids). Based on our search only 9% of the total pharmaceutical load can potentially be removed, which is in line with earlier reported total removal rates (Greenham et al., 2019). Substance removal by secondary treatment mainly depends on the sorption on the sewage

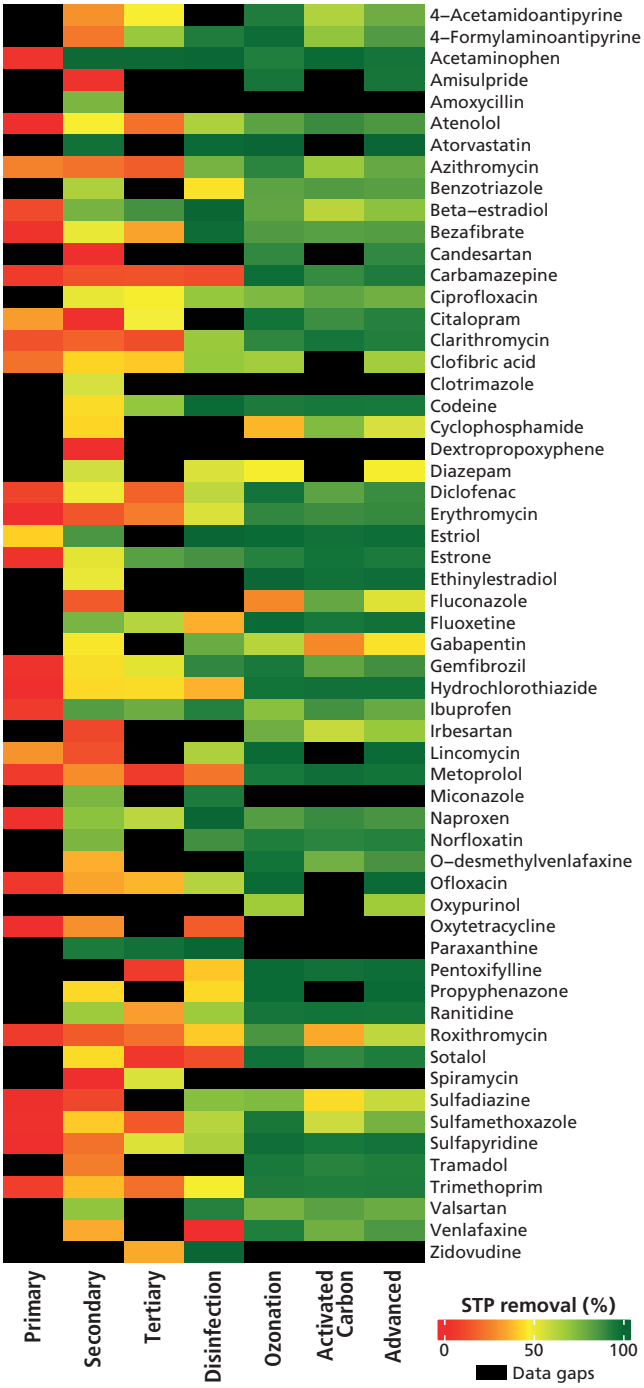

Figure 6.2. Heatmap of the 58 pharmaceuticals and their removal rates in STPs by different treatment techniques. Removal rates refer to the removal by individual treatment levels. Data gaps are shown in black. Full calculations and references on the removal rates are reported in the open data repository (van Dijk et al., 2023).

sludge and their degradation or transformation during the treatment, and therefore likely removes the more hydrophobic and degradable pharmaceuticals (Michael et al., 2013). With regards to advanced treatment -ozonation or activated carbon- overall removal efficiencies are found to be similar in this study however differences might exist for the removal of some specific compounds. Treatment with activated carbon can for example be used for removing many hydrophobic and also some charged pharmaceuticals from water, whilst high removal after ozonation is usually observed for pharmaceuticals with one or more functional groups such as non-aromatic carbon-carbon double bonds, amines and activated aromatic rings and moieties (Ikehata et al., 2006; Michael et al., 2013). Polar chemicals are usually less well removed in STPs (Fischer et al., 2019; Gollong et al., 2022; Sjerps et al., 2021). Moreover, removal rates for non-aromatic compounds by activated carbon is often low, whilst compounds with unoxidable bonds are able to survive ozonation treatments (Hale et al., 2022). Additionally, ozonation can lead to the formation of undesired and highly reactive by-products. Hence, while ozonation and activated carbon can be effective in removing certain contaminants, they are not universally applicable. Following the approach reported by Pronk et al. (2020), who proposed a framework to estimate removal efficiencies of water treatment techniques based on substance characteristics, we could not identify a clear trend between substance properties and removal rates. This might be caused by different study designs or differences in the actual STP removal efficiency due to variations in i) quality of waste water entering the STPs, ii) operating conditions such as sludge retention time, hydraulic retention time and flow rate, and iii) other factors such as difference in climate (McLachlan et al., 2022; Michael et al., 2013; Pomiès et al., 2013; Yang et al., 2017).

6.3.3 Total STP removal potential

The Sankey diagrams of Figure 6.3a-3c show to what type of STP treatment level the population is connected and how the fraction of pharmaceuticals is removed or emitted to the environment. At present, the potential to reduce environmental emissions of pharmaceuticals of all European STPs combined is 48% (± 27) (Figure 6.3a). South-East Europe has currently the highest percentage of untreated wastewater. Around 25% of urban wastewater in this region is emitted without any treatment into freshwater systems. Other differences in treatment level can be observed for specific countries (Figure 6.4). For example, in Southern Europe disinfection is applied relatively often even though this is not required under the UWWTD. This is likely the effect of national legislations. In Italy, for example, a disinfection step needs to be implemented at STPs with a capacity of 2000 p.e. or higher (Collivignarelli et al., 2017).

When full compliance would be reached with the current UWWTD, the STP removal potential is slightly increased to 52% (± 28) (Figure 6.3b). Most changes in the Full Compliance scenario are observed in South, East and South-East Europe (Figure 6.5) as -despite improvements over the last few years- these regions currently remain least compliant with the UWWTD (European

Commission, 2022e). The fact that the current UWWTD has no focus on micropollutants such as pharmaceuticals is reflected by the relatively small increase of the STP potential to reduce pharmaceutical emissions in this Full Compliance scenario. Full compliance to the UWWTD is expected to mainly reduce the nutrient and microorganism loads of wastewater. In the Advanced Treatment scenario, the emission reduction potential for the selected pharmaceuticals is increased to 69% (± 22) (Figure 6.3c). Advanced treatment is placed in bigger cities, and therefore most changes in this scenario are observed in more densely populated areas (Figure 6.6).

In this study only STPs reported under the UWWTD were taken into account, meaning STPs with a capacity of <2 000 p.e. are not included. 364 650 agglomerations with a capacity of 2000 p.e. or less -corresponding to circa 75 million inhabitants- have been identified and are predicted to impact receiving water bodies. The percentage of small agglomerations was on average higher in Czechia, Slovakia, Croatia, Slovenia, Romania and Poland (Pistocchi et al., 2022b). Future updates to the UWWTD will likely include smaller STPs in the UWWTD dataset (European Commission, 2022f), resulting in an completer picture of European STPs and their potential to reduce environmental emission of pharmaceuticals.

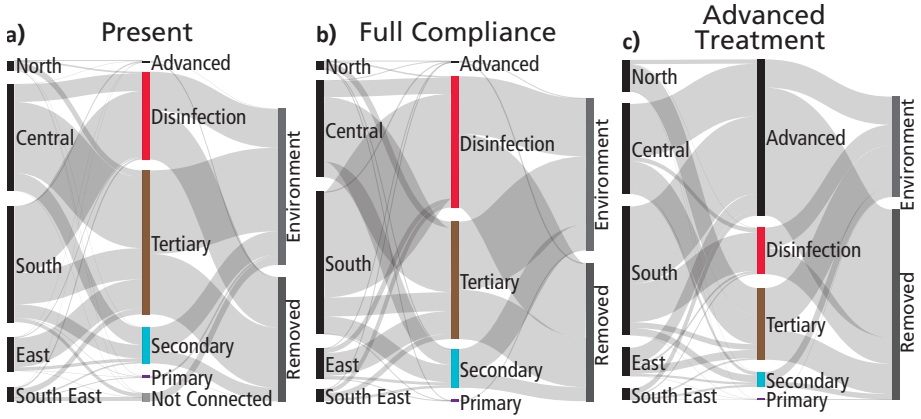

Figure 6.3. The share of the European population connected to each type of STP treatment level and the percentage of pharmaceuticals that are either removed ('removed') or emitted ('environment') via STPs for each European region. Panel A represents the 'Present' scenario, Panel B the 'Full Compliance' scenario, and Panel C the 'Advanced Treatment' scenario, with a respective pharmaceutical emission reduction potential of 48% (±27), 52% (±28) and 69% (±22).

6.3.4 Spatial analysis

6.3.4.1 Water body types

For present day conditions, relatively often only primary treatment is applied to STPs emitting into coastal waters as compared to STPs that emit into estuaries or fresh water bodies (Figure 6.7). This can also be seen in Figure 6.4, in which the geographical location of all STP and their treatment level under present day conditions are shown. Main reason for this is that the UWWTD does not specifically protect marine waters and many STPs are exempted from stricter treatment when primary treatment is in place (Article 2 (7) UWWTD). This is not in line with the WFD, which does specifically cover marine systems. The treatment level of STPs emitting into coastal waters improves under the Advanced Treatment scenario at more densely populated areas. However, in other coastal areas from e.g. Norway and Croatia mainly primary treatment is applied under all scenarios (Figure 6.4 and Figure SI6-1). This is reason of concern as pharmaceutical pollution already affects marine ecosystems (Fabbri and Franzellitti, 2016; Mezzelani et al., 2018). Under the Advanced Treatment scenario, treatment level is improved for STPs emitting into all water types. STP effluent emitted into lakes also receive relatively lower treatment compared to rivers and transitional waters. Different water body types may respond different to (chemical) stressors (Birk et al., 2020; Reid et al., 2019). STPs emitting into smaller water bodies (Figure SI6-2) might be prioritised as, for example, large rivers are reported to be less impacted by chemical pollution due to their higher dilution capacity compared to other river types (Lemm et al., 2021). Future modelling studies should furthermore take chemical consumption data into account to assess whether water bodies and their ecosystems are sufficiently protected and to make (cost-)effective decisions in water quality management with regards to implementation of advanced treatment techniques (Coppens et al., 2015).

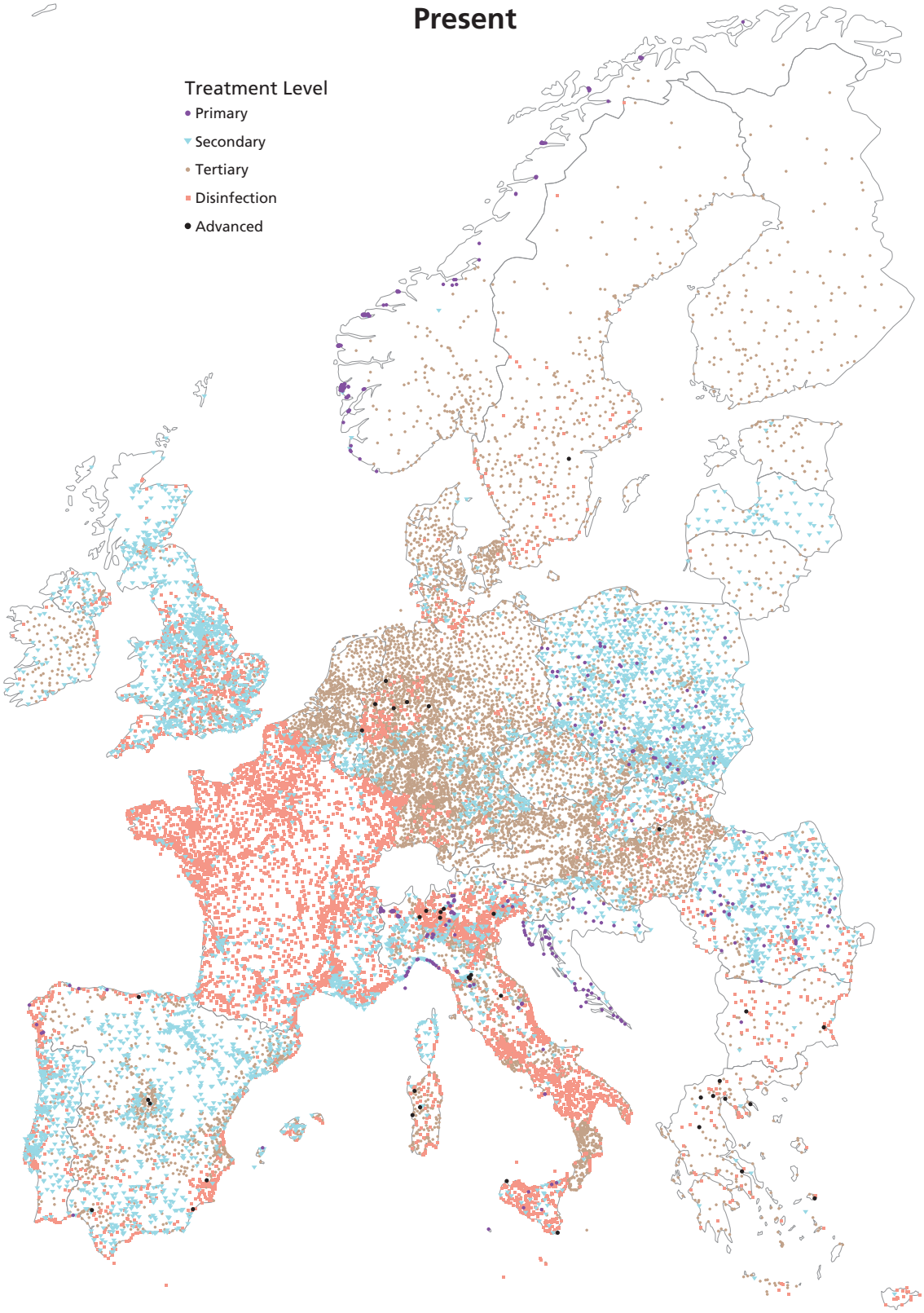

Figure 6.4. STPs and their treatment level under the Present Scenario.

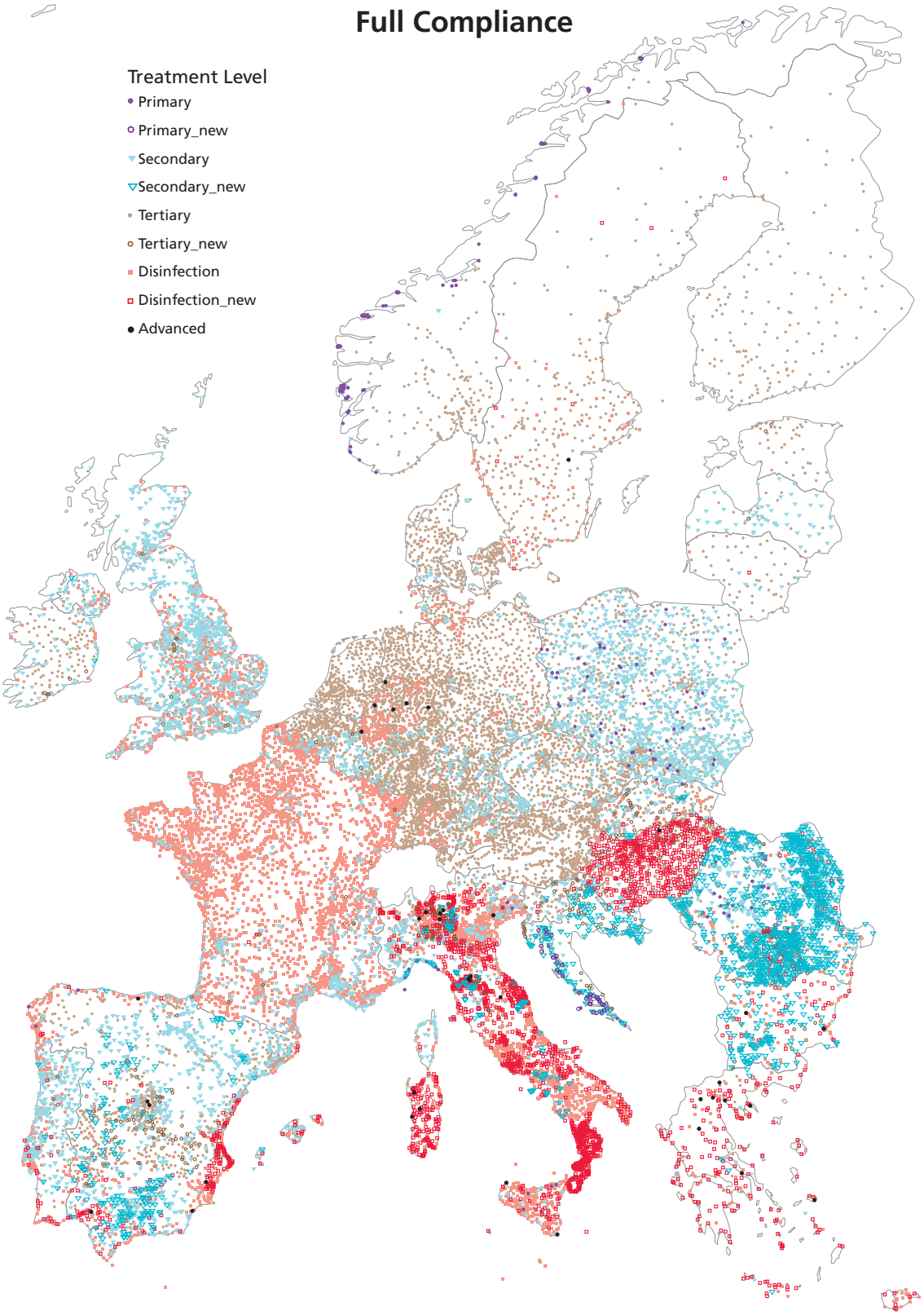

Figure 6.5. STPs and their treatment level under the Full Compliance Scenario. New or upgraded STPs are shown in the figure as Primary_new, Secondary_new, Tertiary_new and Disinfection_new.

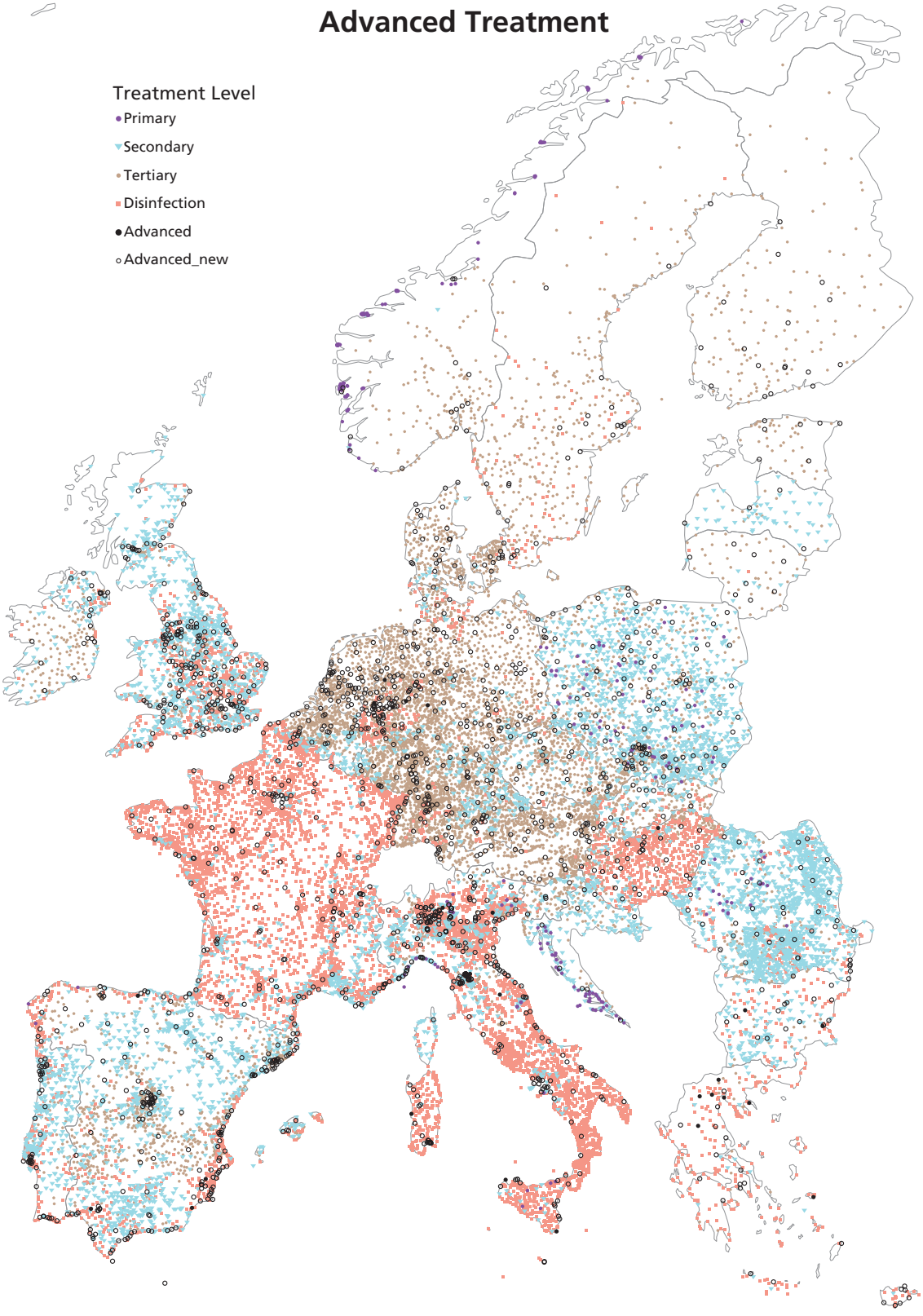

Figure 6.6. STPs and their treatment level under the Advanced Treatment Scenario. The large STPs that will be upgraded with advanced treatment are shown in the figure as Advanced_new.

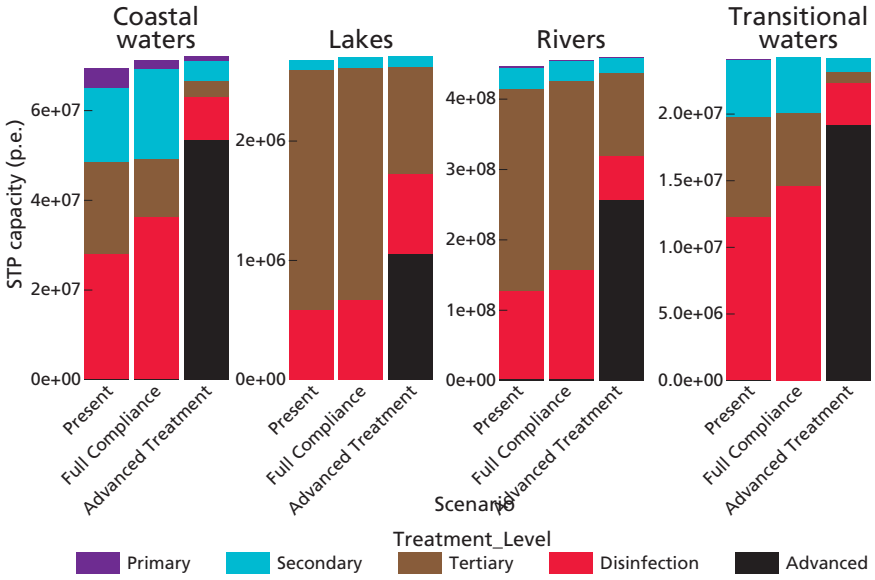

Figure 6.7. Total amount of treated STP effluent (in p.e.) per that is emitted into coastal waters, lakes, rivers and transitional waters (waters between land and sea, including fjords, estuaries, lagoons and deltas) under the Present, Full Compliance and Advanced Treatment scenarios.

6.3.4.2 Ecological status under the WFD

At present, 15.950 out of the 23.568 STPs (with a total treatment capacity of 5.4e+8 p.e.) emit treated effluent into a surface water bodies for which information on the ecological status was available. From Figure 6.8 it can be observed that most (12.396 STPs; with a total treatment capacity of 4.5e+8 p.e.) of these 15.950 STPs emit treated wastewater into water bodies which have a less than good ecological status, while water bodies with a good or high ecological status are influenced by less than 1e+8 p.e. Few changes are observed with regards to STP treatment levels under the Full Compliance scenario compared to the Present scenario (Figures SI1.6 and SI1.7). The Full Compliance scenario, based on envisioned changes reported under Article 17 of the UWWTD, primarily involves improving the performance of existing underperforming STPs through maintenance or expansion. It is anticipated that such changes will mainly lead to a reduction in nutrient enrichment of surface waters, which is one of the main pressures hampering a good ecological status of water bodies together with chemical pollution and habitat alterations (EEA, 2018a). In the Advanced Treatment scenario 809 (total treatment capacity of 2.8e+8 p.e.) out of the 15.950 STPs are updated with advanced treatment (Figure 6.8), which has the potential to reduce the pressure of chemical pollution and improve their ecological status.

Management of water at the river basin level is key for implementing the WFD. Under all scenarios, only primary or secondary treatment techniques are applied to most of the generated wastewater

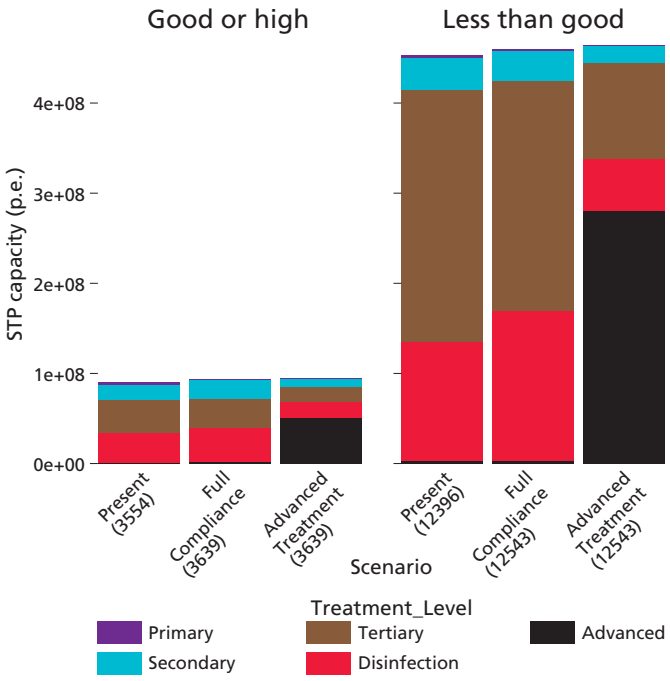

Figure 6.8. European wide analysis of the total STP capacity (in p.e.) per treatment level that emits into water bodies with a good or less than good ecological status as assessed under the WFD. Total number of water bodies are shown in brackets.

load in some river basin districts (RBDs) in Croatia, France, Norway, Poland, Portugal and the UK (Figure SI1.5), whereas some waterbodies in these RBDs have a less than good ecological status (EEA, 2021). Next to prioritization based on a p.e. cut-off, it may be beneficial to prioritise STPs for advanced treatment based on the ecological status. All relevant pressures need to be considered in order to make decisions on the implementation of advanced techniques or other measures to help restore and protect freshwater ecosystems (Carvalho et al., 2019; Lemm et al., 2021, 2019).

6.3.4.3 Natura2000 sites

At present, circa 44% of all treated effluent (corresponding to 3.1e+8 p.e.) is emitted directly within Natura2000 sites or the 2km buffer zone (Figure 6.9). Most of the effluent undergoes tertiary treatment. When envisioned changes reported under article 17 of the UWWTD are made under the Full Compliance scenario, some STPs are no longer used and new STPs are constructed. Outside Natura2000 sites this will result in an increase of total treated effluent, and an increase in the amount of effluent treated with a disinfection step. For STPs emitting in or close to Natura2000 however relatively few changes are observed. Under the Advanced Treatment scenario, 38% of all effluent will be treated with advanced treatment. Then, no difference in treatment level can

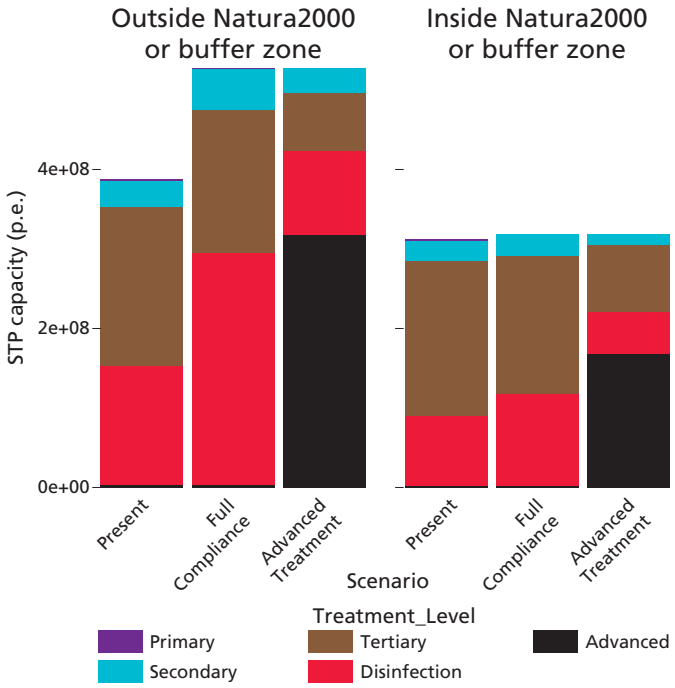

Figure 6.9. European wide analysis of the total STP capacity (in p.e.) per treatment level that is emitted outside or inside a Natura2000 area or the 2,000m buffer zone under the Present, Full Compliance and Advanced Treatment scenarios.

be observed between STPs located near and further away from Natura2000 areas in any of the scenarios. As STPs are identified as one of the main stressors affecting ecological status (EEA, 2018a; Lemm et al., 2021), STPs emitting effluent emitted near Natura2000 sites could be prioritised for implementation of advanced treatment as well. This might especially be relevant in Central Europe, as here the smallest share of effluent is treated with advanced treatment steps (Figure SI6-3).

6.3.5 Benefits and considerations of advanced treatment

Given that not all substances are sufficiently removed by advanced treatment techniques and that it is not feasible to update all STPs (Pistocchi et al., 2022b), other measures focussing on input prevention need to be considered as well (Kümmerer et al., 2019; van Wezel et al., 2017). Furthermore, the increased use of chemicals (Bunke et al., 2019; Nagesh et al., 2022) and demand for clean water (Boretti and Rosa, 2019) asks for a paradigm shift in wastewater management where adequately treated wastewater can for example be re-used (Dingemans et al., 2020; Villarín and Merel, 2020). Climate change is projected to further reduce water availability in sufficient quantity and quality, emphasising the importance of such water reuse practices.

The current study may be used to further model pharmaceutical concentrations in European surface waters and to identify STPs for which more advanced treatment might be required and to protect EU aquatic biodiversity. This study did not aim to assess what advanced treatment should be implemented. The most suitable treatment technique depends on a multitude of factors and will most likely be location specific. For example, ozonation may result in the formation of toxic by-products, which is why a post-treatment step with a biological active sand filter is recommended (von Gunten, 2018). On the other hand, ozonation is unlike activated carbon treatment effective in the inactivation of bacteria. Consequently, when stringent limits for reuse are requested, an additional disinfection step might be needed for when activated carbon is implemented. In addition, other environmental burdens than risks of chemicals need to be assessed. Treatment with ozonation is for example associated with higher environmental impacts due to its high energy consumption (Ganora et al., 2019; Pistocchi et al., 2022b). One of the aims laid down in the UWWTD proposal is to achieve energy neutrality in the wastewater sector by 2040 (European Commission, 2022d). The use of renewable energy resources might help achieve this aim and lower the negative impacts of advanced treatments (Lutterbeck et al., 2020). All this emphasises the need for integrated assessments before deciding whether an STP needs to be updated with advanced treatment (Pistocchi et al., 2017; Schuwirth et al., 2018).

6.4 Conclusion

Treatment of wastewater is a key component to reduce environmental emissions of pharmaceuticals. Here, we showed that implementing advanced treatment at STPs with a capacity of >100.000 p.e. will improve the total pharmaceutical emission reduction potential of STPs in Europe from 48% to 69% based on a set of 58 priority pharmaceuticals. This set of the 58 pharmaceuticals was based on existing prioritisation lists and covers a wide variety of (physical-chemical) properties and different use categories. Average STP removal efficiencies ranged from 9% for primary treatment to 84% for advanced treatment. The data collected in this study can be complemented with other substance types, such as biocides and REACH registered chemicals, and consumption data to obtain a better understanding of the total chemical pressure on water bodies.

Spatial differences with regard to implemented STP treatment levels exist under all three scenarios. Coastal waters and lakes seem for example not as well protected as freshwaters, whilst some of these coastal waters have already a less than good ecological status or potential. Furthermore, more stringent treatment for STPs near Natura2000 sites and STPs that emit effluent into water bodies with a less than good ecological status was not observed but might be required to protect biodiversity. This study did not aim to assess what advanced treatment should be implemented and to define which specific STPs need to be upgraded as the most suitable water management option depends on a multitude of factors and will most likely be location specific. Integrated assessments are needed that estimate total environmental benefits and burdens of STP treatments, as well as

other relevant parameters such as costs in order to decide on water management practices and to achieve long-term environmental goals listed under e.g. the WFD and (revised) UWWTD.

Acknowledgements

We thank Tessa Pronk (KWR Water Research Institute) for the input on the calculated removal efficiencies based on substance characteristics. This work is part of the Innovative Training Network ECORISK2050 and was supported by the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No [813124].

Data availability statement

The metadata that supports the findings of this study are openly available in Mendely Data at https://10.17632/zsrv92557p.1

6.5 Supplementary Information

6.5.1 Methods

6.5.1.1 The emission reduction potential of different UWWTD scenarios

6.5.1.1.1 Calculating the treatment capacity per treatment level

Three scenarios were analysed: 1) the present level of treatment (present scenario), 2) full compliance with the UWWTD in its current form (full compliance scenario) and 3) a scenario when more advanced treatment, either with ozonation or activated carbon, is required at large STPs (advanced treatment scenario).

The first step consists of collecting data for the year 2020 on 28529 STPs reported under article 15 of the UWWTD, and information on 5516 non-compliant STPs reported under article 17, including information how they are going to be updated (EEA, 2022a). Agglomerations with a generated load below 2000 p.e. are not included in the database as the UWWTD does not require reporting on them. Only active agglomerations and STPs (uwwState = 1) were included in our analysis. Furthermore, for some STPs data on the capacity is missing. This was the case for circa 11% of all active units reported under Article 15, which were mainly located in Spain and Italy. After filtering the data, 23568 STPs were left for further analysis.

Treatment levels were assigned according to Table SI6-1. Furthermore, not everyone is connected to a STP or collecting system. The population connected to a collecting system, but not to a treatment system were derived from the Article 15 datafile, by applying the following rules: the collecting system is not connected to a treatment plant (uwwCollectingSystem = NOTCON), but collects and

discharges water (uwwState = 1). Data on the population (in %) not connected to both a collecting system and treatment plant were obtained from Eurostat for the year 2019 (which was at date of the analysis the most recent year), or the most recent year available (Eurostat, 2022a). Used values are presented in Table SI6-1. For Italy and Cyprus, no information was available on the percentage of the population not connected. For the Full Compliance and the Advanced Treatment scenarios, it was assumed that the population reported by Eurostat (2022) as not connected to any type of treatment is now connected to an STP. However, since the exact location of the population not connected to any type of collection system or STP is unknown, an equal distribution over the treatment levels was assumed. Furthermore, under these scenarios envisioned changes to non-compliant STPs as reported under article 17 of the UWWTD are made, resulting in removal of some STPs and inclusion of STPs that will be newly constructed. Under the Full Compliance and Advanced Treatment scenarios, 26.739 STPs are taken into account in our analysis. For the Advanced Treatment scenario, all STPs with a capacity of ≥100.000 p.e. were assigned with advanced treatment (ozonation or activated carbon). Lastly, the data on the total capacity of STPs per treatment level for every scenario were normalized with population data for the year 2020, so that an overview is obtained of the European population connected to each treatment level, and the amount (in %) of pharmaceuticals that is potentially removed and released to the environment. This will allow future work to calculate the volume of pharmaceuticals potentially emitted to the environment when consumption data is available.

6.5.1.1.2 Literature search on removal efficiencies

Information was collected by conducting a literature review between autumn 2021 and spring 2022. Searches were conducted in SCOPUS via the following general search string:

(TITLE-ABS-KEY-AUTH ((**Wastew*** OR **Sewage***) AND "**removal**" AND "**TREATMENT TERM**" AND ("**CHEMICAL NAME**" OR "**CAS NUMBER**"))

With regards to the treatment term, only the most common STP treatment methods were searched. For example, for the secondary treatment step, several biological treatments exist but the most common method is conventional activated sludge (Michael et al., 2013). For every search, the first 20 articles were screened. Additional articles were identified via the reference lists of studies. In the case when no data on the removal rates for individual substances was reported in the text or supplementary information, WebPlotDigitizer (https://apps.automeris.io/wpd/) was used to extract numerical data from plot images. Studies were only included when reported removal efficiencies referred to the removal in full-scale STPs. In total, 63 references were collected for all treatment levels combined (see SI2). Removal efficiencies of a study were averaged in case multiple treatment efficiencies were reported (e.g. when multiple measurements were conducted during different times). If only a range was reported, the middle value of this range was chosen. Negative removal rates were set to zero in our

calculations in order to show no removal of the substance. The definition of the STP treatment levels are shown in Table SI 6-2. Full details on the removal per individual substance are given in the excel sheet available on the open data repository (van Dijk et al., 2023).

Table S6-1. Percentage of the population per European member state that was reported to not be connected to any type of treatment system (Eurostat, 2022a).

Country	Country code	Share of the population per European country not connected to a STP (%)
Austria	AT	0
Belgium	BE	2,77
Bulgaria	BG	12,27
Cyprus	CY	17,35
Czechia	CZ	3,1
Germany	DE	0
Denmark	DK	0
Estonia	EE	0
Spain	ES	8,24
Finland	FI	0
France	FR	0
Greece	GR	0
Croatia	HR	1,7
Hungary	HU	1,57
Ireland	IE	0,98
Italy	IT	0
Lithuania	LT	0
Luxembourg	LU	0,8
Latvia	LV	0
Malta	MT	0
Netherlands	NL	0
Norway	NO	1,7
Poland	PL	0,12
Portugal	PT	0,14
Romania	RO	1,3
Sweden	SE	0
Slovenia	SI	4,5
Slovakia	SK	0,5
United Kingdom	UK	0

6.5.1.1.3 Statistics

Statistical analyses were performed using SPSS Statistics 28 software (IBM Corp, 2022) to identify statistical difference between the removal efficiencies of treatment levels. Normality of data was tested using Kolmogorov-Smirnov and Shapiro-Wilk tests. The data did not follow a (log)normal distribution, hence a non-parametric test was used to show statistical differences.

6.5.2 Results

6.5.2.1 STP treatment levels and their removal rates

Table S6-2. Descriptions of the treatment levels taken from the OECD glossary and the UWWTD.

Treatment level	Description
Primary	Preliminary or primary treatment refers to the removal of large solids, oils, fat and other material from sewage so as to protect waste-water treatment facilities engaged in further treatment. The BOD5 of the incoming wastewater is reduced by at least 20% before discharge and the total suspended solids of the incoming wastewater are reduced by at least 50%.
Secondary	Secondary treatment is the second step in most waste treatment systems during which bacteria consume the organic parts of the wastes. This is accomplished by bringing the sewage, bacteria and oxygen together in trickling filters or within an activated sludge process. Secondary treatment removes all floating and settleable solids and about 90 per cent of the oxygen—demanding substances and suspended solids. In this study, secondary treatment referred to removal techniques to fulfil requirements of the UWWTD as laid down in Table 1 of Annex I (relating to BOD, COD and suspended solid removal) only.
Tertiary	Tertiary treatment is the advanced treatment process, following secondary treatment of waste water, that produces high—quality water. Tertiary treatment includes removal of nutrients such as phosphorus and nitrogen and practically all suspended and organic matter from waste water.
Disinfection	Chemical (UV or chlorination) or physical disinfection (by microfiltration).
Advanced (Ozonation or Activated Carbon)	Refers to processes capable of reducing specific constituents in waste water not normally achieved by other treatment options. According to the approach first introduced in Switzerland, upgraded STPs will contain either ozonation or activated carbon treatment. The removal rate of these techniques were combined in this study and averaged.

The null-hypothesis was rejected as a Kruskal-Wallis H test showed that there was a statistically significant difference in between the removal efficiencies of the different treatment levels ($p<0,05$). Except for secondary treatment compared to tertiary treatment, tertiary treatment compared to disinfection, and ozonation compared to activated carbon and advanced treatment, treatment levels were statistically different from each other ($p<0,05$)(Table SI6-3).

Table S6-3. Summary table of the Present, Full Compliance and Advanced Treatment scenarios for every country, showing the total amount of STPs (number) and treatment capacity (in p.e.) per treatment level.

		Present					Full Compliance					Advanced Treatment				
		Primary	*Secondary*	*Tertiary*	*Disinfection*	*Advanced*	*Primary*	*Secondary*	*Tertiary*	*Disinfection*	*Advanced*	*Primary*	*Secondary*	*Tertiary*	*Disinfection*	*Advanced*
Austria	STP (nr)	0	3	624	6	0	0	3	624	6	0	0	3	585	6	39
	Capacity (p.e.)	0	1,23E+4	2,14E+7	1,62E+5	0	0	1,23E+4	2,14E+7	1,62E+5	0	0	1,23E+4	8,66E+6	1,62E+5	1,27E+7
Belgium	STP (nr)	0	60	339	0	0	0	63	341	0	0	0	63	324	0	17
	Capacity (p.e.)	0	2,35E+5	1,03E+7	0	0	0	2,38E+5	1,03E+7	0	0	0	2,38E+5	6,04E+6	0	4,30E+6
Bulgaria	STP (nr)	1	7	43	59	2	0	188	23	96	2	0	188	20	84	17
	Capacity (p.e.)	1,05E+4	7,05E+5	5,25E+6	2,57E+6	4,53E+4	0	7,65E+5	1,44E+6	7,49E+6	4,53E+4	0	7,65E+5	5,69E+5	2,71E+6	5,70E+6
Cyprus	STP (nr)	0	1	0	16	0	0	1	0	23	0	0	1	0	16	7
	Capacity (p.e.)	0	2,20E+3	0	1,30E+6	0	0	2,20E+3	0	1,64E+6	0	0	2,20E+3	0	3,95E+5	1,25E+6
Czechia	STP (nr)	1	87	511	12	0	1	87	513	12	0	1	86	491	10	25
	Capacity (p.e.)	5,82E+2	8,79E+5	1,41E+7	4,53E+5	0	5,82E+2	8,79E+5	1,41E+7	4,53E+5	0	5,82E+2	4,19E+5	6,76E+6	1,12E+5	8,12E+6
Germany	STP (nr)	0	230	3291	269	6	0	230	3291	269	6	0	230	3102	210	254
	Capacity (p.e.)	0	9,84E+5	1,18E+8	2,70E+7	6,79E+5	0	9,84E+5	1,18E+8	2,70E+7	6,79E+5	0	9,84E+5	6,27E+7	6,35E+6	7,70E+7
Denmark	STP (nr)	0	13	319	5	0	0	13	319	5	0	0	13	291	4	29
	Capacity (p.e.)	0	4,11E+4	1,10E+7	3,88E+05	0	0	4,11E+4	1,10E+7	3,88E+5	0	0	4,11E+4	5,33E+6	2,38E+5	5,83E+6

		Present					Full Compliance					Advanced Treatment				
		Primary	*Secondary*	*Tertiary*	*Disinfection*	*Advanced*	*Primary*	*Secondary*	*Tertiary*	*Disinfection*	*Advanced*	*Primary*	*Secondary*	*Tertiary*	*Disinfection*	*Advanced*
Estonia	STP (nr)	0	2	49	0	0	0	0	51	0	0	0	0	44	0	7
	Capacity (p.e.)	0	5,73E+2	1,70E+6	0	0	0	0	1,86E+6	0	0	0	0	5,35E+5	0	1,32E+6
Greece	STP (nr)	0	7	176	51	8	0	12	22	301	8	0	12	21	288	22
	Capacity (p.e.)	0	5,40E+4	1,20E+7	1,68E+6	3,33E+5	0	8,63E+4	5,84E+6	9,02E06	3,90E+5	0	8,63E+4	2,11E+5	5,22E+6	9,82E+6
Spain	STP (nr)	30	707	955	388	6	6	901	849	573	6	6	842	779	476	232
	Capacity (p.e.)	8,16E+5	1,70E+7	4,52E+7	3,59E+7	1,71E+6	5,51E+4	2,59E+7	3,78E+7	4,43E+7	1,71E+6	5,51E+4	8,97E+6	1,19E+7	1,12E+7	7,76E+7
Finland	STP (nr)	0	0	152	0	0	0	0	152	0	0	0	0	135	0	17
	Capacity (p.e.)	0	0	7,31E+6	0	0	0	0	7,31E+6	0	0	0	0	2,89E+6	0	4,41E+6
France	STP (nr)	0	455	1	3433	0	0	436	15	3438	0	0	420	13	3305	151
	Capacity (p.e.)	0	1,09E+7	1,60E+5	8,44E+7	0	0	1,09E+7	6,04E+5	8,56E+7	0	0	4,11E+6	1,94E+5	4,21E+7	5,06E+7
Croatia	STP (nr)	52	40	13	0	0	41	155	64	0	0	41	150	60	0	9
	Capacity (p.e.)	1,81E+6	1,83E+6	4,73E+5	0	0	3,33E+5	2,53E+6	3,59E+6	0	0	3,33E+5	1,76E+6	1,69E+6	0	2,67E+6
Hungary	STP (nr)	0	54	722	40	1	0	55	238	545	1	0	55	235	519	30
	Capacity (p.e.)	0	4,65E+4	1,36E+7	1,35E+6	7,50E+4	0	4,85E+4	1,23E+6	1,38E+7	7,50E+4	0	4,85E+4	6,63E+5	6,16E+6	8,30E+6
Ireland	STP (nr)	4	51	113	14	0	4	50	118	14	0	4	46	113	13	10
	Capacity (p.e.)	2,03E+4	1,61E+6	2,05E+6	2,00E+6	0	2,03E+4	1,24E+6	2,62E+6	2,77E+6	0	2,03E+4	5,09E+5	1,71E+6	3,69E+5	4,05E+6

		Present					Full Compliance					Advanced Treatment				
		Primary	*Secondary*	*Tertiary*	*Disinfection*	*Advanced*	*Primary*	*Secondary*	*Tertiary*	*Disinfection*	*Advanced*	*Primary*	*Secondary*	*Tertiary*	*Disinfection*	*Advanced*
Italy	STP (nr)	120	329	1397	1859	19	32	628	393	4026	15	32	611	365	3682	404
	Capacity (p.e.)	6,80E+5	5,49E+6	3,28E+7	6,05E+7	2,41E+6	2,77E+5	1,43E+7	1,63E+7	1,91E+8	2,10E+6	2,77E+5	1,01E+7	6,80E+6	7,48E+7	1,32E+8
Lithuania	STP (nr)	0	8	54	1	0	0	8	54	1	0	0	8	46	1	8
	Capacity (p.e.)	0	5,07E+4	3,41E+6	3,20E+4	0	0	5,07E+4	3,44E+6	3,20E+4	0	0	5,07E+4	1,08E+6	3,20E+4	2,36E+6
Luxenbourg	STP (nr)	0	13	19	0	0	0	12	20	0	0	0	12	18	0	2
	Capacity (p.e.)	0	4,50E+4	8,75E+5	0	0	0	4,30E+4	1,01E+6	0	0	0	4,30E+4	6,65E+5	0	3,40E+5
Latvia	STP (nr)	0	55	17	0	0	0	54	18	0	0	0	54	14	0	4
	Capacity (p.e.)	0	3,39E+5	1,82E+6	0	0	0	3,11E+5	1,85E+6	0	0	0	3,11E+5	4,66E+5	0	1,38E+6
Malta	STP (nr)	0	0	1	3	0	0	1	3	0	0	0	0	0	2	2
	Capacity (p.e.)	0	0	5,00E+5	2,46E+5	0	0	5,00E+5	2,46E+5	0	0	0	0	0	1,26E+5	6,20E+5
the Netherlands	STP (nr)	0	1	322	0	0	0	1	322	0	0	0	1	266	0	56
	Capacity (p.e.)	0	2,25E+4	2,16E+7	0	0	0	2,25E+4	2,16E+7	0	0	0	2,25E+4	9,12E+6	0	1,25E+7
Norway	STP (nr)	163	9	154	0	0	163	9	154	0	0	159	7	145	0	15
	Capacity (p.e.)	1,48E+6	7,30E+5	4,30E+6	0	0	1,48E+6	7,30E+5	4,30E+6	0	0	9,07E+5	7,78E+4	2,28E+6	0	3,25E+6
Poland	STP (nr)	56	1016	611	0	0	56	1016	611	0	0	56	1015	511	0	101
	Capacity (p.e.)	4,02E+5	6,76E+6	4,53E+7	0	0	4,02E+5	6,76E+6	4,53E+7	0	0	4,02E+5	6,63E+6	1,59E+7	0	2,94E+7

		Present					Full Compliance					Advanced Treatment				
		Primary	*Secondary*	*Tertiary*	*Disinfection*	*Advanced*	*Primary*	*Secondary*	*Tertiary*	*Disinfection*	*Advanced*	*Primary*	*Secondary*	*Tertiary*	*Disinfection*	*Advanced*
Portugal	STP (nr)	7	286	57	140	1	6	281	48	163	0	5	269	48	134	42
	Capacity (p.e.)	2,68E+5	6,26E+6	9,12E+5	9,48E+6	3,50E+4	2,61E+5	6,13E+6	6,59E+5	1,02E+7	0	1,11E+5	3,17E+6	6,59E+5	2,90E+6	1,05E+7
Romania	STP (nr)	38	409	177	124	0	20	1316	202	217	0	19	1316	178	203	39
	Capacity (p.e.)	1,14E+6	2,33E+6	1,19E+7	2,33E+6	0	6,69E+5	5,29E+6	1,20E+7	5,89E+6	0	4,91E+4	5,29E+6	3,74E+6	2,13E+6	1,26E+7
Sweden	STP (nr)	0	0	366	65	2	0	0	358	74	1	0	0	341	68	24
	Capacity (p.e.)	0	0	8,68E+6	4,82E+6	3,65E+5	0	0	8,62E+6	4,95E+6	3,40E+5	0	0	5,25E+6	1,51E+6	7,16E+6
Slovenia	STP (nr)	0	42	67	0	0	0	37	76	3	0	0	37	72	3	4
	Capacity (p.e.)	0	5,14E+5	1,83E+6	0	0	0	1,27E+5	2,35E+6	1,04E+5	0	0	1,27E+5	1,28E+6	1,04E+5	1,07E+6
Slovakia	STP (nr)	2	81	139	44	0	0	81	169	45	0	0	80	159	43	13
	Capacity (p.e.)	9,00E+3	1,02E+6	4,01E+6	1,28E+6	0	0	9,84E+5	4,19E+6	1,29E+6	0	0	3,60E+5	2,06E+6	9,58E+5	3,09E+6
United Kingdom	STP (nr)	0	939	335	577	0	0	929	347	577	0	0	844	300	526	183
	Capacity (p.e.)	0	4,92E+7	2,36E+7	2,25E+7	0	0	4,87E+7	2,41E+7	2,25E+7	0	0	9,55E+6	9,62E+6	8,68E+6	6,75E+7

Table S6-4. Descriptive statistics of the different treatment levels for their removal efficiency (in %) of the set of 58 pharmaceuticals.

	N	Minimum	Maximum	Mean	Std. Deviation
Primary	26	,0	40,9	8,6	11,2
Secondary	55	,0	99,1	42,1	27,0
Tertiary	33	,0	99,1	42,2	27,3
Disinfection	43	,0	100,0	66,4	68,0
Ozonation	50	27,0	100,0	86,5	16,3
Active Carbon	41	26,9	100,0	81,3	17,7
Advanced	50	26,9	100,0	84,2	17,0

Table S6-5. Pairwise comparison of the removal efficiencies of the different treatment levels. Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same. Asymptotic significances (2-sided tests) are displayed. The significance level (a) was set at <0,05. Values are both corrected by the Bonferroni correction for multiple tests (Adj. Sig.) and non-corrected (Sig.), with a significance level set to p<0,05.

Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj. Sig.[a]
Primary-Secondary	-67,54	20,51	-3,29	<,001	,02
Primary-Tertiary	-69,48	22,59	-3,08	,00	,04
Primary-Disinfection	-133,54	21,41	-6,24	<,001	9,28E-9
Primary-Activated Carbon	-165,65	21,60	-7,67	<,001	3,64E-13
Primary-Advanced	-176,28	20,83	-8,46	,00	,00
Primary-Ozonation	-188,83	20,83	-9,06	,00	,00
Secondary-Tertiary	-1,94	18,97	-,10	,92	1,00
Secondary-Disinfection	-65,99	17,54	-3,76	<,001	,00
Secondary-Activated Carbon	-98,11	17,78	-5,52	<,001	7,18E-7
Secondary-Advanced	-108,74	16,84	-6,46	<,001	2,22E-9
Secondary-Ozonation	-121,29	16,84	-7,20	<,001	1,23E-11
Tertiary-Disinfection	-64,06	19,94	-3,21	,00	,03
Tertiary-Activated Carbon	-96,17	20,15	-4,77	<,001	3,82E-5
Tertiary-Advanced	-106,80	19,33	-5,53	<,001	6,86E-7
Tertiary-Ozonation	-119,35	19,33	-6,18	<,001	1,38E-8
Disinfection-Activated Carbon	-32,11	18,81	-1,71	,09	1,00

Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj. Sig.[a]
Disinfection-Advanced	-42,74	17,92	-2,39	,02	,36
Disinfection-Ozonation	-55,29	17,92	-3,09	,00	,04
Activated Carbon-Advanced	-10,63	18,15	-,59	,56	1,00
Activated Carbon-Ozonation	23,18	18,15	1,28	,20	1,00
Advanced-Ozonation	12,55	17,23	,73	,47	1,00

6.5.2.2 Water types receiving treated waste water

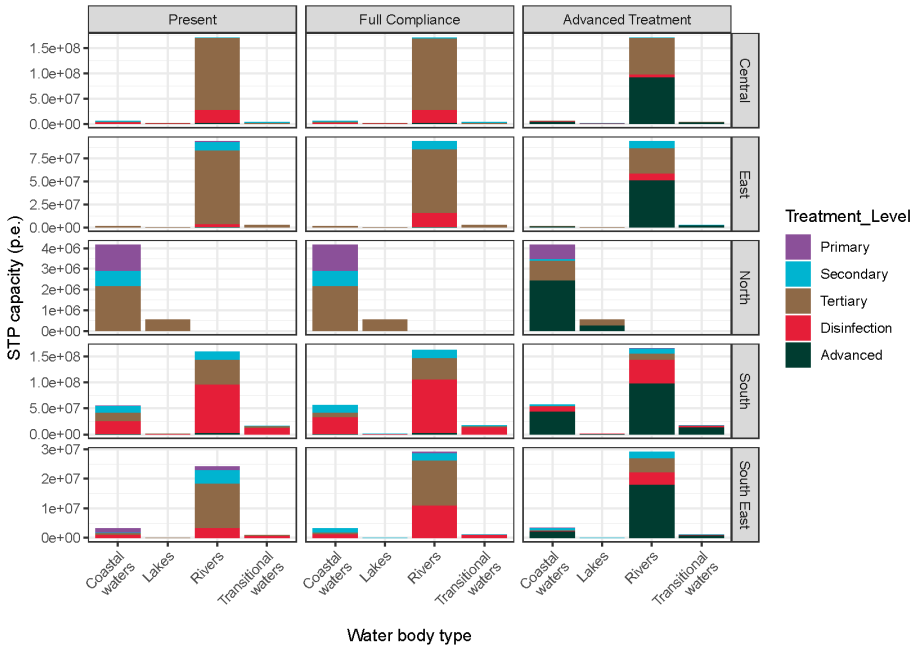

Figure S6-1. Total amount of treated STP effluent (capacity in p.e.) that is emitted into coastal waters, lakes, rivers and transitional water per European region under all three scenarios.

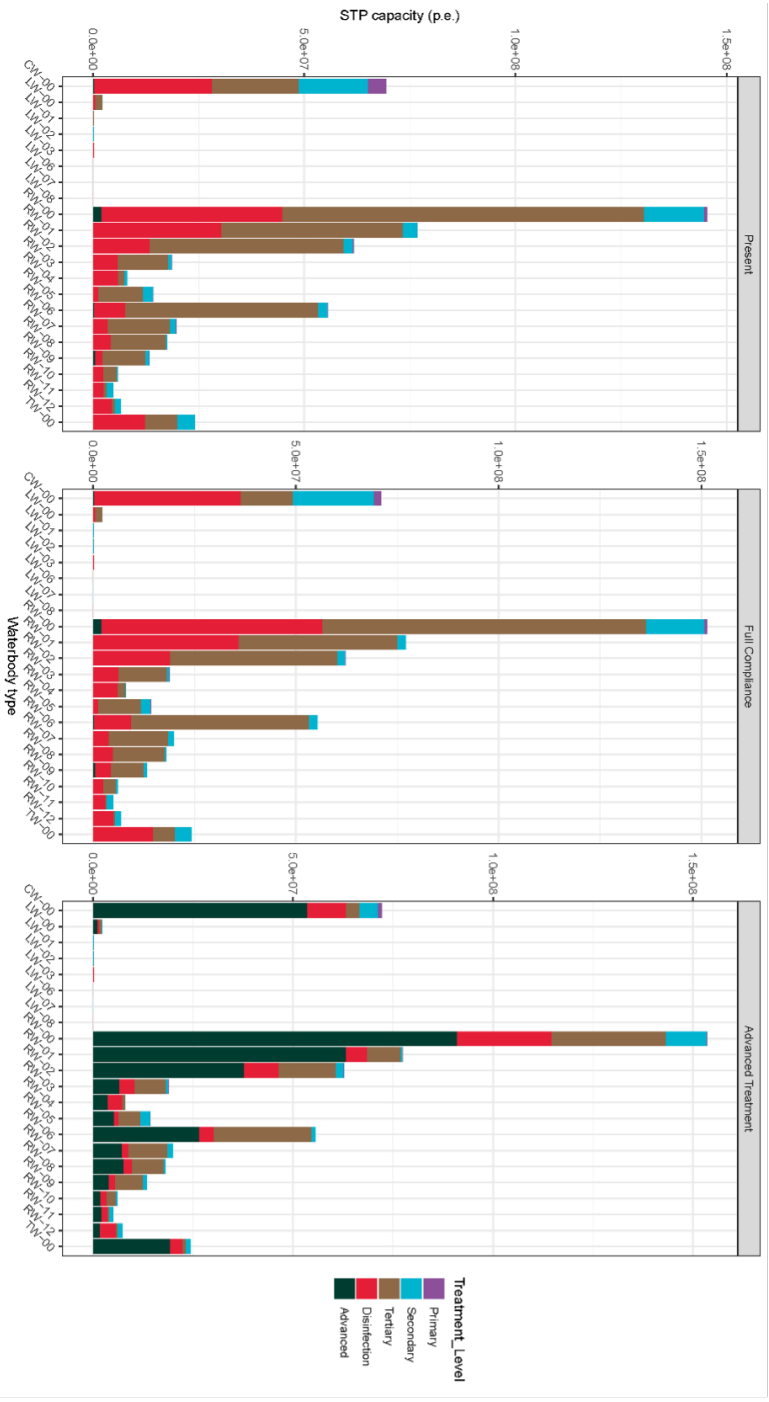

Figure S6-2. Total STP capacity (in p.e.) treatment per treatment level under the Present, Full Compliance and Advanced Treatment scenarios. Abbreviations of the water types are presented in Table SI6-6.

Table S6-6. Water body type codes and the broad and specific water types as reported in the WISE database (EEA, 2021)

Code	Broad water type	Specific type
CW-00	Coastal waters	Not assigned
LW-00	Lake waters	Not assigned
LW-01	Lake waters	Very large lakes
LW-02	Lake waters	Lowland, calcareous, very shallow, unstratified
LW-03	Lake waters	Lowland or mid-altitude, calcareous (including organic)
LW-06	Lake waters	Mid-altitude, siliceous
LW-07	Lake waters	Highland
LW-08	Lake waters	Mediterranean
RW-00	River waters	Not assigned
RW-01	River waters	Very large rivers
RW-02	River waters	Lowland, calcareous or mixed, medium or large
RW-03	River waters	Lowland, calcareous or mixed, very small or small
RW-04	River waters	Lowland, siliceous (including organic), medium or large
RW-05	River waters	Lowland, siliceous (including organic), very small or small
RW-06	River waters	Mid-altitude, calcareous (including organic), medium or large
RW-07	River waters	Mid-altitude, calcareous (including organic), very small or small
RW-08	River waters	Mid-altitude, siliceous (including organic), medium or large
RW-09	River waters	Mid-altitude, siliceous (including organic), very small or small
RW-10	River waters	Highland or glacial
RW-11	River waters	Mediterranean, perennial, medium or large
RW-12	River waters	Mediterranean, temporary or small
TW-00	Transitional waters	Not assigned

6.5.2.3 Natura2000 areas

In Figure SI6-3 the total treatment capacity (in p.e.) per treatment level for every European region under the Present, Full Compliance and Advanced Treatment scenario is shown. In Central Europe, relatively more effluent is emitted inside Natura2000 areas and the buffer zone compared to outside.

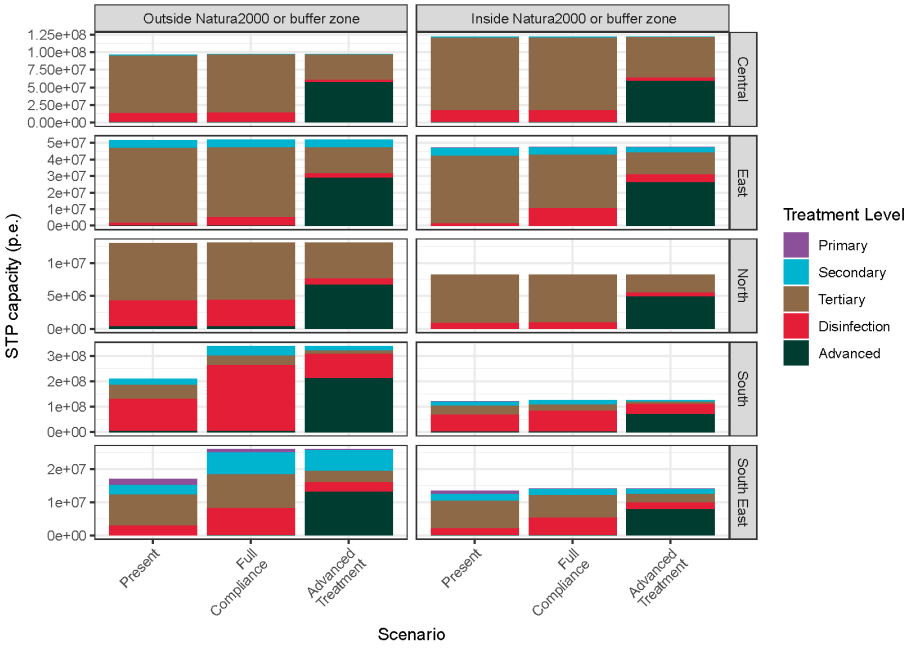

Figure S6-3. Total STP capacity per treatment level in the five different EU regions, and whether the STP is located outside or inside Natura2000 sites or the 2km buffer zone.

6.5.2.4 Treatment level per WFD river basin district

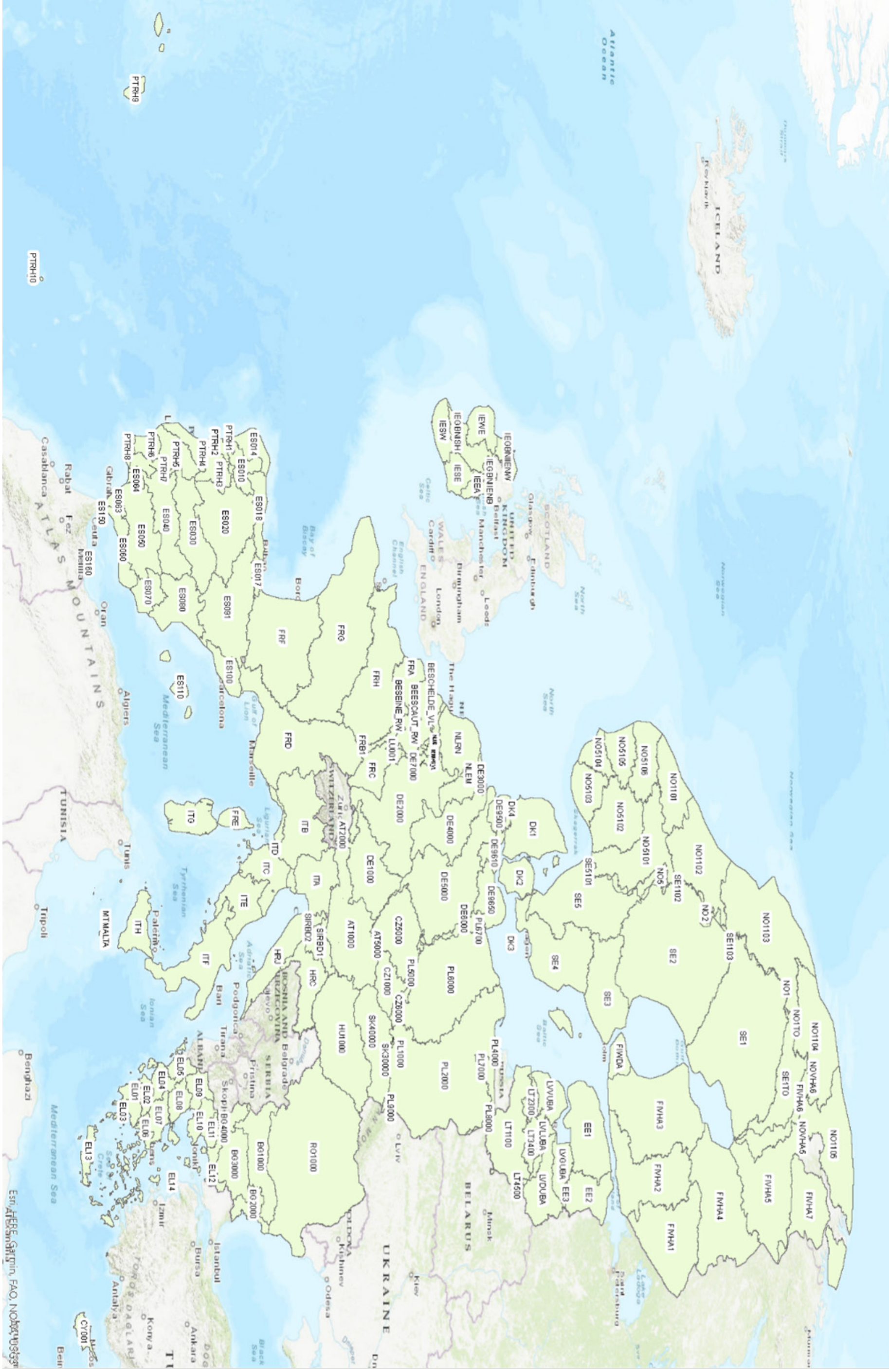

Figure S6-4. The RBDs defined under the water framework directive and their abbreviation.

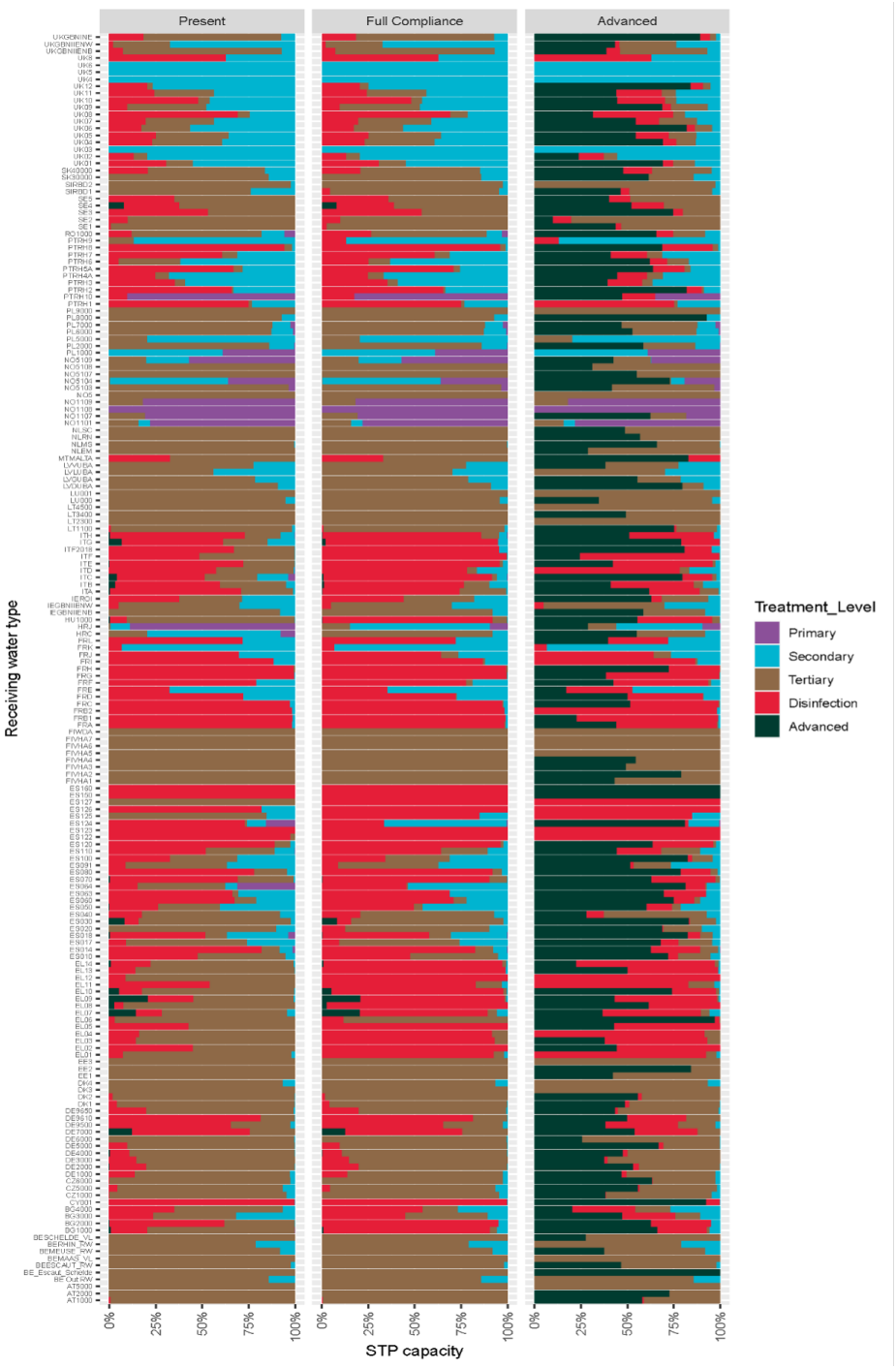

Figure S6-5. Total amount of STP capacity per treatment level (in %) per WFD RBD under the Present, Full Compliance and Advanced Treatment scenarios

6.5.2.5 Ecological status or potential per EU region

Total Europe (Figure SI6-6) and divided per region (Figure SI6-7).

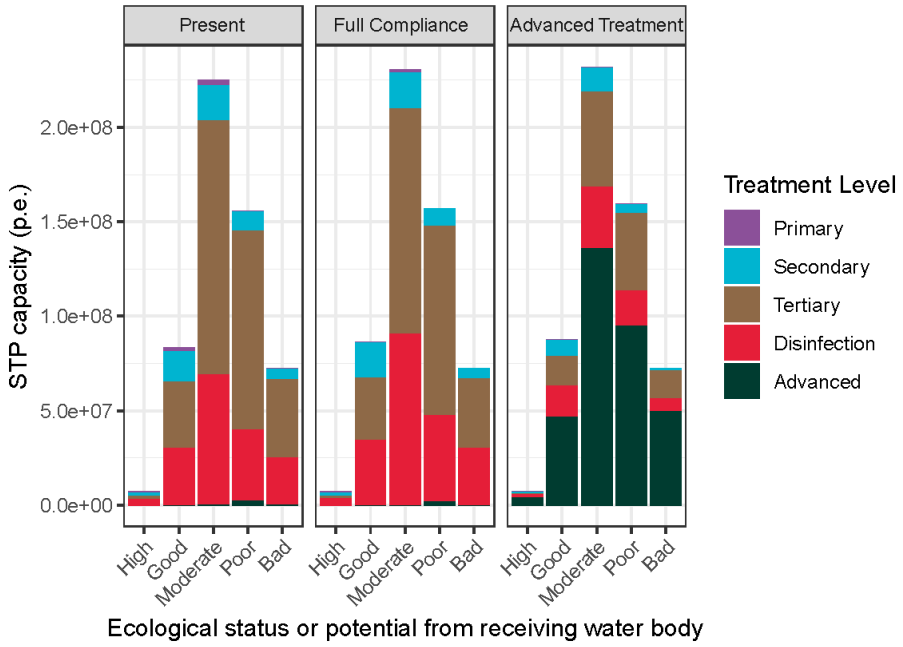

Figure S6-6. Total STP capacity (in p.e.) under every scenario that emits effluent in water bodies with an ecological status (or potential) assessed under the WFD as high, good, moderate, poor or bad.

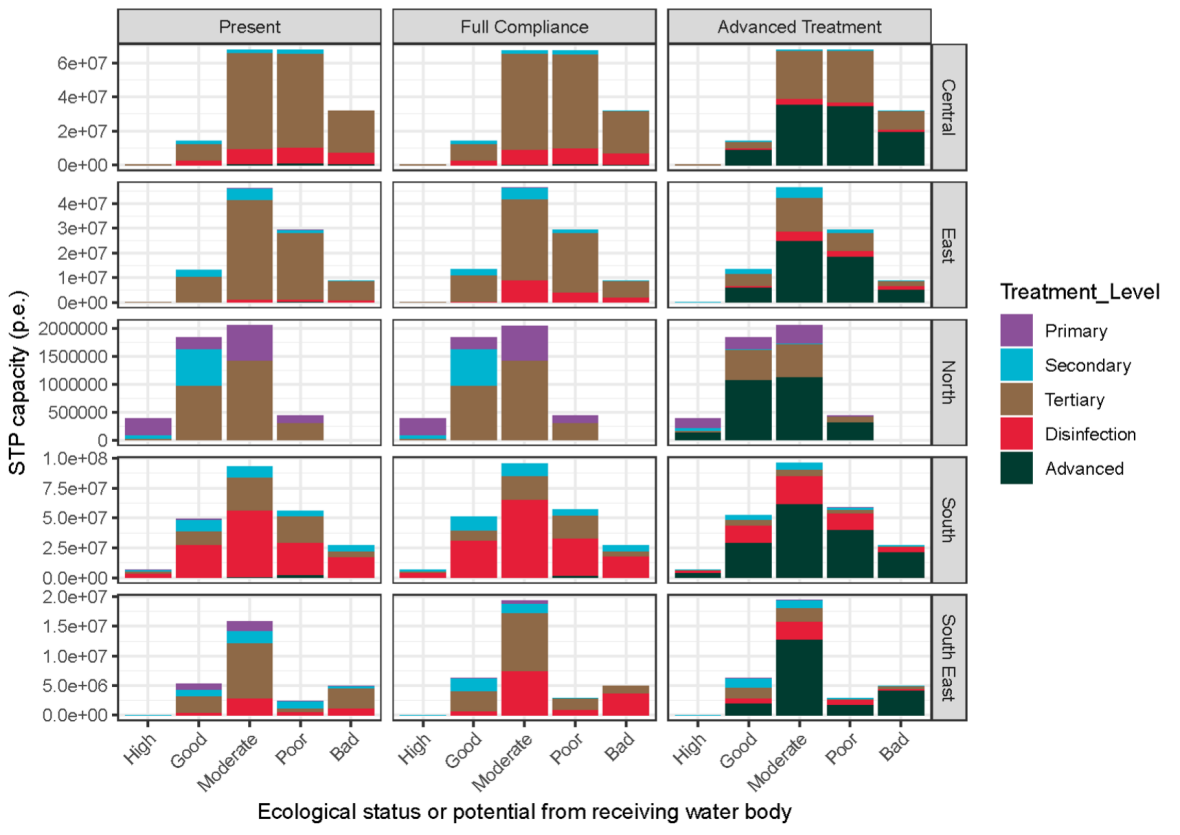

Figure S6-7. Total STP capacity (in p.e.) for all five EU regions under the Present, Full Compliance and Advanced Treatment scenarios that emits effluent into water bodies with an ecological status (or potential) assessed under the WFD as high, good, moderate, poor or bad.

CHAPTER SEVEN

SYNTHESIS | IMPROVING CHEMICALS MANAGEMENT BY TAKING A LIFE CYCLE PERSPECTIVE

Chapter 7 - Synthesis | Improving chemicals management by taking a life cycle perspective

Humanity is facing a triple planetary crisis of climate change, biodiversity loss and pollution. These planetary scale threats are all interlinked, and chemicals can drive these through a variety of mechanisms (Almroth et al., 2022). The chemical industry is for example a major consumer of resources and emitter of greenhouse gases, contributing to the acceleration of global change-related phenomena (IEA, 2022; Levi and Cullen, 2018). Chemical pollution can, furthermore, have long-term negative effects on ecosystems, consequently affecting biodiversity (Jaureguiberry et al., 2022; Sigmund et al., 2023). Chemical production, commerce, and consumption are rising globally due to, among others, rising income levels, with the EU ranking as the second largest chemical producer by sales value (CEFIC, 2023; UNEP, 2019a). In the EU, total chemicals consumption was 299 million tonnes in the year 2021, of which 226 million tonnes of chemicals were classified to be hazardous to human and/or environmental health (Eurostat, 2022b). New chemicals are continuously developed and introduced to the market (Arp et al., 2023; Bernhardt et al., 2017). Starting from the year 1800, the number of new chemical compounds has grown exponentially with 4.4% per year (Llanos et al., 2019). Due to societal developments this increase in both chemical diversity and use is expected to continue (Bunke et al., 2019; Desrousseaux et al., 2022).

Several policy targets have been set at the regional and global scale in order to better manage chemicals and waste to minimise effects on human health and the environment. Till date, however, these targets have not been achieved (Figure 1.2). New ambitions have now been formulated under among others the Strategic Approach and sound management of chemicals and waste beyond 2020 and (SAICM, 2020) the European Green Deal's Chemical Strategy for Sustainability (CSS) (European Commission, 2020b), which both focus on managing chemicals throughout their life cycle.

This thesis aimed to identify and assess multiple mitigation options over the chemical life cycle in order to reduce emission of chemicals into the environment and thereby contribute to environmental policy ambitions. To this end, the following chemical life-stages and research questions were assessed:

- **Policy goals:** Is there agreement within the scientific community on the interpretation of (European) environmental policy goals in order to help its implementation?
- **Chemical design and production:** Can chemicals be (re-)designed by taking both safety and sustainability parameters into account?
- **Registration and market entry:** What regulatory gaps need to be addressed in order to improve environmental risk assessment and management of chemicals?
- **Use stage:** What uses and functions do hazardous chemicals in consumer products have? And do safer alternatives exist?
- **Waste stage:** What is the added benefit to nature by introducing more advanced treatment of urban wastewater to reduce chemical emissions?

I discuss the potential and limitation of the different options assessed in this thesis below, while also placing them in a broader perspective from a societal point of view. It is important to consider the social and technical changes that each option will trigger within our current sociotechnical system, as every option has its own barriers to implementation (Table 7.1).

This chapter will start with the waste-stage, which I believe to require the least change to current systems, but at the same time is the least preferable option in the CSS's toxic-free hierarchy (European Commission, 2020b) (Figure 7.1). Next, the use and registration stages will be discussed, followed by the design phase. Then, the importance of clear policy targets is discussed. Lastly, I argue that a fundamental shift of the current sociotechnical system is needed in order to sufficiently reduce chemical emissions, achieve policy ambitions and facilitate a transition towards a safe and sustainable future. This shift will require a combined effort from regulators, industry, and consumers to establish sustainable practices.

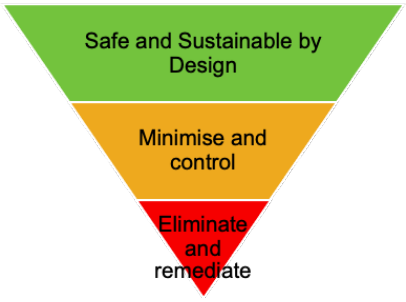

Figure 7.1. Toxic-free hierarchy of the CSS (European Commission, 2020b)

7.1 Waste stage – Introduce more advanced wastewater treatment technologies

Treatment of wastewater is regulated at the European level since 1991 with the introduction of the UWWTD. Conventional wastewater treatment has contributed to the progress in health and environmental protection (European Commission, 2022e). A majority of European surface water bodies do however still not have the desired 'good ecological status', this is among other things caused by chemical pollution for which STPs are important emission routes (EEA, 2018a). The UWWTD does currently not target the removal of synthetic chemicals. This is going to change with the UWWTD revision as part of the EU Green Deal, which will specify that large STPs do need an extra treatment step (European Commission, 2022d). In **Chapter 6**, we aimed to assess the added benefit to nature by introducing more advanced treatment (activated carbon or ozonation) to reduce chemical emissions. Activated carbon and ozonation are reported to be the best performing and most cost-effective treatment techniques for the removal of chemicals (Rout et al., 2021). We estimated

that implementing advanced treatment at STPs with a capacity of >100.000 p.e. will improve the total pharmaceutical emission reduction potential of STPs in Europe from 48% to 69% based on a set of 58 priority pharmaceuticals. What type of treatment (i.e. activated carbon or ozonation) should be implemented however depends on e.g. local conditions such as the size of the STP, the type and dilution capacity of the receiving waterbody (Kosek et al., 2020; Logar et al., 2014).

Wastewater treatment has become decreasingly sufficient as the diversity and volume of chemical consumption have risen in the past and will continue to do so in the future. Till date, no treatment exists that sufficiently eliminates all chemicals. We furthermore observed in **Chapter 6** that currently circa 44% of total STP effluent is emitted near Natura2000 sites (EU nature protection areas) and that not every region is equally protected. Moreover, of all surface waters receiving STP effluent for which the ecological status has been assessed under the Water Framework Directive, 77% have a status of less than good. It is not realistic to implement advanced treatment everywhere, considering the extra costs and e.g. increased energy and material demand (Ganora et al., 2019; Pistocchi et al., 2022b). The OECD estimated that extra investments of 129 to 206 billion euros are needed in order to realise the implementation of advanced treatment at large STPs (OECD, 2020). So whilst implementation of more advanced techniques does not require an alteration of the behaviour of society, it needs to be considered who is going to finance the implementation. Moreover, given the limitations and costs of wastewater treatment, we should enhance our efforts to reduce the use and presence of chemicals in wastewater next to upgrading some (e.g. large) STPs with advanced treatment.

7.2 Use stage – Phase out the use of the most hazardous chemicals in consumer products

Considering the limitations of treatment technologies and the fact that not all chemicals enter the environment via STPs, it is evident that we need to place our focus on other options focussing on input prevention as much as possible. Consumer products are becoming increasingly complex, and the marketing and consumption of these products is increasing rapidly (UNEP, 2019a). As a result of their chemical complexity, waste streams are becoming also more complex and therefore difficult to manage. Simplification of products can thus help to reduce and better manage waste (Fenner and Scheringer, 2021). In the CSS, the European Commission wants to ensure that '*the most harmful chemicals are only allowed if their use is necessary for health, safety or is critical for the functioning of society and if there are no alternatives that are acceptable from the standpoint of environment and health*' (European Commission, 2020b), which is part of actions under 'Safe and Sustainable by Design' in the toxic-free hierarchy (Figure 7.1). In **Chapter 5**, we aimed to identify the use and function of certain hazardous chemicals in consumer products, assess whether they are necessary in these products and if so, identify safer alternatives. This was achieved by applying the concept

of essential use to phaseout hazardous chemicals, and the concept of functional substitution to find safer solutions to the chemical of concern. The focus of this chapter was on PMT/vPvM (Persistent, Mobile and Toxic/very Persistent, very Mobile) substances, which generally are not well removed by wastewater treatment techniques (Hale et al., 2022). We show that the concept of essential use, especially when combined with the concept of functional substitution, is useful to phase out unwanted chemicals from products and on the larger scale make waste streams less hazardous. Some specific uses of PMT/vPvM substances are found to be non-essential, as they did not contribute to the end-function of the product, and for all other cases we found safer alternatives. It is often however not known where, why and in what amounts chemicals are used, hampering the application of the essential use concept. Open, product specific, use data will therefore be key for the essential use concept to reach its full potential.

Although applying the essential use concept on the most hazardous substances will be a step in the right direction, I argue that it is crucial to also extend the concept to all chemicals and products if we want to have a transition to a safe and sustainable future. The use of chemicals that are unnecessary cannot be considered safe or sustainable as they tend to make waste streams complex, contribute to environmental emissions, and consume valuable resources such as energy and raw materials for production. Implementation of the essential use concept as such can be seen as precautionary and preventative actions, which should be guiding principles in decision-making regarding environmental protection and sustainable development in Europe.

Business actors are often involved in decisions to act with precaution. In the past, economic motives have often driven non-precautionary business decisions (EEA, 2013). Successful implementation of the essential use concept will require a shift in current business models, for example by moving from the current business models based on product sales to one of service provision where there are clear economic incentives to reduce material use and increase product efficiency and longevity (Clark et al., 2016; Kindström, 2010). The required change in business models may be facilitated by regulatory pressures under e.g. the extended producer responsibility to meet certain environmental targets, as well as societal pressures from the majority of the European population who are concerned about exposure to chemicals (European Commission, 2016c). Consumer participation in decision-making can also help to identify essential function and performance characteristics, which will inform design choices and avoid unnecessary uses of chemicals (Holmquist et al., 2021). Furthermore, scientific evidence will be important to inform such business actions, highlighting the need for the scientific community to publish data in a transparent and accessible manner, while also communicating about uncertainties. By integrating scientific evidence and consumer input, businesses can design innovative solutions that limit chemical use. Regulatory demands and public concerns can encourage businesses to prioritise sustainable practises. These actions will help create a culture of responsible decision-making and informed action that will ultimately contribute to a safer and more sustainable future.

7.3 Registration and market entry – Harmonise risk assessment frameworks

It is important that we ensure that the most hazardous substances, such as PBT/vPvM (Persistent, Bioaccumulative and Toxic/very Persistent, very Bioaccumulative) and PMT/vPvM substances, are not used in society. This can be ensured by preventing their entry into the market in the first place, except when their use can be considered as essential. At present however, regulators often do not have the complete information that would be necessary for imposing all appropriate constraints. Moreover, there are a vast amount of chemicals on the market for which PBMT data are lacking, and new (often more complex) chemicals are continuously being introduced (Bernhardt et al., 2017; UNEP, 2019a; Wang et al., 2020). Considering the amount of chemicals marketed, it is not realistic to perform single chemical assessments for every individual chemical (Almroth et al., 2022; Persson et al., 2022). In order to simplify and strengthen the legal framework, a 'one substance-one assessment' (OS-OA) approach has been proposed in the CSS (European Commission, 2020b). In **Chapter 3** we aimed to assess what regulatory gaps need to be addressed in order to improve environmental risk assessment and management of chemicals, and how these regulatory assessments can be harmonised to move towards an OS-OA approach.

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 **Chapter 3** 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. We found that the overall function of the frameworks is similar, but that 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. Additionally, some chemicals that are not approved under one framework are allowed on the market under other frameworks. Across all frameworks, industrial chemicals are assessed as the least hazardous for the freshwater environment, whilst biocides are the most toxic following current regulatory assessment schemes. To successfully move towards an OS-OA approach, environmental protection goals and risk assessment strategies should be harmonised. Moreover, emission, use and production data should be made publicly available and criteria used to classify problematic substances should be harmonised as well and registration dossiers should be updated on a more regular basis in order to mitigate chemical risks. Such efforts will facilitate a consistent and transparent approach to chemical risk assessment across all frameworks.

Sharing and access to data in the same structured format is key to realise OS-OA, but to facilitate this some legislative obstacles for the re-use of data need to be addressed. In addition, other efforts need to be made, mainly by EU agencies, in order to better coordinate or distribute tasks (ECHA and EFSA, 2020). One of the CSS actions indeed include the development of a common open

data platform on chemicals, but it is not yet known what data exactly and for who will be available (European Commission, 2022g). Data reported under registration frameworks such as REACH is however not always reliable or relevant (Ingre-Khans et al., 2019a), emphasising the need to also include data from the open scientific literature into a centralised database. By doing so, all relevant data can be included in regulatory risk assessments, therefore limiting data gaps, reducing scientific uncertainty and subsequently improving policy decisions.

7.4 Design – Develop safe and sustainable chemicals

Considering the limitations of options further down the life cycle to reduce the chemical pressure on the environment, it will be most efficient to already design chemicals in such a way that they do not pose harm to human health and the environment. This is also the main focus of the European Commission to achieve a toxic-free environment, that is, to develop and use chemicals that are 'Safe and Sustainable by Design' (European Commission, 2020b). No official definition exists yet, but the OECD has a working definition that describes Safe and Sustainable by Design as *'an approach that focuses on providing a function (or service), while avoiding onerous environmental footprints and chemical properties that may be harmful to human health or the environment'* (OECD, 2022). In **Chapter 3** aimed to facilitate the (re-)design of chemicals, taking both safety and sustainability parameters into account. A workflow was created to first select chemicals for a redesign approach, assure that only chemicals which do not provide an essential function for society and/or health and for which no suitable alternatives are available are selected for a redesign approach.

Despite the growing production of new chemicals every year, most of chemicals belong to a restricted set of compositions (Llanos et al., 2019). For example, when exploring the chemical space for drug discovery, it was found almost all small molecules (>99.9%) have never been synthesized (Reymond and Awale, 2012). The vast majority of the chemistries and chemical processes used today were developed for their functionality, innovative properties, performance, and costs. However, potential health and safety impacts to workers, communities, and ecosystems were generally not considered during their development. As a result, the ways in which many chemicals have been and currently still are designed, produced, transported, used, recycled, and disposed, cause significant damage to humans, ecosystems and the climate. This highlights the huge potential of chemistry to develop chemicals that perform better on chemical safety, recyclability and environmental impact. Furthermore, chemistry can make a critical difference to the future of people and planet by, among others, conservation of material stocks in forms that remain available for use through attention to circularity (Matlin et al., 2022).

Table 7.1. Overview of the different options assessed in this thesis, the most important stakeholders involved in the implementation and potential benefits and drawbacks for these stakeholders.

Stage in the chemical life cycle	Design	Registration and market entry	Use and consumption	Waste stage
Mitigation option	Develop chemicals that are safe and sustainable	Harmonise risk assessments	Prevent the unnecessary the use of (hazardous) chemicals	Improve wastewater treatment
Most important stakeholder(s)	Industry	Government	Industry and government	(Waste) Water managers
Benefits for the stakeholder(s)	Reducing the risk to be liable in the future according to the 'polluter pays principle'; providing them with a competitive advantage; Increased industry reputation by e.g. consumers and investors.	Prevention of double assessments; Access to, and use of, all available data resulting in more robust assessments.	*Industry:* Reducing the risk to be liable in the future according to the 'polluter pays principle'; providing them with a competitive advantage; Increased industry reputation by e.g. consumers and investors. *Government:* decrease of regrettable substitutes.	Potential for waste reduction and energy production, helping to achieve targets for energy-neutrality that now apply to STPs.
Drawbacks for the stakeholder(s)	Necessary tools might not be available; It requires time to build up the necessary knowledge; Capacity and resources needed might not always be available; Not always possible to develop Safe and Sustainable alternatives with the same functionality.	Current data sharing systems are not available; Some data can be protected under EU law, and therefore not be used.	*Industry:* Necessary tools to assess essentiality might not be available; Not always possible to find alternatives with the same functionality; Loss of product image to the consumer (e.g. by loss of colour used for marketing). *Government:* Data on chemical uses might not be available.	It requires (new) knowledge and time to select and implement advanced treatment techniques; Capacity and resources needed for implementation and management of advanced treatment techniques might not always be available.

7.5 Policy goals – Defining clear directions

In order to move forward and improve the management of chemicals and waste, clear policy goals are crucial to provide direction and guidance for decision-makers and stakeholders. Such goals can be shaped by society and science. Without clear goals, it can be difficult to identify what actions need to be taken, who needs to take them, and how progress towards the targets will be measured. Clear policy goals also provide a basis for accountability, as they allow for the evaluation of whether the targets have been met and the effectiveness of the policies implemented. Additionally, they can help to align stakeholders and resources towards a common purpose, making it more likely that the desired outcomes will be achieved. In the EU Green Deal's CSS not all goals have been clearly defined. As a consequence, some goals, such as the zero pollution ambition, have been labelled as unrealistic and unscientific by some (Bridges et al., 2023). It is even possible that different interpretations hamper the implementation of a certain concept, eventually resulting in its collapse (Kirchherr et al., 2017). In **Chapter 2** we aimed to find agreement in the interpretation of a toxic-free environment in order to help its implementation. Knowledge and communication gaps to achieve a toxic-free environment, as well as actions required to address these gaps, are identified.

Via a questionnaire sent to scientific community of the Society of Environmental Toxicology and Chemistry (SETAC), a toxic-free environment was defined as 'an environment in which all chemicals can be emitted as a result of human activities, but in low concentrations, so that no adverse effects to organisms occur'. A need to strengthen the utility of science for policy and to improve the science–policy interface was identified. Politicians require the simplification and standardization of risk assessments, but at the same time, it is essential that the use and utility of novel scientific findings are increased, through the development of a strong science to regulation feedback mechanism and vice versa. As scientists become more involved in the complex deliberations that are required to achieve policy targets, the need intensifies for methods, processes, and tools to increase the robustness and transparency of the deliberation process. However, this can be addressed through interdisciplinary research efforts. Finally, an extra challenge will be to identify how concepts can be applied in a global setting, to address the impacts of chemical pollution in all regions of the world. The scientific community is already interconnected on a global level, so these communities have great potential to share experiences and, by doing so, accelerate the processes that lead to a safe and sustainable future.

7.6 Outlook – Optimising our use of chemodiversity

The several options assessed in this thesis show that mitigation strategies can be implemented during different chemical life-stages. Whilst a set of the most important measures were assessed in this thesis, we must stress that other mitigation strategies to reduce chemical emissions into the environment exist as well. By implementing all options together over the chemical life cycle, we can expect that the

risk of chemicals to human health and the environment will be reduced. As environmental problems are interconnected and chemicals drive planetary threats via numerous mechanisms (Almroth et al., 2022), it is key to take a comprehensive approach to prevent problem shifting. The chemical industry is for example a major consumer of resources and emitter of greenhouse gases, contributing to the acceleration of global change-related phenomena (IEA, 2022; Levi and Cullen, 2018). Furthermore, some measures, such as advanced wastewater treatment, require more energy or other resources (Kümmerer et al., 2019), emphasising the need for comprehensive assessment of all possible impacts in order to decide on the most appropriate management options. The issue of chemical pollution and waste management is complex and spans multiple time and spatial scales and sectors, which all need to be taken into account. In the past, the local environmental in Europe has for example improved in some areas (EEA, 2019), but these achievements are said to have happened at the expense of deterioration elsewhere. Examples are the outsourcing of pollution to other countries (Fang et al., 2019; Joakim Larsson and Fick, 2009) and substituting one pollutant for another (Trasande, 2017).

Next to implementing measures such as the ones assessed in this thesis, I argue that we need to change our own behaviour to achieve global and regional policy ambitions. After all, the way chemicals are used is shaped by the social context in which they occur. With the ever increasing number of chemicals, in other words chemodiversity, some mitigation options such as wastewater treatment are becoming less effective. Hence, the question needs to be asked whether we really need all these chemicals? Do they really add value to society, or do their negative effects outweigh their benefits? In this final chapter I argue that, inspired by Kallis (2018), if we want to achieve policy goals relating to the management of chemicals and waste, we should drastically change course and extract, produce and consume less chemicals as a society.

7.6.1 The (non)necessity of chemicals in society

As a consequence of the increasing chemical pollution, an overall reduction of chemical production volume is deemed necessary to reduce the total impact of the chemicals on the environment (Mueller et al., 2023). It has therefore been proposed to reduce chemodiversity (Fenner and Scheringer, 2021; Persson et al., 2022). On the other hand however, it has been argued that new chemistries are needed to, among others, move away from fossil fuel stocks and transform industry (Tickner et al., 2021). I argue that, whilst there are probably many unnecessary uses of chemicals (as observed in **Chapter 5**), we should focus not per se on reducing chemodiversity alone but rather optimise our use of all possible chemicals. Optimising our use of chemodiversity includes innovation of new chemicals where we need them as well as reducing - or sometimes even eliminating - the of use of substances where possible. This will be a major task considering the already large amount of chemicals available on the market. The reduction of chemical uses could therefore start with substances of concern, such as PBT/vPvM or PMT/vPvM substances. Next, the non-essential use of chemicals in

products could be reduced, first focussing on consumer products. Furthermore, we should consider whether nonchemical alternatives for a specifically required function or service are possible and if they are more sustainable (Kümmerer, 2017; Tickner et al., 2015). For the innovation of new chemicals and materials, the concept of Safe and Sustainable by Design should become a guiding principle. This will however require initial investments in research and development to improve our understanding of the fate and behaviour of chemicals in the environment and to develop tools that facilitate the design of safe and sustainable chemicals. Moreover, the implementation of this concept involves a network of many stakeholders, requiring communication, cooperation, and transparency of decisions (ECOSChem, 2023).

To effectively reduce the use of chemicals in society, a system change is needed (Wöhler et al., 2020). Achievement of policy targets for improved chemical management has been hampered in the past as complex interactions between economic, social, technological, and political dynamics were not considered. This resulted in so-called "lock-ins" that maintain the status quo of chemical production, marketing and use (Blumenthal et al., 2022; Hüesker and Lepenies, 2022). Examples of lock-ins for better management of plastics, paraquat (a herbicide) and asbestos show that industry can be a major stakeholder hampering better management of chemicals due to economic lock-ins (Blumenthal et al., 2022; Tickner et al., 2021). Economic interests might thus prevent hazard reductions (Coria et al., 2022). For most mitigation options, including the strategies assessed in the current thesis, economic lock-ins exist (Table 7.1). These mitigation options will often require initial investments and could therefore negatively impact industry's profit margins. Here, it is also important to note that many positive feedback loops can generally be observed once industrial transformations begin to occur, leading to cost reduction, upscaling and wider citizen acceptance, albeit only becoming clear on the long-term (Seto et al., 2016). A transition towards a system with restricted chemical use will result in lower chemical emissions into the environment (Wöhler et al., 2020). In order to stimulate such a transition, above mentioned lock-ins need to be prevented. This will require comprehensive efforts, including raising awareness and accountability among all stakeholders and identifying opportunities for social and institutional change (Blumenthal et al., 2022; Hüesker and Lepenies, 2022).

Moreover, consumer practices need to change, especially in wealthier countries (Obura et al., 2023). This is needed as certain user consumer practices and life styles can prevent sustainability transitions (Geels, 2018; Klitkou et al., 2015). Moreover, society can - just like clear policy goals - influence priority setting for (industrial) research and development, and thus influence the direction of technological change (Hekkert et al., 2007; Wöhler et al., 2020). Reducing consumption is not merely about abstaining from consumption, but also about making more sustainable choices (Poças Ribeiro, 2023). Consumers might however not be able to make (more) sustainable purchases yet, as the full costs of pollution (in other words, the true cost on society) are not reflected in product prices. By incorporating right pricing for pollution, consumers can be encouraged to make more sustainable purchasing decisions (Sterner et al., 2019). Thus, it is critical to raise awareness among

consumers and provide them with accurate information on the environmental impact of products, as well as incentivize sustainable consumption practices through appropriate pricing of products.

7.6.2 Towards a safe and sustainable future

A transition to a circular economy is often presented as a solution to reduce our impact on Earth and stay within the planetary boundaries (e.g. Desing et al., 2020; Syberg et al., 2021; Wijkman and Skånberg, 2015). It is also one of the policy targets within the European Green Deal (Figure 1.2), and chemistry is said to be key for achieving a this (Clark et al., 2016). Currently, most chemical products are synthetic, based on non-renewable resources, and formed into complex articles and we are running out of resources needed for manufacturing (Kümmerer et al., 2020). Moreover, the presence of (hazardous) chemicals in materials and products pollute waste streams and hamper recycling (Geueke et al., 2018; Wang and Praetorius, 2022). Material and product complexity need to be reduced so that the use of chemicals, and consequently material flows, are downsized and a transition towards a circular economy is enabled (Groh et al., 2023). This, together with keeping different waste flows separate, will improve the reuse, recycling and removal of chemicals and subsequently reduce their emission into the environment (Jonkers et al., 2016; Zuin and Kümmerer, 2022). It is important to note that a circular economy without unwanted effects will not be possible, but with the right actions, chemical losses can be reduced to the lowest possible level (Kümmerer, 2017). As chemical emissions can never be prevented completely, conversations need to be held to better define what effects on ecosystems we accept and where, so that safe operating spaces can be established (Kosnik et al., 2022).

In addition, regulatory assessments of chemicals need to be updated to guarantee safety of a circular economy. As in a circular economy, materials and products are reused or recycled, regulatory assessments need to consider multiple use cycles. For example, after standard hazard and risk assessments, an additional "sustainable circularity" assessment stage can be introduced (Wang and Hellweg, 2021). Here, next to the origin, characteristics, properties and fate of chemicals, the processes to obtain or transform chemicals and the services they provide can be assessed (Zuin and Kümmerer, 2022). Parameters that can be taken into account in this assessment stage can be aligned with the concept of circular chemistry (Keijer et al., 2019a).

In conclusion, the mitigation strategies assessed in this thesis can optimise our use of the available chemodiversity and, when combined with societal and institutional change, have the potential to sufficiently reduce chemical use in order to meet regional and global policy ambitions. The concept of essential use can be used to simplify products and phase out the use of some chemicals, whereas criteria for Safe and Sustainable by Design need to be used during for development of new chemicals and materials. When the use of a chemical and its subsequent release cannot be prevented, treatment of waste streams via e.g. STPs can be used as a last step. In an ideal safe and sustainable future, this will enable society to stay within the planetary boundaries.

APPENDIX

Appendix

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Summary

Human-made synthetic chemicals are important for our society and economy, often contributing to our health and comfort. The overall production and use of these chemicals have been increasing over the past decades. Recently, it was estimated that over 350,000 chemicals are registered for use world-wide and are present in, for example, household and consumer products, industrial processes, agriculture and medicines. Driven by societal and technological developments, the number of chemicals on the market and the volumes used will only increase further. Despite the benefits that chemicals can bring to society, their usage, production, and disposal also lead to releases into the environment. Here, these chemicals are affecting both human and environmental health. Chemical pollution is for example a major contributor to the decline of global biodiversity and ecological status of European surface waters. Certain chemical properties make some substances of higher concern to human and environmental health than others. This are toxicological (T) properties, as well as properties determining the fate and behaviour of chemicals, such as persistency (P), mobility (M) and bioaccumulation (B).

The management of chemicals and waste has been on the global and regional (i.e. European) policy agenda since the 1960's and 70's. Traditionally, actions to manage chemicals consist for a major part of regulatory and technological (end-of-life) measures. Even though chemicals' management improved over the last decades due to legislation, many issues related to chemical pollution still persist. Additional mitigation options should therefore be developed and implemented. A more comprehensive approach is needed in which various options throughout the chemical life cycle are combined, taking various sectors and environmental pathways into account. Consequently, new targets have been developed, for example under the European Green deal which aims for a 'toxic-free environment'. In the context of the EU Green Deal, the Chemicals Strategy for Sustainability (CSS) was developed to safeguard human health and the environment by addressing pollution from all sources and move towards a toxic-free environment. The CSS is part of the EU Green Deal's zero-pollution ambition for air, water and soil. This dissertation focussed on the identification and assessment of multiple mitigation options over the chemical life cycle in order to help reduce chemical emissions into the environment in a more comprehensive manner, thereby contributing to environmental policy ambitions.

Clear policy goals are crucial to move forward and improve the management of chemicals and waste by providing direction and guidance for decision-makers and stakeholders. In **Chapter 2**, which was based on a survey and discussion held at the 2020 SETAC Europe Annual Meeting, a definition for a "toxic-free environment" is proposed in order to facilitate the implementation of the CSS. In addition, key issues that are absent from the CSS but are considered to be key for the realization of a toxic-free environment were identified. It is for example recommended to align the definition of risk across the different chemical legislations, to establish a platform for open data and data sharing, and to increase the utility and use of novel scientific findings in policymaking, through the development of a strong science to regulation feedback mechanism and vice versa.

The chapter concludes that environmental scientists have the tools to address the key challenges presented in the CSS, but that more effort is needed from both scientists and policymakers to develop methods, processes, and tools that enhance the robustness and transparency of deliberation processes, as well as the utility of science.

Chapter 3 focusses on the chemical design and production stage, contributing to the development of Safe and Sustainable chemicals. A systematic and computer-aided workflow is proposed that can facilitate the chemical redesign for reduced environmental hazards whilst also taking sustainability parameters into account in order to mitigate chemical pollution and help enable a safe circular economy. The approach implements several concepts mentioned in the CSS, such as essential use and Alternatives Assessments, and is based on openly available software to generate potential alternative structures and predict chemical properties using quantitative structure–activity relationships (QSARs). Only chemicals that provide an essential function and for which no suitable alternatives are available were deemed relevant for redesign. The organophosphate chemical triisobutylphosphate (TiBP) was used as a case study for exploration of the approach. Emission of TiBP as a result of its use as a flame retardant was expected to be inevitable. Therefore, a redesign approach was chosen to improve degradability. Over 6.3 million potential alternative structures to TiBP were created in silico and filtered based on QSAR outputs to remove potentially non-readily biodegradable structures. With a multi-criteria analysis (MCDA) based on predicted properties and synthesizability a list of most desirable structures was identified. The target structure (di-n-butyl (2hydroxyethyl) phosphate) was manually selected out of the top 500 structures and synthesized in the lab to allow experimental testing of the chemical. Whilst QSAR predicted properties of the selected alternative showed better biodegradation characteristics compared to TiBP, the first experimental results did not confirm enhanced biodegradability. In order to explain these results and further expand and verify the redesign approach, it is key that the knowledge on the mechanisms of biodegradation will be improved in the future.

The registration and market entry stage is presented in **Chapter 4**. Here, the risk assessment procedures for the freshwater environment for (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) and (v) Veterinary medicines (Directive, 2001/82/EC) are analysed and compared. It was found that, even though the general principles of the registration of chemicals are the same, environmental protection goals and the assessment strategies to obtain regulatory Predicted No-Effect Concentrations (PNECs) differ. This can result in inconsistent assessments between frameworks, i.e. different PNECs for the same substance under different frameworks. Moreover, some substances were found to be banned under one framework, but still marketed under another framework. Recommendations in this chapter are given in order to better harmonise the analysed registration frameworks and move towards a 'one substance-one assessment' (OS-OA) approach.

Measures that can be implemented to manage chemicals in the use phase are discussed in **Chapter 5**. The market share of PMT/vPvM substances in cosmetic products was identified via cosmetic ingredient information contained in governmental and industry databases. PMT/vPvM substances were found in all product types, and the three most prevalent PMT/vPvM substances (Allura red, Benzophenone-4 and Climbazole) were selected as case studies to assesses their functionality in cosmetic products, availability of safer alternatives, and essentiality in order to reveal whether the use of these case-study chemicals can be phased-out or substituted. Following the functional substitution framework, it was found that the technical function of Allura red was not necessary for the performance of some cosmetic products, making the use non-essential. For other applications of Allura red, as well as all applications of Benzophenone-4 and Climbazole, the technical function of the chemical was considered necessary for the performance. Via the alternatives assessment procedure, which used experimental and QSAR data and three different MCDA strategies, safer alternatives were identified for all case-study chemicals. All assessed uses of PMT/vPvM substances were thus deemed non-essential and should consequently be phased out.

Options that manage chemicals during the waste stage are presented in **Chapter 6**. A European-wide analysis of sewage treatment plants (STPs) reported under the urban wastewater treatment directive (UWWTD) was made, including an assessment of the current STP treatment levels and the potential to remove a set of 58 prioritised pharmaceuticals. It was calculated that the introduction of advanced treatment techniques, such as ozonation and activated carbon, at large STPs (serving 100.000 people or more) will improve the emission reduction potential of STPs in Europe from 48% to 69%. Spatial differences with regard to implemented STP treatment levels were however found, and coastal waters and lakes seemed for example not as well protected as freshwaters. Furthermore, more stringent treatment for STPs near nature protection areas and STPs that emit effluent into water bodies with a less than good ecological status was not observed but might be required to protect biodiversity.

Lastly, the overall findings of this thesis are synthesised and put into perspective in **Chapter 7**. The assessment of the options in **Chapter 3-6** of this thesis revealed that environmental emission of chemicals can be reduced, thereby helping to achieve policy targets for chemical and waste management. However, given the expected increase in the diversity and use volume of chemicals, it is key to optimize and, when possible, reduce the wide variety of uses of the vast amount of chemicals. In other words, we must optimize the use of chemodiversity to move towards a safe and sustainable future. This transformation will require societal and institutional changes that strike a balance between the advantages of chemical use, innovation and the need for sustainability and safety.

Samenvatting

Door de mens gemaakte synthetische chemische stoffen zijn alomtegenwoordig in ons dagelijks leven. Zij maken deel uit van bijna alle hulpmiddelen die we gebruiken om ons welzijn te waarborgen en onze gezondheid te beschermen. De totale productie en het gebruik van deze chemische stoffen is de afgelopen decennia ontzettend toegenomen. Onlangs werd geschat dat er wereldwijd momenteel meer dan 350.000 chemische stoffen geregistreerd zijn voor gebruik, zoals bijvoorbeeld in huishoudelijke- en consumentenproducten, industriële processen, gewasbeschermingsmiddelen en medicijnen. Door verschillende maatschappelijke en technologische ontwikkelingen zullen het aantal verschillende chemische stoffen op de markt en hun gebruikte hoeveelheden alleen maar verder toenemen. Ondanks de voordelen die deze chemische stoffen de maatschappij kunnen bieden, leiden de productie en het gebruik van deze stoffen ook tot emissies naar het milieu. Eenmaal aanwezig, kunnen zij de menselijke gezondheid en het milieu schaden. Chemische vervuiling draagt bijvoorbeeld nu al in belangrijke mate bij aan het wereldwijde verlies van biodiversiteit en de achteruitgang van de ecologische status van Europese oppervlaktewateren. Bepaalde chemische eigenschappen maken sommige stoffen zorgwekkender voor mens en milieu dan andere. Dit zijn de toxicologische (T) eigenschappen en eigenschappen die het gedrag van chemische stoffen bepalen, zoals persistentie (P), mobiliteit (M) en bioaccumulatie (B).

Het beheer van chemische stoffen en afval staat sinds de jaren 1960 en 1970 op de globale en regionale (d.w.z. Europese) beleidsagenda. Traditioneel gezien bestaan maatregelen voor het beheren van chemische stoffen voor een groot deel uit beleids- en technologische maatregelen. In de laatste decennia is het beheer van de risico's van chemische stoffen erg verbeterd dankzij de wet- en regelgeving. Echter zijn er momenteel toch nog veel problemen met betrekking tot chemische vervuiling. Dit betekendt dat er extra maatregelen moeten worden ontwikkeld en geïmplementeerd. Er is een aanpak nodig die naar de hele levenscyclus van chemische stoffen kijkt, rekening houdend met het verschillende door verschillende sectoren en verschillende emissie routes. Er moeten verschillende maatregelen kunnen worden ingezet tijdens verschillende fasen van de chemische levenscyclus om chemische emissie naar het milieu voldoende te verminderen. In het kader van de Europese Green Deal zijn er daarom nieuwe doelstellingen ontwikkeld. Als deel van de Green Deal is de Strategie voor Duurzame Chemische Stoffen (CSS) ontwikkeld om de menselijke gezondheid en het milieu te beschermen door verontreiniging uit alle bronnen aan te pakken en te streven naar een gifvrij milieu. De CSS is onderdeel van de nulvervuilingsambitie van de EU Green Deal voor lucht, water en bodem. Dit proefschrift richtte zich op de identificatie en beoordeling van maatregelen die geimplementeerd kunnen worden in verschillende stadia van de chemische levenscyclus om chemische emissies naar het milieu te verminderen en zo bij te dragen aan de beleidsambities voor het milieu.

Duidelijke beleidsdoelen zijn cruciaal om vooruitgang te boeken en het beheer van chemische stoffen en afval te verbeteren door beleidsmakers en belanghebbenden richting en richtsnoeren

te geven. In **hoofdstuk 2**, dat gebaseerd is op een enquête en discussie tijdens de jaarlijkse SETAC Europa-bijeenkomst van 2020, wordt een definitie voor een "gifvrij milieu" voorgesteld om de tenuitvoerlegging van de CSS te vergemakkelijken. Daarnaast zijn er belangrijke kwesties geïdentificeerd die ontbreken in de CSS, maar die als belangrijk worden beschouwd voor de realisatie van een gifvrij milieu. Er wordt bijvoorbeeld aanbevolen om de definitie van risico in de verschillende chemische wetgevingen op elkaar af te stemmen, om een open platform op te richten voor het delen van gegevens, en om het nut en het gebruik van nieuwe wetenschappelijke bevindingen in de beleidsvorming te vergroten door de ontwikkeling van een sterk feedbackmechanisme tussen wetenschap en regelgeving en vice versa. In dit hoofdstuk wordt geconcludeerd dat milieuwetenschappers over instrumenten beschikken om bij te dragen aan de belangrijkste uitdagingen van de CSS, maar dat er meer inspanning nodig is van zowel wetenschappers als beleidsmakers om methoden, processen en instrumenten te ontwikkelen die de robuustheid, transparantie en het nut van de wetenschap vergroten.

Hoofdstuk 3 richt zich op de chemische ontwerpfase en draagt bij aan de ontwikkeling van veilige en duurzame chemicaliën (Safe and Sustainable by Design). Er wordt een systematische in silico workflow voorgesteld die het (her)ontwerpen van chemische stoffen voor minder milieurisico's kan vergemakkelijken, waarbij er ook rekening wordt gehouden met duurzaamheidsparameters om chemische vervuiling te verminderen en een veilige circulaire economie mogelijk te maken. De aanpak implementeert verschillende concepten die in de CSS worden genoemd, zoals 'essentieel gebruik' en de 'beoordeling van alternatieven', en is gebaseerd op algemeen beschikbare software om potentiële alternatieve structuren te genereren en chemische eigenschappen te voorspellen met behulp van kwantitatieve structuur-activiteitsrelaties (QSARs). Alleen chemische stoffen die een essentiële functie vervullen en waarvoor geen geschikte alternatieven beschikbaar zijn, weden relevant geacht voor herontwerp. De organofosfaatchemicalie triisobutylfosfaat (TiBP) werd gebruikt als casestudy om de aanpak te verkennen. De emissie van TiBP als gevolg van het gebruik als vlamvertrager werd onvermijdelijk geacht, waardoor er werd gekozen voor een herontwerpbenadering om de afbreekbaarheid in het milieu te verbeteren. In silico werden meer dan 6,3 miljoen potentiële alternatieve structuren voor TiBP gecreëerd en vervolgens gefilterd op basis van QSAR-resultaten om potentieel niet-afbreekbare structuren te verwijderen. Met een multi-criteria analyse (MCDA) gebaseerd op voorspelde eigenschappen en synthetiseerbaarheid werd een lijst van meest wenselijke structuren geïdentificeerd. De structuur (di-n-butyl(2hydroxyethyl) fosfaat) werd handmatig geselecteerd uit de top 500 structuren en gesynthetiseerd in het lab om de chemische stof experimenteel te kunnen testen. Hoewel de QSAR voorspelde eigenschappen van het geselecteerde alternatief betere biologische afbraakeigenschappen lieten zien dan TiBP, bevestigden de eerste experimentele resultaten de verbeterde biologische afbreekbaarheid niet. Om deze resultaten te verklaren en de herontwerpbenadering verder uit te breiden en te verifiëren, is het belangrijk dat de kennis over de biologische afbreekmechanismen in de toekomst wordt verbeterd.

De registratie en toelating van chemische stoffen tot de markt wordt behandeld in **hoofdstuk 4**. Hier worden de risicobeoordelingsprocedures voor het zoetwatermilieu voor (i) biociden (Verordening (EG) nr. 528/2012); (ii) industriële chemicaliën (REACH, Verordening (EG) nr. 1907/2006); (iii) pesticiden (Verordening (EG) nr. 1107/2009); (iv) geneesmiddelen voor menselijk gebruik (Richtlijn 2001/83/EG) en (v) diergeneesmiddelen (Richtlijn 2001/82/EG) geanalyseerd en vergeleken. Het bleek dat, hoewel de algemene principes van de registratie van chemische stoffen hetzelfde zijn, de milieubeschermingsdoelen en de beoordelingsstrategieën om veilige milieuconcentraties (PNEC's) te verkrijgen verschillen. Dit kan leiden tot inconsistente beoordelingen tussen kaders, d.w.z. verschillende PNEC's voor dezelfde stof in verschillende kaders. Bovendien bleken sommige stoffen in het ene kader verboden, maar in een ander kader nog steeds in omgang te zijn. In dit hoofdstuk worden aanbevelingen gedaan om de geanalyseerde registratiekaders beter te harmoniseren en te komen tot een "één stof-één beoordeling"-aanpak (OS-OA).

Maatregelen die kunnen worden geïmplementeerd om chemische stoffen in de gebruiksfase te beheren, worden besproken in **hoofdstuk 5**. Eerst werd het marktaandeel van peristente, mobiele en toxische (PMT) en zeer persistente en zeer mobiele (vPvM) stoffen in cosmetische producten bepaald aan de hand van informatie over cosmetische ingrediënten in databanken van overheden en de industrie. PMT/vPvM-stoffen werden in alle producttypen aangetroffen en de drie meest voorkomende PMT/vPvM-stoffen (Allura rood, Benzofenon-4 en Climbazool) werden geselecteerd als casestudy's. Om te beoordelen of het gebruik van deze chemische stoffen geleidelijk kan worden afgeschaft of kan worden vervangen werd hun functionaliteit in cosmetische producten, de beschikbaarheid van veiligere alternatieven en de essentialiteit van de toepassing van de chemicaliën beoordeeld. Op basis van het kader voor functionele substitutie werd vastgesteld dat de technische functie van allura rood niet noodzakelijk was voor de prestaties van sommige cosmetische producten, waardoor het gebruik niet essentieel was. Voor andere toepassingen van allura rood, evenals voor alle toepassingen van benzofenon-4 en climbazool, werd de technische functie van de chemische stof noodzakelijk geacht voor de prestaties. Via de procedure voor de beoordeling van alternatieven, waarbij gebruik werd gemaakt van experimentele en QSAR-gegevens en drie verschillende MCDA-strategieën, werden veiliger alternatieven geïdentificeerd voor alle drie de casestudy stoffen. Alle beoordeelde toepassingen van PMT/vPvM-stoffen werden dus als niet-essentieel beschouwd en zouden dus kunnen worden uitgefaseerd.

Opties voor het beheer van chemische stoffen tijdens de afvalfase worden gepresenteerd in **hoofdstuk 6.** Er werd een Europese analyse gemaakt van rioolwaterzuiveringsinstallaties (RWZIs) die onder de richtlijn voor de behandeling van stedelijk afvalwater (UWWTD) vallen, inclusief een beoordeling van de huidige zuiveringsniveaus van deze RWZIs en hun potentieel om een reeks van 58 als prioritair aangemerkte farmaceutische stoffen te verwijderen. Er werd berekend dat de impelentatie van geavanceerde behandelingstechnieken, zoals ozonisatie en actieve kool, bij grote RWZIs (die 100.000 mensen of meer bedienen) het emissiereductiepotentieel van

RWZIs in Europa zal verbeteren van 48% tot 69%. Er werden echter ruimtelijke verschillen met betrekking tot de toegepaste zuiveringsniveaus van RWZIs gevonden. Kustwateren en meren leken bijvoorbeeld minder goed beschermd dan andere wateren. Bovendien werd geen strengere zuivering waargenomen voor RWZIs in de buurt van natuurbeschermingsgebieden en RWZIs die effluent lozen in waterlichamen met een minder dan goede ecologische toestand. Dit zou echter wel nodig kunnen zijn om de biodiversiteit te beschermen.

Ten slotte worden de algemene bevindingen van dit proefschrift in **hoofdstuk 7** samengevat en in perspectief geplaatst. Uit de **hoofdstukken 3-6** van dit proefschrift bleek dat er verschillende opties bestaan om de uitstoot van chemische stoffen in het milieu te voorkomen of verminderen, wat bij zal dragen aan het behalen van de beleidsdoelstellingen voor het beheer van chemische stoffen en afval. Gezien de verwachte toename van de diversiteit en het gebruiksvolume van chemische stoffen, is het echter van cruciaal belang om de grote verscheidenheid aan toepassingen van de enorme hoeveelheid chemische stoffen te optimaliseren en waar mogelijk te verminderen. Met andere woorden, we moeten het gebruik van chemodiversiteit optimaliseren om naar een veilige en duurzame toekomst toe te werken. Deze transformatie zal maatschappelijke en institutionele veranderingen vereisen, waarbij een balans moet worden gevonden tussen de voordelen van het gebruik van chemische stoffen en hun veiligheid en duurzaamheid.

List of Publications

Scientific articles

van Dijk, J., Gustavsson, M., Dekker, S. C., & van Wezel, A. P. (2020). Towards 'one substance – one assessment': An analysis of EU chemical registration and aquatic risk assessment frameworks. Journal of environmental management, Volume 280, Article 111692. DOI: 10.1016/j.jenvman.2020.111692.

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Other types of publications

Moermond, C., Venhuis, B., van Elk, M., Oostlander, A., van Vlaardingen, P., Marinković, M., **van Dijk, J.** (2018). Cytostatics in Dutch Surface Water: Use, Presence and Risks to the Aquatic Environment. RIVM letter report 2018-0067. Rijksinstituut voor Volksgezondheid en Milieu.

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About the Author

I was born on the 8th of April 1993 in Deventer, the Netherlands, where I also grew up. In Deventer, I dedicated many hours to rhythmic gymnastics -a sport that barely anyone in the Netherlands knows- and developed an interest in travelling during the many national and international competitions and training camps. In my free (a.k.a. school) time, I developed an interest in biology and chemistry, leading me to follow a BASc in Biomedical Sciences with a focus on toxicology. Whilst with this Bachelor I focussed on how the environment can affect human health, I developed a greater interest in how humans are affecting environmental health. This led me to pursue a MSc in Environmental Sciences with, again, a focus on toxicology. After graduating in 2017, I spent some time at the RIVM, working on a project that aimed to assess the risks of cytostatic drugs to the aquatic environment, after which I got the opportunity to join the European Food Safety Authority in Parma, Italy, as a trainee. Here, I continued assessing environmental risks of chemicals, only this time for pesticides. After working and enjoying life in Italy for a year, I moved back to the Netherlands for my PhD research within the ECORISK2050 project under supervision of prof. dr. Annemarie van Wezel and prof. dr. Stefan Dekker. This time mainly focussing on finding solutions rather than problems with regards to chemicals in the environment. The results of this research are presented in this dissertation. Upon completing my PhD research, I continued in research and started in June 2023 as a postdoctoral researcher at EMPA in Switzerland, where I am excited to be above sealevel, see some elevation in the landscape and contribute further to the field of 'Safe and Sustainable by Design'.